

# Recent Advances in the Management of Smoldering Multiple Myeloma

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## Abstract

There is remarkable progress in the treatment of multiple myeloma (MM) with significant improvement in survival in the past 10 years. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) can evolve into symptomatic multiple myeloma (sy-MM) with organ involvement. SMM has associated with a much higher progression to MM compared to MGUS. In 2014, International Myeloma Working Group (IMWG) reclassified ultra-high-risk smoldering myeloma patients with bone marrow plasma cells > 60% or serum-free light chain ratio (FLCr) > 100 or > 1 focal bone lesion on the magnetic resonance imaging as MM. SMM is a heterogeneous disorder with probability for progression to myeloma up to 50% in the first 5 years. Several risk models and clinical features have been identified to stratify the risk of progression to MM. Thanks to advances in our understanding of the genomic profile of MM, there are several ongoing clinical trials, and genomic studies are being done to assess the risk of progression to MM and early intervention. There is still no standard criterion regarding when to start therapy. This review discusses identifying SMM patients who are at high risk of progression to sy-MM and recent development of new and early treatment strategies and ongoing clinical trials for these high-risk SMM patients.

**Keywords:** Multiple myeloma; Smoldering multiple myeloma; Risk stratification; Diagnostic criteria

## Introduction

Multiple myeloma (MM) accounts for 1.3% of all new cancer

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cases in the USA, and ranks as the second most frequent blood malignancy, after non-Hodgkin lymphoma [1, 2]. Symptomatic multiple myeloma (sy-MM) may have end-organ damages leading to hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) (Table 1) [3].

Asymptomatic, or smoldering multiple myeloma (SMM), is a distinct clinical entity from active myeloma, though it is associated with risk of progression to sy-MM and amyloidosis (AL) [4, 5]. There is still no standard criterion regarding when to start therapy. In this review, we summarized the factors and tools that can aid in distinguishing between low- and high-risk SMM, as well as the value of early treatment in high-risk SMM patients.

## Diagnostic Criteria

The seminal recognition of SMM came from Kyle and Greipp in 1980, based on a case series of six patients who met the criteria of MM, but showed no evidence of the characteristic clinical CRAB manifestations of sy-MM, nor any progression to sy-MM for 5 or more years [6, 7]. In 2003, the International Myeloma Working Group (IMWG) announced a consensus on diagnostic criteria for classifying and differentiating plasma cell (PC) proliferative disorders including sy-MM, SMM, as well as monoclonal gammopathy of unknown significance (MGUS) (Table 1) [3, 8, 9].

SMM was defined as the presence of bone marrow plasma cells (BMPCs) of  $\geq 10\%$ , and/or a serum monoclonal protein (M-protein) of  $\geq 3\text{g/dL}$ , with no evidence of end-organ damage assessed by CRAB criteria [8]. The criteria were further refined by the Mayo group, clarifying that the M-protein must be of immunoglobulin G (IgG) or IgA subtype and that the BMPC be clonal in nature [9].

Due to the lack of population-based studies, and change in criteria for the diagnosis of MM, the actual prevalence of SMM in the USA is unclear. American National Cancer Database Study estimated the incidence of 0.9 cases per 100,000 persons, and the median age at diagnosis was 67 years. These findings were similar to Swedish population-based study, with an incidence of 0.4 cases per 100,000 persons [2]. The incidence proportion of SMM is estimated to be between 10% and 15% of diagnosed MM and the median patient age at diagnosis ranged from 65 to 70 years, similar to other PC disorders [3, 10]. Without consensus on diagnostic criteria until 2003, reports varied in their inclusion/exclusion criteria (i.e. inclusion/

**Table 1.** IMWG Diagnostic Criteria for SMM, MGUS and sy-MM

	MGUS	SMM	Multiple myeloma
Serum monoclonal protein (IgG or IgA)	< 3 g/dL	≥ 3 g/dL	≥ 3 g/dL
	And	And/or	And/or
Clonal bone marrow plasma cells	< 10%	≥ 10%	≥ 10%
	And	And	And
CRAB	Absent	Absent	Present

MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; sy-MM: symptomatic multiple myeloma; CRAB: hypercalcemia, renal insufficiency, anemia, bone lesion; Ig: immunoglobulin; IMWG: International Myeloma Working Group.

exclusion of patients with small lytic bone lesions on skeletal survey vs. on magnetic resonance imaging (MRI) [10-13].

## Progression

Kyle et al stated that the overall risk of progression of SMM to active MM or AL in the first 5 years is 10% per year, for the next 5 years it is approximately 3% per year, and for the last 10 years, it is 1% per year [6]. The cumulative probability of progression was 73% at 15 years. In their study of 276 patients who fulfilled the criteria for SMM in over 26 years period, 158 patients (57%) developed active MM with a median survival of 3.4 years after the diagnosis. The significant risk factors for progression included the serum level and type of monoclonal proteins, the presence of urinary light chain, the extent and pattern of bone marrow involvement, and the reduction in uninvolved immunoglobulins [6].

The monoclonal gammopathy of undetermined significance (MGUS) may precede the appearance of SMM. There is an annual risk of one percent of progression to myeloma or a related malignant disease [3]. A multistep development model suggests that MGUS might progress to SMM, and ultimately to symptomatic intramedullary and extramedullary MM, or PC leukemia [1].

## Factors Predicting Progression to sy-MM

Majority of patients diagnosed with SMM will progress to develop sy-MM. There have been multiple studies aimed at predicting the progression of SMM to sy-MM or primary AL. Before the 2003 IMWG criteria, presence of bony lesions was the most common risk factor for progression to active myeloma; this led to its exclusion from the definition of SMM subsequently [8, 14]. In this section, we will discuss the widely

accepted criteria assessing the risk prediction of SMM patients to develop MM/AL and throw light on some ongoing advances and newer prognostic modalities.

The Mayo Clinic group retrospectively studied a cohort of 276 patients having SMM as defined by IMWG criteria (Table 2) [6]. The risk factors considered were M-protein concentration and bone marrow infiltration. Patients were divided into three subgroups. Group 1 had ≥ 3 g/dL of M-protein, and ≥ 10% BMPCs. Group 2 had < 3 g/dL of M-protein and ≥ 10% BMPC, while Group 3 had ≥ 3 g/dL M-protein concentration and < 10% BMPCs. Groups 1, 2, and 3 respectively had a median time to progression (TTP) of 2, 8, and 19 years. The annual risk of progression as calculated by the Mayo Clinic group is 10% per year for the first 5 years, 3% per year for the next 5 years and 1% per year following that [6]. Dispenzieri et al studied that an abnormal free light chain ratio (FLCr) (< 0.125 or > 8) was independently associated with earlier progression to symptomatic disease [15]. Together, the three criteria, as mentioned above (BMPC, M-protein size, and FLCr) resulted in an improved prognostic classification of SMM. In the same series, SMM patients with an involved/uninvolved FLCr ≥ 100 were found to develop MM within a median of 15 months versus 55 months for patients with a ratio < 100 [15].

The Programa Espanol de Tratamientos en Hematologia (PETHEMA) model proposed by Perez-Persona et al uses the percentage of abnormal BMPCs found using multiparameter flow cytometry and absence or presence of immunoparesis [16]. The aberrant phenotype of BMPC is defined as ≥ 95% phenotypically abnormal cells (i.e. with overexpression of CD59 and CD19, CD45 negative and/or decreased reactivity for CD38). This was the most important predictor of early progression of SMM to MM, the cumulative progression at 5 years being 64% in patients with ≥ 95% abnormal phenotype versus 8% in patients with < 95%. Immunoparesis, defined as the reduction in one or two of the uninvolved immunoglobulins at 25% below normal value, is also a significant prognostic

**Table 2.** Risk Stratification of SMM Patients According to Mayo Clinic Criteria

	M-protein size	Bone marrow plasma cells	Time to progression (years)
Group 1	≥ 3 g/dL	≥ 10%	2
Group 2	< 3 g/dL	≥ 10%	8
Group 3	≥ 3 g/dL	< 10%	19

SMM: smoldering multiple myeloma.

**Table 3.** Updated Risk Stratification Model for SMM Incorporating Revised IMWG Diagnostic Criteria Using (20/2/20) Parameter

Risk factor	Number of Subjects (n)	Hazard ratio	P value	2-year progression (n (%))
0	424		Not available	21 (5%)
1	312	2.25 (1.68 - 3.01)	Significant	53 (17%)
2	415	5.63 (4.34 - 7.29)	Significant	190 (46%)

Serum M-protein (2 g/dL); involved to uninvolved serum-free light chain ratio (20); and marrow plasma cells % (20%). SMM: smoldering multiple myeloma; IMWG: International Myeloma Working Group.

factor. Based on the above parameters, the 5-year cumulative probability of progression was 4%, 46%, and 73% when 0, 1, or 2 factors, respectively, were present. The advantage of this model is that it assists in identifying SMM patients with very low risk of progression by permitting more distinction in individual risk of progression. The Mayo Clinic model is more user-friendly and spares patients with the low risk disease from undergoing a bone marrow biopsy [15]. These two models were compared and found to be significantly discordant (28.6% concordance), implying that there is a need for prospectively validated models to characterize the individual patient risk of transformation to MM [17].

Apart from the first two widely studied and used criteria, several other prognostic markers have been evaluated. The Mayo Clinic group studied peripheral blood circulating PCs in 171 SMM patients and in those with high levels of circulating PCs ( $> 5 \times 10^6/L$  and/or  $> 5\%$  PCs per 10 cytoplasmic immunoglobulin positive mononuclear cells). At the end of 2 years, progression in the group with low levels was 24% versus 71% in those with high levels [18]. The same group also evaluated SMM patients with ultra-high risk of progression. They found 21 out of 655 patients with BMPCs more than 60%. TTP was less than 2 years in 95% of patients in the ultra-high-risk group [18].

An updated multicenter, retrospective study of SMM patients diagnosed after January 2004 identified factors that predict progression to myeloma at 2 years through evaluation of various clinical and laboratory data. A total of 2,004 patients were included in the study. Serum M-protein (2 g/dL), involved to uninvolved serum-FLCr, and marrow PCs % (20%) were the factors independently associated with progression to MM. Patients were stratified using these risk models (20/2/20 risk model, 20% PC, M-protein 2 g/dL and FLCr 20) as low (0), intermediate (1), and high-risk ( $\geq 2$ ) (Table 3). The study showed that patients with any two of three risk factors were considered to be at high risk with 50% progression to MM at 2 years [19].

Also, genetic factors may impact progression and overall survival (OS). Neben et al studied chromosomal abnormalities in myeloma cells of 248 SMM patients using interphase fluorescent *in situ* hybridization (iFISH). They concluded that del (17p13), t (4; 14), and +1q21 which are considered high-risk chromosomal aberrations are adverse prognostic markers with similar significance, independent of the tumor mass in both SMM and active MM. The above aberrations were present in 6.1%, 8.9%, and 29.8% of patients, respectively with significant hazard ratio (HR), conferring adverse prognosis in SMM. Hyperploidy, present in 43.3% of patients, was also

found to be an adverse prognostic factor (HR, 1.67; 95% confidence interval (CI), 1.10 to 2.54) with a median TTP of 3.92 years. This contrasts with the conditions in active myeloma, thus being the first example for an adverse prognostic factor in SMM of opposite predictiveness in active myeloma. Other factors that conferred significant adverse prognosis include malignant BMPCs, assessed by iFISH, and the combination of PC infiltration and M-protein as indirect measure of tumor load with HRs of 4.37 (95% CI, 2.79 to 6.85) and 4.27 (95% CI, 2.77 to 6.56), respectively. The median TTP for patients with and without del (17p13) was 2.04 years and 5.62 years, respectively. The presence of t (4; 14) was associated with a median TTP of 2.91 years versus 5.71 years associated with absence. Patients with +1q21 aberration had a median TTP of 3.86 years, whereas TTP was not reached in patients without it [20].

A single institutional Gene Expression Profile study to predict time to myeloma therapy (TTT) among 105 SMM patients showed four genes (GEP4) in descending order including RRM2 (2p25-p24), DTL (1q32), TMEM48 (1p32.3), and ASPM (1q31), which were significantly associated with TTT. The study generated high-risk SMM based on four genes at an optimal cut-point of 9.28, with a predictive for the 2-year probability of therapy of 85% in 14 patients (13%). A low four gene risk score ( $< 9.28$ ) with baseline monoclonal protein  $< 3$  g/dL and albumin  $> 3.5$  g/dL is associated with 5% chance of progression at 2 years in 61 patients [21].

Bolli et al reported that cytogenetic, mutational, and rearrangement profile was similar to MM. Two different patterns of progression were observed from premalignant stage to MM. In the static progression model, same subclonal architecture was retained as the disease progressed to accumulate enough disease burden to become clinically significant. Here, all the genomic features of overt myeloma were already present when the disease was defined as SMM based on the clinical parameters. Early identification and treatment of these patients will be the focus of future studies. The spontaneous evolution model represents the evolution of subclonal acquisition of additional mutation conferring a proliferative advantage to one of the subclones. Patients in these groups will be a candidate to undergo preventive therapeutic strategies to prevent clonal mutations from preventing progression to MM [22].

Rosinol et al classified the monoclonal component in SMM into two subtypes: evolving and non-evolving, in a sample of 53 patients. Patients with evolving SMM showed a constant increase in M-protein level until progression to symptomatic myeloma while a stable M-protein level characterized those with non-evolving type until the onset of symptomatic

disease. Patients with evolving SMM had a shorter TTP to active disease than those with non-evolving SMM (1.3 vs. 3.9 years) [13].

Researchers over these years have studied radiologic assessment of SMM progression. MRI studies are more suited than skeletal surveys and computed tomography (CT) scans for evaluating bone marrow involvement and different patterns of infiltration. About 30-50% of SMM patients have abnormal bone marrow MRI studies. Patients with an abnormal MRI had a median TTP of less than 1 year, while those with no MRI findings had a median TTP of more than 3 years [23]. Mouloupoulos et al reported in a study that patients with abnormal MRI studies ( $n = 19$ ) required treatment earlier against those with normal MRI studies ( $n = 19$ ) (median time 16 months vs. 43 months). The 19 patients with abnormal MRI findings had focal, diffuse, or variegated patterns. The focal pattern is associated with the shortest TTP, on an average 6 months, as compared with 16 and 22 months for diffuse and variegated patterns, respectively [23]. Mariette et al identified that abnormal MRI studies independently predicted TTP. In their study, where 10 out of 55 SMM patients progressed to symptomatic disease over a follow-up period of 25 months, eight out of 17 had abnormal MRI findings while two out of 38 had abnormal findings [24]. Wang et al found that the median TTP was shorter for patients with abnormal MRI (1.5 years vs. 5 years) in a study of 72 SMM patients [25].

Metabolic imaging studies like dynamic contrast-enhanced MRI (DCE-MRI) improve the specificity by identifying functional lesions as opposed to false positive degenerative bone lesions imaged by X-ray, CT, and MRI. Hillengass et al evaluated 222 patients with MGUS, SMM and active MM, with 22 healthy controls using DCE-MRI of the spine. Gradually increasing diffuse microcirculation patterns were found in healthy controls, MGUS, and SMM patients, while focal lesions were identified in 42.6% of sy-MM patients. Increased microcirculation patterns were associated with significantly higher bone marrow plasmacytosis [26].

Positron emission tomography (PET) is another functional imaging study that allows whole-body screening using  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake by tumor cells, based on their glucose demand. Durie et al performed a retrospective study of active MM patients between 1996 and 2000, and found that 25% of patients had an abnormal PET scan despite a normal skeletal survey [27].

Zamagni et al prospectively studied bone marrow involvement with PET/CT at baseline in a cohort of 73 patient with a median age of 61 years with SMM. Approximately 10% of patients with SMM have a positive PET/CT without underlying osteolytic lesions. PET/CT positivity significantly increased the risk of progression of SMM to active MM. A total of 66% of patients with positive PET/CT progressed to MM in comparison to 33% of patients with negative PET/CT ( $P = 0.034$ ) with a relative risk of 2.3 ( $P = 0.06$ ) with a median TTP of 2.2 years with positive PET scan compared to 7 years with negative PET/CT [28]. However, it should be noted that 11% patient presented with FLCr  $> 100$ , now classified under MM according to the 2014 international myeloma working definition [3]. Results of these studies were summarized in Table 4 [6, 13, 15, 16, 18-23, 25, 26, 28, 29].

## Treatment Strategies to Delay Progression

As mentioned earlier, most patients with SMM progress to develop sy-MM, with increasing anemia, skeletal involvement including lytic lesions and/or osteoporosis, renal dysfunction, or hypercalcemia. The actuarial probability of SMM progressing to MM or AL is 78% at 20-year follow-up [5]. The current standard of care is adapting a “wait and watch” approach; treatment is indicated only on the development of the symptomatic disease. Serum protein electrophoresis (SPEP), complete blood count, 24-h urine protein electrophoresis (UPEP) and immunofixation, and physician follow-up visits are recommended every 2 to 3 months for the first year after diagnosis. Bone marrow biopsy and MRI spine are also recommended to detect occult lesions. If results are stable at the end of the first year, the above studies are repeated every 6 months for a year, and then every 6 to 12 months [24]. Treatment is not recommended outside of clinical trials.

The earliest trials for the treatment of SMM included three small studies using melphalan-prednisone (MP) combination versus observation [30-32]. Early treatment of SMM had no significant survival benefit over observation. Hjorth et al observed that the response rate in patients treated at diagnosis was similar to that of patients who received treatment at the time of progression (52% versus 55%) [30]. The median survival of patients treated in the study by Grignani et al was 54 months as opposed to 58 months in the observed arm [31]. In the study by Riccardi et al the median survival in the treatment group was 64 months, and in the observation group was 71 months [32]. These observations led to the conclusion that treatment was not recommended for the treatment of asymptomatic or indolent MM. However, the MP combination is a regimen with a poor therapeutic index, and the studies were performed at a time when no better alternatives for myeloma treatment were available.

Thalidomide has been extensively studied for the treatment of SMM. Rajkumar et al studied thalidomide in 16 SMM patients and had a partial response (PR) in 38% of the patients [33]. This data may be confounded by the involvement of patients with indolent MM, an entity that is now classified as MM. Barlogie et al studied the response of thalidomide and pamidronate in 76 patients with SMM in a 7-year long phase II trial [34]. They did not show an overall benefit of treatment with thalidomide and pamidronate versus observation. Most patients quit the study due to development of adverse effects, most notably, peripheral neuropathy and dizziness. Paradoxically, patients with a PR to thalidomide went on to have a shorter median time to treatment ( $< 2$  years) than those who did not receive treatment ( $> 8$  years). This could be due to the selection of more aggressive clones due to treatment or due to higher initial response in patients with more proliferative tumors. A small Spanish study comprising of 12 patients demonstrated that pamidronate induced bone formation but had no antitumor properties in SMM patients [35]. Two randomized trials by Musto et al using pamidronate and zoledronic acid, respectively for the treatment of SMM patients had similar results, reduced number of skeletal events but no improvement in OS or prolongation of TTP [36, 37]. A phase III randomized

**Table 4.** Summary of Prognostic Factors for Progression of SMM to MM

Investigators	Risk factors	Progression
Moulopoulos et al (1995) [23]	Abnormal MRI	Normal MRI: TTP 43 months; abnormal MRI: TTP 16 months; variegated pattern: TTP 22 months; diffuse pattern: TTP 16 months; focal pattern: TTP 6 months
Rosinol et al (2003) [13]	Evolving disease	Evolving type: TTP 1.3 years; non-evolving type: TTP 3.9 years
Wang et al (2003) [25]	Abnormal MRI	Normal MRI: TTP 5 years; abnormal MRI: TTP 1.5 years
Kyle et al (2007) [6]	M-protein ≥ 3 g/dL, BMPC ≥ 10%: Group A; M-protein < 3 g/dL, BMPC ≥ 10%: Group B; M-protein ≥ 3 g/dL, BMPC < 10%: Group C	Group A: TTP 2 years; Group B: TTP 8 years; Group C: TTP 19 years
Perez-Persona et al (2007) [16]	95% aberrant BMPC (absence of CD19 and/or CD45 expression, overexpression of CD56, or weak expression of CD38); immunoparesis of the uninvolved immunoglobulins	0 risk factor: 5-year TTP of 4%; 1 risk factor: 5-year TTP of 46%; 2 risk factors: 5-year TTP of 72%
Dispenzieri et al (2008) [15]	M-protein ≥ 3 g/dL; BMPC ≥ 10%; abnormal FLCr < 0.125 or > 8	1 factor: 5-year TTP of 25% (TTP 10 years); 2 factors: 5-year TTP of 51% (TTP 5.1 years); 3 factors: 5-year TTP of 76% (TTP 1.9 years)
Hillengass et al (2009) [26]	Focal lesion on whole body MRI	≤ 1 focal lesion: 2-year TTP of 20% (TTP NR); > 1 focal lesion: 2-year TTP of 70% (TTP 13 months)
Neben et al (2012) [20]	High-risk FISHs: t(4:14), deletion 17p or 11q21; high tumor burden: M-protein of 20 g/L	Both absent: 3-year TTP of 8%; high-risk FISH only: 3-year TTP of 30%; high tumor load only: 3-year TTP of 40%; both present: 3-year TTP of 59%
Larsen et al (2013) [29]	Involved/uninvolved FLCr of ≥ 100	FLCr < 100: TTP 55 months; FLCr ≥ 100: TTP 15 months
Bianchi et al (2013) [18]	> 5,000 × 10 <sup>6</sup> /L PCs and/or > 5% cytoplasmic immunoglobulin positive PCs per 100 peripheral mononuclear cells	Absent: 5-year TTP of 25% (TTP 57 months); present: 5-year TTP of 71% (TTP 12 months)
Zamagni et al (2016) [28]	Number of focal lesions	Risk of progression with positive PET/CT was 3.00 (95% CI 1.58 - 5.69, P = 0.001), with a median TTP of 1.1 versus 4.5 years for PET/CT-negative patients; median TTP of 2.2 years versus 7 years with negative PET/CT (1)
Khan et al (2015) [21]	Gene signature from four genes (GEP4): the top genes in the GEP4 model includes RRM2 expression, DTL, implicated in oncogenesis via a role in apoptosis and cell cycle control, and ASPM	Gene signature binary cutoff > 9.28 associated with a 2-year risk of therapy 85.7%
Bolli et al (2018) [22]	Whole-genome sequence of 11 patients with SMM progressed to MM	Static progression model: clonal architecture retained, progression occurs with accumulation of enough disease burden; spontaneous evolution model: via accumulation of new mutations progress to MM
Miguel et al (2019) [19]	M-protein (2 g/dL), involved to uninvolved FLCr (20), and marrow plasma cell % (20%); 20/2/20 risk model	Intermediate risk (1) and high risk (> 2) had a significantly high risk for progression in 2 years: 17% and 46% respectively

SMM: smoldering multiple myeloma; MM: multiple myeloma; TTP: time to progression; BMPC: bone marrow plasma cell; MRI: magnetic resonance imaging; M: monoclonal; FLCr: free light chain ratio; NR: not reached; FISH: fluorescent *in situ* hybridization; PCs: plasma cells; PET: positron emission tomography; CT: computed tomography; CI: confidence interval.

controlled trial (RCT) showed that thalidomide, when added to zoledronic acid, significantly improved progression-free survival (PFS) according to the study protocol in patients with asymptomatic myeloma, against using zoledronic acid alone (29 months vs. 14 months). However, there was no difference in PFS as defined by CRAB criteria as recommended by IMWG (40 months vs. 33 months). Median TTP for the first

group was 2.4 years, compared with 1.2 years for the latter group. However, there was no difference in OS between the two arms [38].

The PETHEMA group from Spain studied the use of lenalidomide and low-dose dexamethasone in high-risk SMM patients versus observation; the findings were published in 2013 [39]. High-risk disease was defined as plasma-cell bone mar-

row infiltration of at least 10% and a monoclonal component (defined as an IgG level of  $\geq 3$  g per deciliter, an IgA level of  $\geq 2$  g per deciliter, or a urinary Bence Jones protein level of  $> 1$  g per 24 h) or only one of the two criteria described above, plus at least 95% phenotypically aberrant PCs in the bone marrow plasma-cell compartment, with reductions in one or two uninvolved immunoglobulins of more than 25%, as compared with normal values. The treatment group received 9 months of induction therapy with both drugs (revlimid (lenalidomide), dexamethasone (IRd)) followed by a maintenance phase for 15 months with single agent lenalidomide. The median TTP was not reached in the treatment group and was 21 months in the observation group. The symptomatic disease developed in 76% of patients in the observation arm versus 23% patients in the treatment arm. After a median follow-up of 46 months, the survival rate in the treatment group was 94% at 5 years, and that in the observation group was 78% at 5 years. These findings are certainly encouraging and require further validation before the development of management strategies for SMM. The study also showed a projected 5-year OS of 94% in the treatment arm versus 78% in the observation arm. Long-term analysis median 75-month follow-up results also confirms that early treatment with lenalidomide-dexamethasone for high-risk SMM improves TTP as well as OS [39]. However, the general applicability of these results is limited as the patients were not screened using advanced imaging as well as due to methods to define high-risk SMM, which required flow cytometric analysis of PC immunophenotype that is not routinely available.

Subsequently, a prospective phase III E3A06 intergroup trial compared lenalidomide versus observation in intermediate- and high-risk SMM with BMPCs  $> 10\%$  and serum FLCr ( $< 0.26$  or  $> 1.65$ ) eligible for the study. A total of 182 patients were randomized to lenalidomide 25 mg daily for 21 of the 28 days cycle ( $n = 90$ ) or observation ( $n = 92$ ). The 3-year PFS was 91% for lenalidomide group versus 66% for the observation arm (HR 0.28,  $P = 0.0005$ ) favoring lenalidomide arm, significantly delaying the progression of smoldering myeloma [40]. No difference existed in the quality of life between both groups. The 3-year cumulative incidence of invasive secondary malignancy was 5.2% in the lenalidomide group and 3.5% in observation. Overall this trial in conjunction with Spanish data [39] shows that both intermediate- and high-risk patients may benefit, and these patients probably benefit from early treatment with lenalidomide to reduce the risk of progression to symptomatic myeloma. Ongoing phase III EGOG EAA173 trial is enrolling patients with high-risk SMM to treat aggressively, randomized to daratumumab plus lenalidomide and dexamethasone, versus lenalidomide and dexamethasone high-risk smoldering myeloma [41]. Several other studies employing novel agents like isatuximab, carfilzomib, elotuzumab, siltuximab, anti-killer inhibitory receptor (KIR) monoclonal antibodies are currently being studied [42-46]. Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant (ASCENT) is a phase 2 trial currently recruiting patients to evaluate the use of carfilzomib, lenalidomide, daratumumab, and dexamethasone in an attempt to cure patients with high-risk SMM [29]. The completed clinical trials were summarized in Table 5 [30-34,

36-40]. The ongoing clinical trials were summarized in Table 6 [29, 43, 47-54].

## Conclusions

National Comprehensive Cancer Network (NCCN) and IMWG currently do not believe in the treatment of all patients with smoldering myeloma with a high risk of progression to active MM with any anti-myeloma therapy. Experts in myeloma also differ in opinion about the management of SMM. However, there is growing evidence for the early treatment of SMM, especially high-risk SMM. Long-term data of phase III randomized trial (QuiRedex) by Spanish Multiple Myeloma Group for early treatment of high-risk smoldering with lenalidomide and dexamethasone versus observation reported improved progression to myeloma compared to observation. Most recently another phase III randomized trial E3A06 as well showed early treatment of high-risk smoldering myeloma patients with lenalidomide versus observation delays the progression to SMM. However, there are concerns for toxicity, OS benefit, cost of therapies, as well as the long-term effectiveness of therapy. Based on the review of current literature, at the time of diagnosis of SMM, PET-CT or MRI of the whole body or spine and pelvis is recommended in addition to laboratory studies. With more sensitive imaging, patients who were once considered as SMM were diagnosed as MM. Close follow-up in 2 - 3 months with repeat blood work measured evolving M-protein. In patients with an equivocal focal lesion on the initial MRI, repeat imaging in 3 to 6 months is recommended. With advances in radiological testing, incorporating genomics and molecular profile of SMM, future clinical trials should focus on identifying early treatment strategies to prevent progression or cure SMM.

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**Table 5.** Summary of Completed Clinical Trials in SMM Patients

Investigators	Study	Treatment	TTP	OS
Hjorth et al (1993) [30]	RCT	Initial versus delayed MP	12 months	No difference
Grignani et al (1996) [31]	RCT	MP versus observation		No treatment: 58 months; treatment: 54 arms
Riccardi et al (2000) [32]	RCT	Initial versus delayed MP	13 months	Initial MP: 64 months; delayed MP: 71 months
Rajkumar et al (2001) [33]	Single arm phase 2 trial	Thalidomide	35 months	Treatment: 49 months; observation: 86 months
Barlogie et al (2008) [34]	Single arm phase 2 trial	Thalidomide and pamidronate	4-year EFS 60%	4-year OS 91%
Musto et al (2003) [36]	RCT	Pamidronate versus observation	Treatment: TTP 16 months; observation: TTP 17.4 months	OS not reported
Musto et al (2008) [37]	RCT	Zoledronate versus observation	Treatment: TTP 67 months; observation: TTP 59 months	OS not reported
Witzig et al (2013) [38]	RCT	Thalidomide and zoledronate versus zoledronate	Thalidomide/zoledronate: TTP 2.4 years; zoledronate: TTP 1.2 years	OS > 70% after 6 years in both arms (no difference)
Mateos et al (2013) [39]	RCT	Lenalidomide and dexamethasone versus observation	Treatment: TTP NR; observation: TTP 21 months	5-year OS; treatment: 94 months, observation: 78 months
Lonial et al (2019) [40]	RCT	Lenalidomide versus observation	Treatment arm of PFS 91% versus 66% in the observation arm	OS not reported

SMM: smoldering multiple myeloma; TTP: time to progression; OS: overall survival; RCT: randomized controlled trial; MP: melphalan-prednisone; NR: not reached; PFS: progression-free survival.

**Table 6.** Summary of Ongoing Clinical Trials in SMM

Treatment	Study	Primary objectives
Denosumab [47]	Open label, phase II, single group	Proportion of patients with decreased risk of progression of SMM within 1 year
Trial of Combination of Ixazomib and Lenalidomide and Dexamethasone [48]	Open label, phase II, single group	High-risk SMM patient who received IRd combination therapy, progression free at 2 years
Ibrutinib [49]	Open label, phase II, single group	High-risk SMM; efficacy of ibrutinib to prevent progression to symptomatic MM in 1 year
Personalized vaccine [50]	Early phase I, single group	Feasibility and safety of personalized vaccine
Carfilzomib, lenalidomide, and dexamethasone [43]	Open label, phase II, single group	Response rate at 8 months, progression-free survival and duration of response
PVX-410, a multi-peptide cancer vaccine, and citarinostat (CC-96241), a HDACi with and without lenalidomide [51]	Open label, phase I, nonrandomized	Safety and tolerability of this vaccine regimen in 2 years
Daratumumab in patients with high-risk MGUS and low-risk SMM [52]	Open label, phase II, single group	Proportion of patients in deep response at 2 years
Carfilzomib, lenalidomide, daratumumab, and dexamethasone in subjects with high-risk SMM ASCENT trial [29]	Multicenter, phase II, open label	Stringent complete response, deep MRD, and potentially achieving cure or long-term disease quiescence
Lenalidomide and dexamethasone work with or without daratumumab [53]	Open label, phase III, RCT	Overall survival, assess health related quality of life
Carfilzomib, lenalidomide and dexamethasone versus lenalidomide and dexamethasone [54]	Open label, phase II, RCT	Progression-free survival until 5 years

Most studies are in high-risk SMM unless specified. SMM: smoldering multiple myeloma; IRd: revlimid (lenalidomide), dexamethasone; MM: multiple myeloma; HDACi: histone deacetylase inhibitor; MGUS: monoclonal gammopathy of undetermined significance; ASCENT: Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant; MRD: minimal residual disease; RCT: randomized controlled trial.

tion of tables and review of references; and TCG is the supervising senior author.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

## Abbreviations

MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; MM: multiple myeloma; sy-MM: symptomatic multiple myeloma; FLCr: free light chain ratio; CRAB: hypercalcemia, renal insufficiency, anemia, or bone lesions; IMWG: International Myeloma Working Group; PETHEMA: Programa Espanol de Tratamiento Hematologia; TTP: time to progression; BMPC: bone marrow plasma cell; TTT: time to myeloma therapy; DCE-MRI: dynamic contrast-enhanced MRI; PET: positron emission tomography; <sup>18</sup>F-FDG: <sup>18</sup>F-fluorodeoxyglucose; Ig: immunoglobulin; MRI: magnetic resonance imaging; CT: computed tomography; M: monoclonal; iFISH: interphase fluorescent *in situ* hybridization; IRd: revlimid (lenalidomide), dexamethasone; HR: hazard ratio; AL: amyloidosis; OS: overall survival; CI: confidence interval; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; PR: partial response; PFS: progression-free survival; KIR: killer inhibitory receptor; ASCENT: Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant; NCCN: National Comprehensive Cancer Network; NR: not reached; PCs: plasma cells; RCT: randomized controlled trial; MP: melphalan-prednisone; MRD: minimal residual disease

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