

# Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma: A Review of the Current Understanding of Epidemiology, Biology, Risk Stratification, and Management of Myeloma Precursor Disease

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## Abstract

The term monoclonal gammopathy of undetermined significance (MGUS) was coined in 1978. The recent advances in our knowledge about MGUS and smoldering multiple myeloma (SMM) have helped us better understand the pathogenesis of myeloma. It seems that myeloma evolves from a precursor state in almost all cases. We do not completely understand the multistep process from the precursor state to myeloma, but studies like whole genome sequencing continue to improve our understanding of this process. The process of transformation may not be linear acquisition of changes, but rather a branched heterogeneous process. Clinical features that are prognostic of rapid transformation have been identified, but no specific molecular markers have been identified. Even with recent advances, multiple myeloma remains an incurable disease in the vast majority, and intervening at the precursor state provides a unique opportunity to alter the natural history of the disease. A limitation is that a vast majority of patients with precursor disease, especially low-risk MGUS, will never progress to myeloma in their lifetime, and treating these patients is not only unnecessary but may be potentially harmful. The challenge is to identify a subset of patients with the precursor state that would definitely progress to myeloma and in whom interventions will have a meaningful impact. As our understanding of the molecular and genetic processes improves, these studies will guide the selection of high-risk patients more appropriately and ultimately direct a tailored management strategy to either delay progression to symptomatic myeloma or even "cure" a person at this premalignant stage. *Clin Cancer Res*; 19(5); 985–94. ©2012 AACR.

## Introduction

Multiple myeloma is a plasma cell neoplasm characterized by multifocal proliferation of clonal, long-lived plasma cells associated with an overproduction of monoclonal gammaglobulin (1). In 1961, Jan Waldenström described "essential benign hypergammaglobulinemia" as an asymptomatic condition wherein the monoclonal gammopathy is not associated with any symptoms (2). The term monoclonal gammopathy of undetermined significance (MGUS) was coined in 1978 (3) and smoldering multiple myeloma (SMM) in 1980 (4). It has always been recognized that some cases of MGUS progressed to symptomatic multiple myeloma, but recent studies have shown

that multiple myeloma is consistently preceded by MGUS (5, 6). This has given rise to the concept of a myeloma precursor disease and raised questions about the biologic events leading to progression of these precursor states to symptomatic myeloma. We will review the current understanding of the biology of these precursor states and also discuss trials looking at interventions.

## Definition

In 2010, the International Myeloma Working Group (IMWG) defined MGUS by the presence of serum M-protein ( $< 3\text{ g/dL}$ ), clonal plasma cell population in the bone marrow ( $< 10\%$ ), and the absence of end-organ damage such as hypercalcemia (serum calcium  $\geq 11.5\text{ mg/dL}$ ), renal insufficiency (serum creatinine  $\geq 2\text{ mg/dL}$ ), anemia (hemoglobin value below the lower limit of normal by  $>2\text{ g/dL}$  or hemoglobin value  $< 10\text{ g/dL}$ ), and lytic bone lesions (CRAB features) that can be attributed to the plasma cell proliferative disorder (7). SMM was defined by the presence of serum M-protein ( $\geq 3\text{ g/dL}$ ) and/or clonal bone marrow plasma cells ( $\geq 10\%$ ) and the absence of CRAB features, clinically.

Recently, 3 clinical subtypes of MGUS have been defined on the basis of the type of immunoglobulin involved—non-

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IgM MGUS, IgM MGUS, and light-chain MGUS (8) and are characterized by a unique natural history in each subtype.

### Epidemiology

In his initial description of monoclonal gammopathy, Jan Waldenström speculated that "essential benign hypergammaglobulinemia" was more common than multiple myeloma (2). We now know that indeed MGUS is the most prevalent plasma cell disorder (9). In a large population-based study in Olmsted County, Minnesota, Kyle and colleagues analyzed serum samples of more than 75% of residents, 50 years or older, within the county (9). They identified MGUS in 3.2% of 21,463 patients tested. While the overall prevalence was noted to be 3.2%, there was a significant age-dependent increase in both sexes with the prevalence among persons aged 80 years or older 4 times as high as among those aged 50 to 59 years. In a subsequent study on a majority of the same patients from Olmsted County, Dispenzieri and colleagues used the free light-chain assay (FREELITE) and showed that 0.8% of people aged more than 50 years had light-chain MGUS. The total MGUS prevalence including the light-chain MGUS cases was noted at 4.2% (10). Other studies from across the globe have shown significant variation in the prevalence of MGUS (Table 1). The prevalence seems to be low in Mexico and among the Asian countries, based on studies from Japan, Taiwan, and Thailand (11–14), while much higher in Africans and African-Americans (15, 16).

In a study of 4 million veterans in Veterans Affairs hospitals across the nation, Landgren and colleagues showed that the age-adjusted prevalence rate of MGUS was 3-fold higher for African-American patients than for white patients (16). This study also showed that the rate of progression to multiple myeloma was similar among whites and African-Americans.

The possible role of genetic factors in MGUS is suggested by the racial and ethnic differences mentioned above and also the increased prevalence of MGUS in blood relatives of persons with lymphoproliferative and plasma cell disorders. First-degree relatives of multiple myeloma and MGUS

patients were found to have a 2.6-fold risk of MGUS as compared with the general population (17).

Environmental factors have been evaluated, and a study showed that exposure to pesticides increases the risk of MGUS (18). In a French study, the prevalence of monoclonal gammopathy was higher in the rural areas as compared with urban areas (19). A link between obesity and MGUS has also been suggested (20).

### MGUS consistently precedes multiple myeloma

Since the early description of MGUS, it was known that some cases of MGUS progressed to symptomatic myeloma, but it was not clear whether all cases of myeloma are preceded by MGUS. In a study of more than 77,000 individuals, 55 to 74 years of age, from a cancer screening trial, Landgren and colleagues found 71 patients who developed multiple myeloma (5). The study showed that patients who eventually developed multiple myeloma consistently had MGUS in the years preceding development of multiple myeloma. A second study by Weiss and colleagues found a monoclonal gammopathy in 27 of 30 patients (90%) in sera 2 or more years before the diagnosis of myeloma (6).

### Biology of Myelomagenesis—Precursor Disease to Symptomatic Myeloma

Studies looking at the epigenetic, genetic, transcriptional, and phenotypic changes within the transforming plasma cell as well as the microenvironment have improved our understanding of this process. The process of transformation, from a normal plasma cell to the premalignant MGUS/SMM state and finally to symptomatic multiple myeloma, involves several oncogenic events within the plasma cell as well as in the bone marrow microenvironment (Figure 1).

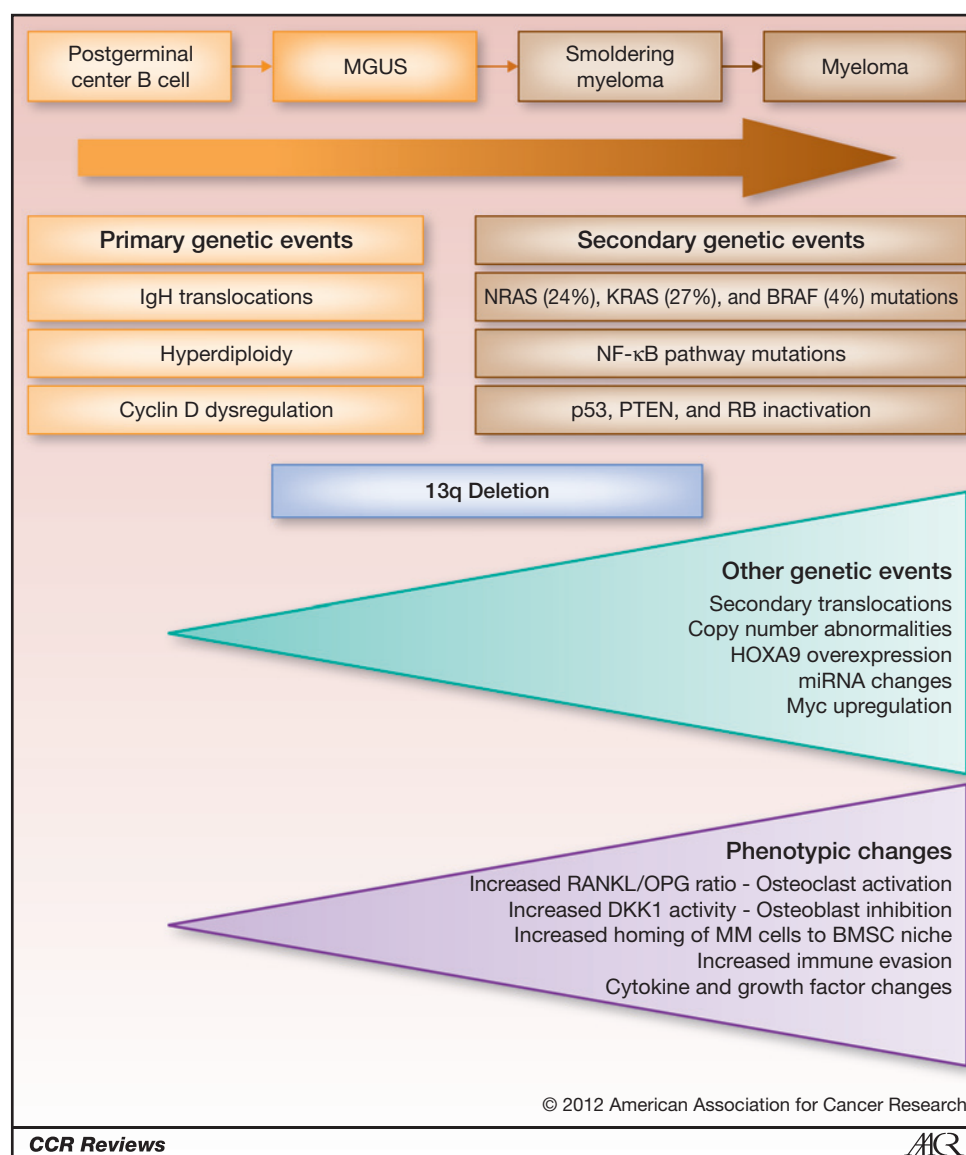
A recent study using single-nucleotide polymorphism-based arrays compared MGUS, SMM, and multiple myeloma samples (21). They found copy number abnormalities in all stages. The incidence of genomic imbalance increased from a median of 5 per case for MGUS to 7.5 per case for SMM and 12 per case for multiple myeloma. The study also noted certain genomic changes that were apparently

**Table 1.** Worldwide incidence of MGUS

Study population	Age	No. of participants	Prevalence of MGUS (%) with 95% CI
Olmsted County, MN-2006 (9)	>50	21,463	3.2 (3.0–3.5)
Olmsted County, MN-2010 (10)	>50	18,357	4.2 (3.9–4.5)
Nagasaki City, Japan (11)	>42	52,802	2.1 (1.9–2.2)
Thailand (13)	>50	3,260	2.3 (1.8–28)
Ghana (15)	50–74	917	5.84 (4.27–7.4)
Udine, Italy (64)	18–67	8,197	1.3
Finistere, France <sup>a</sup> (19)	>30	30, 279	1.1
General Hospital, Italy <sup>a</sup> (65)	—	102,000	0.7
Sweden <sup>a</sup> (66)	>25	6,995	0.9

<sup>a</sup>These older studies did not use the modern definition of MGUS.

**Figure 1.** Biology of myelomagenesis. Progression from a normal postgerminal center B cell to symptomatic myeloma involves a series of genetic and phenotypic changes. Early genetic events can be categorized into 2 major types, hyperdiploid type and nonhyperdiploid type. These are unified by cyclin D dysregulation (30). The role of 13q seems to be less certain and it may be an early or late event. Secondary genetic changes include Ras mutations, NF- $\kappa$ B pathway-activating mutations, and inactivating mutations of p53, PTEN, or RB pathways (1). Several other genetic changes also occur along the way, including secondary translocations, increase in copy number abnormalities, HOXA9 overexpression, and Myc upregulation (21, 36). The end result of these changes includes a clonal expansion of abnormal plasma cells that occupy bone marrow stem cell niches (45). Lytic bone lesions are seen due to increased osteoclast activation resulting from RANK-L signaling and osteoblast inhibition from DKK1 activity (41, 44). Immune evasion, paracrine, and autocrine signaling mediated by cytokine and growth factors are important final steps (46, 51).



exclusive to multiple myeloma, including 11q and 21q gains and 16q and 22q deletions. Interestingly, the study found these abnormalities in a small subclone in patients with MGUS indicating that most, if not all, of the chromosomal changes may be already present at the MGUS state.

Several studies have found varying rates of the different translocations between MGUS, SMM, and multiple myeloma (Table 2; refs. 22–27). The rate of t(11;14) seems to be uniform from MGUS to multiple myeloma, but there is some discrepancy in the rate of the other IgH translocations—t(4;14) and t(14;16), as well as del13q. Some studies have suggested that the incidence of these changes increases from MGUS to multiple myeloma, whereas other studies have indicated that the rate is the same among patients with MGUS and multiple myeloma. Some studies have suggested that 13q deletion may be an early event, whereas others point to del13q as the next step in the

pathogenesis of myeloma, especially following IgH translocations (25, 27). The presence of these translocations in MGUS and SMM does not seem to affect the rate of progression in either condition, whereas in multiple myeloma some of these translocations are associated with adverse outcomes (24, 28, 29). A recent study has shown that there is a clonal expansion of these genetically abnormal plasma cells from MGUS to SMM and multiple myeloma (26). IgH translocations and 13q deletion were seen in a higher proportion of plasma cells in SMM compared with MGUS and in multiple myeloma compared with SMM.

#### Cyclin D overexpression as a unifying early event

Using gene expression analyses, overexpression of the cyclin D genes seems to be one possible unifying event that is seen in almost all multiple myeloma cases with or without an immunoglobulin translocation as compared

**Table 2.** Common cytogenetic abnormalities and their incidence in MGUS, SMM, and multiple myeloma (22–27)

Cytogenetic abnormality	Involved oncogene	MGUS%	SMM%	Multiple myeloma%
IgH translocations	See below	40%–50%	40%–50%	50%–70%
t(11;14)(q13;q32)	<i>CCND1</i> (cyclin D1)	10%–25%	10%–25%	15%
t(4;14)(p16;q32)	<i>FGFR3</i> and <i>MMSET</i>	2%–9%	3%–13%	10%–15%
t(14;16)(q32;q23)	<i>C-MAF</i>	2%–5%	2%–5%	2%–5%
Other IgH translocations				
t(6;14)(p21;q32), t(14;20)(q32;q11) etc.	<i>CCND3</i> (cyclin D3), <i>MAFB</i> , etc.	6%–10%	1%–10%	10%
13q deletion	Unknown	25%–50%	35%–50%	40%–50%
Hyperdiploidy	Unknown	40%–50%	40%–50%	40%–50%

NOTE: Studies investigating the cytogenetic abnormalities in MGUS and SMM are limited by the small number of subjects in each group as well as by technical limitations in the ability to select abnormal plasma cells using CD138+ sorting methods. The numbers of subjects in each study are as follows: 123 high-risk SMM (22); 62 MGUS and 10 SMM (24); 189 MGUS, 127 SMM, and 400 multiple myeloma (25); 90 MGUS, 102 high-risk SMM, and 373 multiple myeloma (26); and 147 MGUS, 39 SMM, and 669 multiple myeloma (27).

with normal plasma cells (30). IgH translocations directly dysregulate *cyclin D1* or *D3* [t(11;14) and t(6;14), respectively] and the *C-MAF* or *MAFB* transcription factors dysregulate cyclin D2 [t(14;16) and t(14;20); ref. 31]. In this study, 12 MGUS samples had a similar pattern of cyclin D dysregulation despite a lower proliferative index, suggesting that cyclin D perturbation may indeed be an early and unifying event in plasma cell dyscrasias.

MicroRNAs (miRNA) are single-stranded RNA molecules that regulate gene expression posttranscriptionally and are being implicated in a large number of cancers (32). A study comparing miRNA profiles of normal plasma cells (PC), MGUS, SMM, and multiple myeloma found overexpression of mir-21, mir-106~25, and mir181a, and mir-181b in MGUS and multiple myeloma compared to normal PCs (33). The study also found mir-32 and mir17~92 clusters to be upregulated only in multiple myeloma and not in any other forms. mir-17~92 and mir-106~25 are known to have a role in B-cell development as well as B-cell lymphomas targeting PTEN, E2F1, Bcl-2, and BIM (32, 33). The mir-17 cluster has been shown to upregulated by the transcription factor c-Myc, which is considered a late event in myeloma progression (34, 35).

Cytogenetic and gene expression studies in myeloma precursor disease are limited by technical limitations in the ability to sort out the abnormal plasma cells for evaluation. The ratio of abnormal cells to normal plasma cells will be lower in a MGUS sample than in a multiple myeloma sample if CD 138+ sorting is used.

With the advances in deep sequencing techniques, we are now able to study the whole genome of myeloma cells and compare that with the normal human genome. Several studies using these techniques are beginning to shift our understanding of the pathogenesis of myeloma. These studies have revealed that the previously held dogma that cancer progres-

sion occurred through a linear cumulative acquisition of mutational changes may be too simplistic. A new model of clonal heterogeneity is beginning to emerge (36). In this model, various subclones exist in a dynamic equilibrium and, over time, the subclonal populations ebb and flow under environmental evolutionary pressures with alternating dominance of various subclones (37–40). Most of these studies were done on patients with symptomatic multiple myeloma and as similar studies involving MGUS and SMM emerge, our understanding of the pathogenesis of myeloma from these precursor states will continue to evolve.

#### Role of microenvironment in progression of MGUS to multiple myeloma

The transition from MGUS to multiple myeloma involves changes to the complex interaction with the microenvironment along with the genetic changes described above. In multiple myeloma, there is an upregulation of osteoblast RANK-L expression and a decrease in osteoprotegerin (OPG), a decoy for RANK-L that inhibits osteoclast differentiation. This increases the ratio of RANK-L/OPG, which leads to osteoclast activation and development of the characteristic lytic lesions (41). Interestingly, although lytic bone lesions are not seen in MGUS, the RANK-L/OPG ratio is higher in MGUS subjects and they are at a higher risk of fractures than healthy controls (42, 43). The role of other pathways including Wnt/ $\beta$ -catenin involving activation of FRZB and Dickkopf 1 (DKK1), a Wnt inhibitor, is also being studied (44). The homing of multiple myeloma cells to bone marrow stromal cell niches is essential for their survival. A recent study suggests that these bone marrow stromal cell niches are limited, and a progressive competition and replacement of normal bone marrow cells by clonal plasma cells is associated with more advanced disease (45). The evasion of the immune system is an important step in the progression from

**Table 3.** Risk stratification model for MGUS using Mayo Clinic model (54)

Model	No. of risk factors	20-year progression, %	Relative risk
Mayo Clinic model	0	5	1
Risk factors:	1	21	5.4
M-protein $\geq 1.5$ g/dL;	2	37	10.1
non-IgG MGUS;	3	58	20.8
FLC ratio $<0.26$ or $>1.65$	Total	20	NA

Abbreviation: NA, not applicable.

MGUS to multiple myeloma. Oligoclonal T-cell expansion can be found in both MGUS and multiple myeloma with lower disease burden states showing a more robust T-cell expansion (46, 47). A defect in the T-cell function is seen during progression from MGUS to multiple myeloma (48, 49). Several cytokines and growth factors including interleukin (IL)-6, SDF-1, macrophage inflammatory protein (MIP)-1 $\alpha$ , insulin-like growth factor (IGF)-I, VEGF, and hepatocyte growth factor (HGF) have been implicated in myeloma pathogenesis and transition from MGUS (50, 51).

### Risk of Progression from Precursor Disease to Symptomatic Myeloma

It is clear from the description above that there are no major genetic differences between the plasma cells in MGUS and multiple myeloma. Since the prevalence of MGUS/SMM is much higher than multiple myeloma, and several people with precursor disease will never progress to symptomatic myeloma in their lifetime, it is important to identify patients that are at greatest risk for progression to myeloma. Several studies have tried to predict subgroups of precursor disease at higher risk of progression using different tools.

### Size of M protein

In 1,384 patients with MGUS, the risk of progression to multiple myeloma or a related disorder after 20 years was 14% with an initial protein level of 0.5 g/dL or less, 25% for 1.5 g/dL, 41% for 2 g/dL, 49% for 2.5 g/dL, and 64% for 3 g/dL (52). A progressive increase in the M-protein in the first year of follow-up (evolving MGUS) has also shown to be prognostic (53).

### Type of immunoglobulin

Patients with MGUS with IgM or IgA monoclonal protein have an increased risk of progression to disease as compared with patients with IgG protein (52).

### Serum-free light-chain ratio and the Mayo Clinic model

In a study of 1,148 patients with MGUS, Rajkumar and colleagues showed that an abnormal free light-chain (FLC) assay was an independent risk factor for progression from MGUS to multiple myeloma (54). For patients with MGUS, a non-IgG isotype, M-protein concentration more than 1.5 g/dL, and an abnormal FLC ratio are considered adverse prognostic factors. At 20 years, the risk of progression in patients with 0, 1, 2, and 3 risk factors is 5%, 21%, 37%, and 58%, respectively (Table 3). For patients with SMM, an M-protein  $\geq 3$  g/dL, an FLC ratio outside the range of 0.125 to 8, and  $\geq 10\%$  plasma cells in the bone marrow are considered as adverse factors in this model (55, 56). The 5-year rate of progression in patients with 1, 2, and 3 risk factors was 25%, 51%, and 76%, respectively (Table 5). Recently, Rajkumar and colleagues have proposed that SMM with more than 60% plasma cells progresses to multiple myeloma within 2 years in 95% cases and should be treated at diagnosis even in the absence of symptoms (57).

### Flow cytometry and the Spanish model

Perez-Persona and colleagues used immunophenotyping with multiparameter flow cytometry to identify aberrant plasma cell (aPC) in the bone marrow of 407 MGUS and 93 SMM patients (58). A ratio of aPC/BMPC of more than 95% was shown to be an independent

**Table 4.** Risk stratification model for MGUS using Spanish (PETHEMA) model (58)

Model	No. of risk factors	5-year progression, %	Relative risk
Spanish (PETHEMA) model	0	2	1
Risk factors: $\geq 95\%$	1	10	5
aPC; DNA aneuploidy	2	46	23
	Total	8.5	NA

Abbreviation: NA, not applicable.

**Table 5.** Risk stratification model for SMM using Mayo Clinic model (56)

Model	No. of risk factors	5-year progression, %	Relative risk
Mayo Clinic model	1	25	1
Risk factors: M-protein	2	51	2.0
≥3 g/dL; ≥10% bone marrow plasma cells;	3	76	3.0
FLC ratio <0.125 or >8	Total	51	NA

Abbreviation: NA, not applicable.

risk factor for progression in both MGUS and SMM. In a multivariate analysis, DNA aneuploidy (hypo- or hyperdiploidy) was also noted to be a prognostic factor in MGUS and was combined with aPC/BMPC of more than 95% to form a prognostic index. The presence of 0, 1, or 2 of these factors was associated with a progression risk of 2%, 10%, and 46%, respectively, in MGUS (Table 4). The analysis identified immunoparesis as an independent prognostic factor in SMM. Using aPC/BMPC of more than 95% and immunoparesis as the 2 factors the study found 5-year risk of 4%, 46%, and 72% in patients with 0, 1, or 2 factors, respectively (Table 6).

#### Other prognostic factors

Other studies have identified various factors that are prognostic for progression to symptomatic disease. Cesana and colleagues proposed a prognostic index for MGUS based on the presence of BMPC infiltrate more than 5%, presence of Bence-Jones proteinuria, polyclonal serum Ig reduction, and erythrocyte sedimentation rate (ESR) and showed that these features were associated with higher rate of transformation to myeloma (59). Whole body MRI has been shown to be more sensitive to a skeletal survey in detecting focal lesions and the presence of such focal lesions were an adverse prognostic factor for progression to multiple myeloma (60). An earlier study showed that an abnormal MRI was associated with a shorter time to progression compared with a normal MRI (1.5 vs. 5 years) in SMM (61). Immunoparesis (suppression of uninvolved immunoglobulins) has been shown to be prognostic in SMM but its value in MGUS is less clear (52, 55, 58, 59). A recent study also looked at each isotype-specific heavy and light chain in MGUS and suppression of the uninvolved HLC (e.g., IgG-λ

suppression in an IgG-κ MGUS patient) was shown to be prognostic for progression (62). In a study of 325 patients with MGUS, the presence of circulating plasma cells was shown to be prognostic for progression (HR, 2.1; *P*, 0.03) compared with patients who did not have any circulating plasma cells (63). Age, sex, race, and chromosomal translocations are not prognostic factors for progression from precursor disease to symptomatic myeloma.

#### Intervention Trials in Myeloma Precursor Disease

Despite all the recent advances in the treatment of multiple myeloma, it remains an incurable disease. The myeloma precursor conditions provide an opportunity to be able to intervene at an earlier stage to either delay or prevent progression altogether. Several trials have looked at early intervention in an attempt to change the natural history of multiple myeloma. These trials have produced mixed results and other than the Programa para el Estudio de la Terapeutica en Hemopatias Malignas (PETHEMA) trial have not shown an improvement in overall survival (Table 7). A longer follow-up will be necessary to ascertain whether the benefits from early treatment are sustained without long-term adverse effects. Several other studies testing novel drugs are ongoing for patients with SMM (Table 8). The current standard of care based on the IMWG recommendations (Supplementary Fig. S1) is to monitor patients with MGUS or SMM until they progress to multiple myeloma before starting treatment (7).

#### Conclusions

The recent advances in our knowledge about MGUS and SMM have helped us better understand the

**Table 6.** Risk stratification model for MGUS using Spanish (PETHEMA) model (58)

Model	No. of risk factors	5-year progression, %	Relative risk
Spanish (PETHEMA) model	0	4	1
Risk factors: ≥95% aPC; immunoparesis	1	46	11.5
	2	72	18
	Total	46	NA

Abbreviation: NA, not applicable.

**Table 7.** Completed intervention studies for myeloma precursor disease

Drug/s	Reference	Comments
Melphalan and prednisone	(67)	Fifty patients with SMM were randomized to receive melphalan and prednisone immediately upon diagnosis or at the time of disease progression. The study found no difference in the response rate or overall survival in the 2 groups.
Thalidomide	(68)	A small single-arm study of 16 subjects showed that thalidomide produced a PR or better in 6 of 16 subjects.
Thalidomide and pamidronate	(69)	In this phase I study, 76 patients with SMM were administered thalidomide daily and pamidronate monthly. The study had a 50% discontinuation rate within the first 2 years due to adverse effects. Unexpectedly, the study found that attaining a PR was associated with a shorter time to salvage therapy for disease progression.
Zoledronic acid	(70)	A prospective, open label, randomized trial comparing zoledronic acid versus observation in 163 patients with SMM. Monthly zoledronic acid for 1 year in patients with SMM reduced the development of skeletal-related events (SRE) at the time of progression (55.5% vs. 78.3%; $P = 0.041$ ) but did not affect the time to progression to symptomatic disease (67 vs. 59 months; $P = 0.83$ ).
Curcumin	(71)	In a double-blind placebo-controlled study, curcumin was shown to have a modest effect in decreasing the FLC ratio among a quarter of MGUS and SMM subjects, but the effect on progression to symptomatic disease was not reported.
Lenalidomide and dexamethasone	(72)	A phase III PETHEMA trial of high-risk SMM randomized patients to induction with lenalidomide and dexamethasone followed by lenalidomide maintenance versus no treatment. After a median follow-up of 32 months, 9 (15%) patients in the treatment arm and 37 (59%) patients in the observation arm had progressed (HR, 6.0; 95% CI, 2.9–12.6; $P < 0.0001$ ). The estimated 3-year overall survival was 93% in the treatment arm and 76% in the observation arm ( $P = 0.04$ ).

pathogenesis of myeloma. It seems that myeloma evolves from a precursor state in almost all cases. We do not completely understand the multistep process from the precursor state to myeloma, but studies including whole

genome sequencing will continue to help in improving our understanding of this process. The process of transformation may not be linear acquisition of changes but rather a branched heterogeneous process. Clinical

**Table 8.** Currently ongoing intervention studies for precursor disease (73)

Drug	Target/MOA	Study phase	Comments
IPH2101	Anti-KIR monoclonal Ab	2	Single-arm study assessing response of drug in SMM and measuring toxicity.
BHQ880	Anti-Dickkopf (DKK1) Ab	2	Single-arm study assessing response of drug in high-risk SMM.
Elotuzumab	Anti-CS1 monoclonal Ab	2	Study looking at association between NK cell status and efficacy of elotuzumab monotherapy in high-risk SMM.
Slituximab	Anti-IL6 monoclonal Ab	2	Randomized, blinded, placebo-controlled trial looking at one-year progression-free survival (PFS) in high-risk SMM.
MLN 9708 and dexamethasone	Proteasome inhibitor and steroid	2	A single-arm study in high-risk SMM with response rate as primary outcome and PFS and duration of response as secondary outcomes.
Lenalidomide	IMiD	3	A phase III randomized Eastern Cooperative Oncology Group (ECOG) trial of lenalidomide vs observation in high-risk SMM.
Bortezomib	Proteasome inhibitor	2	Study looking at the effects of low-dose (0.7 mg/m <sup>2</sup> i.v.) bortezomib on bone formation and natural history in SMM.
Carfilzomib, lenalidomide, and dexamethasone	Proteasome inhibitor, IMiD, and steroid	2	Single-arm study in high-risk SMM assessing the safety and response rate of the triple-drug combination in SMM.

features that are prognostic of rapid transformation to symptomatic disease have been identified, but no specific molecular markers have been identified. Intervening at the precursor state provides a unique opportunity to alter the natural history of the disease. A limitation is that a vast majority of patients with precursor disease, especially low-risk MGUS, will never progress to myeloma in their lifetime and treating these patients is not only unnecessary but may be potentially harmful. The challenge is to identify a subset of patients with the precursor state that would definitely progress to myeloma and in whom interventions will have a meaningful impact. As our understanding of the molecular and genetic processes improves, these studies will guide the selection of high-risk patients more appropriately and ultimately direct a tailored management strategy.

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## Disclosure of Potential Conflicts of Interest

I.M. Ghobrial is a consultant/advisory board member of Novartis, Onyx, Millennium, and Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other author.

## Authors' Contributions

**Conception and design:** A. Agarwal, I.M. Ghobrial

**Development of methodology:** A. Agarwal, I.M. Ghobrial

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** A. Agarwal

**Writing, review, and/or revision of the manuscript:** A. Agarwal, I.M. Ghobrial

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