The road to cure in multiple myeloma starts with smoldering disease

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Abstract

Introduction—Smoldering multiple myeloma (SMM) is a heterogeneous clinical entity that defines patients in the spectrum of disease progression from monoclonal gammopathy of undetermined significance to multiple myeloma (MM). Current standard of care is observation until end organ damage occurs. In spite of this, the scientific community has begun to question whether the strategy of watchful waiting should be replaced with earlier therapeutic intervention with the ultimate goal of preventing clonal heterogeneity and end organ damage.

Areas covered—In this review, we challenge the concept of observation as the best option of therapy in SMM. We present current data on diagnosis, prognostic factors of disease progression and studies that have been conducted to date to determine whether earlier therapeutic interventions will lead to an improvement in overall survival of patients with MM.

Expert opinion—If the recommendations of treatment of SMM were to change, the scientific body of evidence would have to overcome four major hurdles: to demonstrate that early intervention leads to prolonged survival and delay in development of end organ damage, that it does not have long-term toxicities, that it is implemented in patients with a high-likelihood of developing myeloma and that it does not lead to the outgrowth of more resistant clones. Only well-designed clinical trials will determine whether cure can be achieved with earlier interventions.

Keywords

early treatment; multiple myeloma; precursor disease; prevention of progression; prognosis; risk factors of progression; smoldering myeloma

1. Introduction

Multiple myeloma (MM) is the second most common hematological malignancy and presents with symptoms and signs requiring therapy as defined by the 'calcium elevation, renal failure, anemia, and bone lesions (CRAB)' criteria; namely hypercalcemia (serum calcium   11.5 mg/dl), renal failure (defined by creatinine   2 mg/dl with no other etiology),

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anemia (hemoglobin   10 g/dl), or skeletal lesions (lytic lesions by skeletal survey, osteoporosis with pathologic fractures, or cord compression) [1]. However, interestingly, many patients are diagnosed with asymptomatic precursor conditions including monoclonal gammopathy of undermined significance (MGUS) and smoldering MM (SMM) [2]. In fact, recent studies have indicated that almost all cases of MM are preceded by a precursor state of MGUS or SMM [3]. To date, screening studies are not performed to detect MGUS or SMM in the general population. Part of the reason why screening for these conditions can be challenging is that there is no curative therapy for these patients and older therapeutic interventions had high toxicity with stem cell damage. In addition, many patients with MGUS or asymptomatic disease may not develop symptoms of myeloma during their lifetime. As such, most patients with these precursor conditions are diagnosed incidentally. The current standard of care of MGUS and SMM is observation or 'watch and wait' until symptoms develop or end organ damage occurs at which point therapy is initiated [4].

The concept of initiating therapy after end organ damage is analogous to initiating treatment after the development of metastatic cancer in solid tumors. Indeed, screening, early detection and intervention have played a large part in the major curative advances that have been achieved in solid tumors whereas metastatic cancer remains incurable in these same malignancies. It is, therefore, not surprising that MM remains incurable, in spite of all the advances in therapeutic interventions. Could it be because we are waiting too long – until metastatic myeloma occurs – to treat our patients? In such a condition, watchful waiting may actually be more harmful to the patient than early intervention.

In this review, we challenge the concept of observation as the best option of therapy for patients with precursor conditions. We present the current data on diagnosis, prognostic factors for disease progression in SMM and studies that have been conducted to date to determine whether earlier therapeutic interventions will lead to an improvement in overall survival (OS) of patients with myeloma.

2. Defining clonal evolution from MGUS to overt MM

The first initiating events that lead to transformation of a normal plasma cell to a malignant plasma cell are driven by the acquisition of chromosomal translocations involving the *Ig* loci or hyperdiploidy [2,5]. These are considered founder genetic changes and are present in all clones. Secondary alterations then occur including copy number variations, which allow certain subclones to be 'fit' for further progression and proliferation.

Based on this, one would believe that plasma cells in the MGUS stages or SMM stages should not be as genetically aberrant as those present in overt MM. However, as recent studies show, the transition from MGUS to MM does not appear to be associated with a particular chromosomal imbalance, but rather with an expansion of altered clones that are already present in MGUS [6]. Some genetic abnormalities seem to correlate with disease progression from MGUS to SMM including point mutations such as N-RAS, K-RAS, MYC up-regulation [7], and gain or loss of chromosome 1q or 1p [8].

Therefore, the current understanding is that transformation of MGUS/SMM to MM is likely due to a clonal evolution and clonal competition/selection that is Darwinian-like [9,10]

leading to expansion of 'winner clones' that have a more proliferative advantage leading to disease progression [11,12]. Most studies defining this model in MM have been performed using samples of patients with MM or relapsed MM [13-15]. There is minimal data available on samples of patients with MGUS or SMM. The only study that examined patients with precursor conditions was that of four patients with MGUS and another three patients with paired samples of SMM and MM demonstrating the presence of subclones at low frequencies indicating that disease progression is likely due to clonal competition [12]. However, the mechanisms by which this clonal expansion occurs and the cell autonomous or non-autonomous drivers of this selection remain poorly understood and are beyond the scope of this review. For example, one of the important non-cell autonomous regulators of tumor progression is evasion and suppression of the host immune system. During the early stages of tumor growth in MGUS, there is an active immune response that controls growth but does not fully eliminate the tumor clone. As the tumor growth progresses to the stages of SMM and MM, there are associated cellular and humoral immune deficiencies, indicating that evolution of disease in MM is associated with an immunosuppressive milieu that fosters immune escape [16].

3. Diagnosis of smoldering myeloma

SMM is a heterogeneous disease entity that includes patients who have a disease burden that is higher than that in patients with MGUS but who are not yet symptomatic [17]. The term SMM was first described by Greipp and Kyle in 1980 [18] and was followed by many other descriptions terming it indolent MM [19], or Durie Salmon Stage I [20]. It was not until 2003 that the International Myeloma Working Group (IMWG) described the exact definition of this disease. SMM was defined as serum M-protein 3 g/1 and/or 10% monoclonal plasma cells in the bone marrow (BM) (Table 1) [1,21]. Whereas the incidence and prevalence of SMM in the population is not well defined, it has been estimated to represent ~ 8 to 20% of patients within the MM spectrum [17].

Most recently, the IMWG further re-defined the group of patients who meet criteria for treatment and included asymptomatic SMM patients who are likely going to have end-organ damage in the near future, previously defined as 'ultra-high risk smoldering myeloma'. These include patients with BM plasmacytosis 60% [22]; an abnormal free light-chain (FLC)-ratio 100 (involved kappa) or < 0.01 (involved lambda) [23]: and/or 2 or more focal BM lesions detected by functional imaging including positron emission tomography (PET) (PET-CT) and/or MRI [24,25]. These patients should therefore not be considered SMM anymore but rather re-defined as patients with myeloma-defining events that require therapy.

4. Risk of progression of SMM to active MM

The overall risk of progression of SMM is 10% per year for the first 5 years and 3% per year for the next 5 years [26]. The most common factors used to stratify patients with SMM are the Mayo Clinic criteria [26,27] and the Spanish PETHEMA criteria [28]. The Mayo Clinic criteria are based on the tumor burden defined by the serum protein level (by serum protein electrophoresis or light chain ratio) or by the percent BM plasma cell involvement (Table 2)

[26,27], leading to risks of progression at 5 years of 25% for low risk, 51% for intermediate risk and 76% for high risk individuals who have 1, 2 or 3 risk factors respectively [26,27]. The risk stratification of the PETHEMA group is based on identifying the number of clonal plasma cells in the BM by flow cytometry (95% ratio of abnormal neoplastic plasma cells to normal plasma cells) and reduction of uninvolved immunoglobulins, with 5 year-risk of progression being 4, 46, and 72% for patients with 0, 1 or 2 risk factors, respectively [28]. Unfortunately, there is no concordance between these two criteria, indicating that a patient can be considered high risk by one model but low risk by the other [29]. In addition, several smaller studies have described other criteria that also indicate a high risk of progression of ∼ 50% at 2 years. These include IgA myeloma, circulating plasma cells, high-risk cytogenetics (deletion 17p, t(4;14), amplification of 1q21) and abnormal MRI findings [2,5,17,30,31]. Notably, both the Mayo and PETHEMA criteria rely heavily on tumor load as a predictor of progression, which has interestingly been found to be discordant with several more recent studies focusing on tumor biology as markers of disease. Recent publications have considered re-defining high-risk smoldering myeloma to include all these new criteria as described in Table 2 [32].

Overall, these risk stratifications demonstrate that there is a need for further molecular studies to better define progressors and non-progressors and differentiate those who will have an indolent MGUS-like course compared to those with rapid progression to overt MM.

5. Clinical diagnosis of patients with SMM

The first step in the workup of a patient with a monoclonal protein is to define whether the patient has MGUS, SMM or overt symptomatic MM. The basic laboratory criteria as well as level of M spike in the serum protein electrophoresis, the ratio of the serum FLC, skeletal survey and the BM plasma cell percentage help define patients in these categories (Tables 1 and 2). We would strongly encourage a diagnostic BM biopsy to be performed in all patients suspected to have a monoclonal gammopathy to better assess the disease burden and stage of disease.

Skeletal surveys are still the gold standard for the initial work-up of patients with MM [33]; however, observing lesions in a skeletal survey requires loss of 30 – 50% of the bone mass. Therefore, it is critical to use a new imaging modality such as low-dose CT scan or MRI that also provides information on the actual tumor burden [34]. Patients with SMM with two or more focal BM lesions were found to have a significantly shorter time to progression to MM making this one of the new criteria that is now being used to initiate therapy for MM. Future studies such as PET/CT or PET/MRI, dynamic contrast-enhanced-(DCE)-MRI and diffusion weighted imaging-MRI will be used to allow functional imaging of BM activity [25]. Our recommendations therefore, based on the new IMWG criteria, are to stage all patients with suspected SMM with a PET-CT, low-dose whole-body CT, or MRI of the whole-body or spine, with the exact imaging modality determined by availability and resources.

In addition, it is critical to identify asymptomatic patients who meet the 'myeloma defining event' criteria, which indicate the need for active therapy. These again include 60% or more

plasma cell involvement, involved/uninvolved sFLC ratio > 100 and the presence of two or more focal lesions.

The next step is to define patients with high-risk factors as they may require treatment. The list of new criteria defining high-risk SMM will help distinguish these patients from other non-progressing SMM and avoid confusions surrounding the use of Mayo and Spanish criteria. Therefore, it is critical to perform a BM biopsy with FISH and cytogenetics along with an MRI of the whole spine or a PET-CT scan to complete the workup of these patients.

6. Follow-up of patients with SMM

The overall risk of progression from SMM to MM is 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year for the last 10 years [26]. Based on the 2010 IMWG guidelines, we would recommend follow-up of patients diagnosed with SMM to be every 2 – 3 months for the first year, followed by every 4 – 6 months for 1 year, with eventual 6 – 12 months evaluations if clinically stable thereafter [35]. We would encourage close follow-up for patients with high-risk SMM every 2 – 3 months until initiation of therapy for MM.

During follow-up, patients should be monitored for the development of signs of symptoms of MM as well as progression of serum protein markers including SPEP and serum FLC. The role of bone biomarkers in follow-up for occult bone disease is not well established. Repeat imaging by PET/CT scan or MRI has not been established but could be considered once a year to follow-up patients for the development of focal lesions of MM, especially in patients with high-risk SMM.

Interestingly, a recent study has shown that close monitoring and follow-up of MGUS and SMM before the diagnosis of MM can help improve the OS of these patients [36]. The study showed that patients with prior knowledge of the diagnosis of MGUS can have an improved OS compared to those with MM who did not have a pre-diagnosed MGUS condition. This may be due to the fact that patients with MGUS are evaluated more often for signs of progression to MM and may be diagnosed and started on therapy for myeloma at an earlier stage [36]. Therefore, these results reconfirm the need for lifelong follow-up for individuals diagnosed with MGUS and stress the importance of monitoring all patients independent of risk score.

This study raised another critical question of whether screening for the presence of MGUS in a normal older population should be performed. To date, the cost, inconvenience and anxiety produced by the awareness of potential progression of a recognized MGUS, as well as the low absolute risk of progression (0.5 – 1%), probably override the possible potential benefit of screening for MGUS. However, future studies are needed to address this question.

7. Should we treat patients with SMM

To date, current recommendations of therapy are observation as a so-called 'watch and wait' strategy [17,21] until end organ damage or 'CRAB' criteria develop. Patients should be monitored for signs or symptoms of progression every 2 – 3 months for the first year,

followed by every 4 – 6 months for 1 year, with eventual 6 – 12 months evaluations if clinically stable thereafter [35]. The most recent change in these recommendations of observation is the inclusion of new 'myeloma defining events' that allow treatment of patients who were previously classified as ultra-high risk SMM (Table 1).

The reasoning for this recommendation is that therapeutic agents are often associated with toxicity and many of the older regimens included alkylating agents, which can lead to secondary malignancies. For many years, there were attempts to investigate whether earlier therapeutic interventions will lead to an improvement in survival or delay in disease progression from SMM to MM [17]. These efforts have not proven to be successful except for the most recent study of lenalidomide and dexamethasone in high-risk SMM that showed progression-free and OS differences [37], thus causing a paradigm shift in the concept of early treatment in MM.

Therefore, if treatment recommendations for SMM were to change, the scientific body of evidence has to overcome four major hurdles; to demonstrate that early intervention leads to prolonged survival and delay in development of end organ damage, that it does not have long-term toxicities, that it is selectively implemented in patients with a high-likelihood of developing myeloma in the near future (high-risk smoldering myeloma) and finally that it does not lead to the outgrowth of more resistant clones that lead to worse response at the time of development of MM. Though it remains to be formally proven, one may speculate that because it is genetically less diverse, SMM may be more susceptible to cure through earlier therapy.

The concept of initiating early therapy was first examined in the 1990s using melphalan and prednisone [38-41]. These trials did not demonstrate a survival advantage, although they were not adequately powered to make definitive conclusions (Table 3). These were followed by studies using bisphosphonates to avoid the toxicity of melphalan. Two randomized controlled studies were conducted and showed no improvement in OS or time to progression but did demonstrate fewer skeletal related events [42]. With the introduction of novel agents in the treatment of MM, thalidomide was next examined and showed significant improvement in progression-free survival (PFS) in the thalidomide/zoledronic acid arm compared with the zoledronic acid alone arm (29 vs 14 months) but no difference in PFS as defined by CRAB events (49 vs 40 months; p 5. 18) or in OS (6-year OS. 70%) [43-46]. These studies were the basis for the strong recommendation of observation in patients with SMM.

It was not until the study by Mateos *et al.* [37] that used lenalidomide and dexamethasone in comparison to observation in 119 patients with high-risk SMM that the concept of observation in SMM was first challenged. This study demonstrated a superior 3-year survival without progression to symptomatic disease (77 vs 30%; p <0.001) and a superior 3-year OS (94 vs 80%; p = 0.03). However, this study was criticized because of how asymptomatic biochemical progression was handled in both arms, the short OS of the abstention group and the use of salvage therapy in the abstention group. Because of these concerns, the combination of lenalidomide and dexamethasone has not been implemented as a standard of care in the current management of SMM. Still, this trial opened the door for

challenging the 'watch and wait' concept in SMM. Currently, many clinical trials are ongoing to examine the role of therapy in this patient population (Table 4). Many agents are being tested including combinations of therapy to achieve deep responses, novel immunotherapies such as Elotuzumab alone or in combination with lenalidomide and CD38 targeting antibodies such as Daratumumab. One promising ongoing trial by Landgren *et al.* examined early treatment with Carfilzomib, lenalidomide, and dexamethasone showed high rates of complete response and minimal residual disease negativity by multi-color flow cytometry in patients with high-risk SMM. Additional studies demonstrating positive outcomes might further encourage the adoption of earlier therapy as standard of care in patients with high-risk SMM.

8. Expert opinion

As discussed, SMM is a heterogeneous disease entity that lies on a continuum from MGUS to MM with some patients rapidly progressing to symptomatic disease and others having an MGUS-like disease that shows no progression throughout their lifetime. The first challenge towards developing a successful therapeutic intervention for patients with SMM is to identify those who will really benefit from therapy. We would recommend a simplified updated classification of high-risk SMM that does not only include tumor burden markers such as M spike and percent plasma cells in the BM but also molecular markers including chromosomal abnormalities. Further studies of molecular markers including genetic and epigenetic factors that lead to progression may better define the subpopulation that will benefit most from therapy.

We would also recommend that clinical trials being designed for SMM should have no major long-term toxicities such as stem cell damage. Stem cell collection at time of remission should be strongly encouraged. Therapies should aim at reducing the tumor burden and prolonging time to development of MM. In addition, monitoring for the development of drug-resistant clones should be encouraged such as monitoring response and time of the second PFS during therapy for symptomatic MM after initial therapy for SMM.

The question remains whether these efforts will indeed lead to a cure in myeloma or potentially an early screening and intervention modality to completely eradicate the progression to symptomatic disease, making myeloma a preventable disease. Only well-designed clinical trials will determine whether this can be achieved or whether this would only result in lead-time bias and development of resistant clones that are more aggressive by the time myeloma is symptomatic.

Acknowledgments

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Article highlights

- Smoldering multiple myeloma is a heterogenous entity on the spectrum between MGUS and overt multiple myeloma.

- Current standard of therapy is observation or 'watch and wait' but research and clinical trials are challenging this long-held paradigm.

- Early treatment, if effectively implemented in high-risk SMM patients, might be the key towards preventing or even curing myeloma.

Table 1

Definition of MGUS, SMM and symptomatic multiple myeloma.

International Myeloma Working Group criteria, 2010 version [35]	
MGUS	Serum M protein < 3 g/dl Clonal bone marrow plasma cells < 10% Absence of myeloma defining events and amyloidosis
SMM	Serum M protein 3 g/dl and/or clonal bone marrow plasma cells 10 - 60% or urinary monoclonal protein > 500 mg per 24 or FLC ratio < 0.125 or > 8 or 95% abnormal plasma cells in the bone marrow or immunoparesis of one or more immunoglobulins Absence of myeloma defining events and amyloidosis
MM	Clonal bone marrow plasma cells 10% and/or biopsy proven plasmacytoma Presence of serum and/or urinary monoclonal protein at any level
CRAB criteria	Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder (CRAB criteria) Hypercalcemia: serum calcium > 0.25 mmol/l above upper limit of normal or > 2.75 mmol/l (> 1 mg/dl above upper limit of normal) Renal insufficiency: creatinine clearance < 40 ml per min or serum creatinine > 177 μmol/l (> 2 mg/dl) Anemia: normochromic, normocytic with a hemoglobin value of > 2 g/dl below the lower limit of normal or a hemoglobin value < 10 g/dl Bone lesions: lytic lesions, or osteoporosis with compression fractures. If osteoporosis is used as the sole criterion, then the bone marrow has to be > 30% involved
MDE criteria	Or any MDE as follows: Clonal bone marrow plasma cell percentage 60% [22] An abnormal FLC-ratio 100 (involved kappa) or < 0.01 (involved lambda) [23] Two or more focal lesions on MRI or positron emission tomography-CT studies measuring > 5 mm in diameter [24,25]

FLC: Free light-chain; MDE: Myeloma defining events; MGUS: Monoclonal gammopathy of undermined significance; SMM: Smoldering multiple myeloma

Table 2

Risk stratification of patients with smoldering myeloma based on mayo clinic and Spanish criteria.

Model	Risk factors	No. of risk factors	5-year progression (%)	Relative risk
Mayo clinic model	M-protein 3 g/dl 10% BM plasma cells FLC ratio < 0.125 or > 8	1	25	1
		2	51	2.0
		3	76	3.0
		Total	51	NA
Spanish (PETHEMA) model	95% aPC Immunoparesis	0	4	1
		1	46	11.5
		2	72	18
		Total	46	NA
Proposed new criteria for high risk SMM	10% BM plasma cells with one of the criteria in the right row	Serum M protein 30 g/l IgA SMM Immunoparesis with reduction of two uninvolved immunoglobulin isotypes Serum involved/uninvolved FLC ratio 8 (but <100) Progressive increase in the M protein level (Evolving type of SMM) Bone marrow clonal plasma cells 50 - 60% Abnormal plasma cell immunophenotype (95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotype t(4;14) or del 17p or 1q gain Increased circulating plasma cells MRI with diffuse abnormalities or 1 focal lesion Positron emission tomography-CT with focal lesion with increased uptake without underlying osteolytic bone destruction		

aPC: Aberrant plasma cells; BM: Bone marrow; FLC: Free light-chain; SMM: Smoldering multiple myeloma

Table 3

Select clinical trials in SMM.

Type of therapy	Clinical trial design and outcome	Number of patients	Ref.
Melphalan and prednisone	Retrospective Cohort Study of VAD versus MP. Because the treatment of multiple myeloma remains palliative, chemotherapy should be withheld until symptoms Initial versus delayed MP. Randomized-controlled trial. Similar response rate, response duration, and survival TTP of 12 months Initial versus delayed MP. TTP of about 12 months. No difference in OS (64 vs 71 months) Observational study of delayed therapy: 54 DSSI. 2 years. PFS 75%. Tumor-specific OS 80% at 60 months	23 SMM, 10 IMM 50 SMM IMM (25/25) 145 DSSI 54 DSSI	Alexanian 1988 [39] Hjorth 1993 [38] Riccardi *et al.* 1994 and 2000 [40,41] Peest *et al.* 1995 [47]
Pamidronate or zolendronate	Single-arm, Phase II Trial Pamidronate versus Observation. 5 years. PFS 53% both arms. SRE 74 versus 39%, p = 0.009. Median OS 46 and 48 months Open-label randomized controlled trial Zolendronate versus Observation × 1 year. TTP not significant. SRE 55 versus 78%, p = 0.04. Zoledronate for 1 year decreased risk of skeletal-related disease, but TTP was similar (p = 0.83). OS no difference	177 SMM 163 SMM	Musto 2003 [48,49] and D'arena 2011 [50] Musto 2008 [42]
Thalidomide	Single-arm, Phase II Trial Phase II of Thalidomide Pamidronate. 4 years. EFS 60%. 4 yes OS 91 %. Median TTP 7 years; PR identifies subset requiring earlier salvage therapy for symptomatic disease Single-arm pilot study of thalidomide. Median 35 months OS 86 months OS from treatment 49 months. MR or better in 11/16. Microvessel density did not predict response Phase II of Thalidomide. Patients were treated with thalidomide 100 - 200 mg. The response rate was 36% Phase III Randomized Trial to evaluate combination therapy with Pamidronate and thalidomide Thalidomide +ZA vs. ZA. 29 mo. vs. 14 mo. 6 yrs OS >70%	76 SMM 19 SMM and I0 IMM 28 high risk SMM 68 SMM	Barlogie 2008 [43] Rajkumar 2001 [45] Weber 2003 [44] Witzig 2013 [46]
IL-1 antagonist	Anakinra (IL-1 receptor antagonist). IL-1 antagonist ± dexamethasone. Median PFS was 37.5 months MR (n = 3), PR (n = 5). Eight patients stable on drug for 4 years	47 SMM and IMM	Lust 2009 [51]
Curcumin	Randomized, double-blind placebo-controlled crossover study. Administering 8 g dose of curcumin. Curcumin therapy decreased the FLC ratio, reduced the difference between clonal and nonclonal light-chain (dFLC) and involved FLC	17S MM	Golombick T [52]
Lenalidomide and dexamethasone	Lenalidomide + dex versus. observation. 2-years PFS 92 versus 30%, p < 0.001; 3 years-OS 93 versus 76%, p < 0.04	119 high risk SMM	Mateos *et al.* 2013 [37]

DSSI: Durie-Salmon stage I; EFS: Event-free survival; FLC: Free light-chain; IMM: Indolent multiple myeloma; MP: Melphalan-prednisone; MR: Minimal response; OS: Overall survival; PFS: Progression free survival; PR: Partial response; SMM: Smoldering multiple myeloma; SRE: Skeletal-related events; VAD: Vincristine, doxorubicin, dexamethasone

Table 4

Select ongoing clinical trials.

Type of therapy	Clinical trial and design	Number of patients	Ref.
Celoxicib versus Placebo	Phase II, double-blind, randomized controlled trial Aim: to test if celoxicib reduces the M-protein concentration	36 monoclonal gammopathy of undermined significance and SMM	Baz 2004-ongoing
Lenalidomide versus Observation	Open-label, randomized controlled trial Aim: to evaluate if lenalidomide extends TTP	370 'High Risk' SMM	Lonial 2010-ongoing
Anti-KIR monoclonal antibody	Phase II, open-label, single-arm trial Aim: to evaluate if anti-KIR reduces the M-protein concentration 50% from Baseline	21 SMM	Landgren 2010-ongoing
BHQ880, a fully human, anti-Dickkopf1 (DKK1) Neutralizing Antibody	Phase II, open-label, single-arm trial Aim: to evaluate the overall response rate	58 'High Risk' SMM	Novartis Pharmaceuticals 2011-ongoing
Elotuzumab (humanized anti-CS1 monoclonal lgG1 antibody)	Phase II, non-randomized, open-label trial Aim: to assess the association between NK cell status and efficacy	40 'high risk' SMM	BMS pharmaceuticals 2012-ongoing
Siltuximab (Anti IL 6 Monoclona Antibody)	Phase II, randomized multicenter blinded, placebo-controlled Trial Aim: 1-year progression-free survival rate	100 'High Risk' SMM	Janssen pharmaceuticals 2012-ongoing
Carfilzomib, Lenalidomide, and DEX	Pilot (Phase II) single-arm trial Aim: to evaluate overall response rate	12 pilot + 18 expansion cohort (n = 30) 'High Risk' SMM	Landgren 2012-ongoing
Fenofibrate	Phase II, open-label trial Aim: to determine response rate to fenofibrate therapy	30	Pereira 2013-ongoing
PVX-410, a multi-peptide cancer vaccine	Open-label, non-randomized A Phase I/IIa dose escalation study of PVX-410, a multi-peptide cancer vaccine, in patients with SMM Aim: to determine safety and tolerability of PVX-410	22 SMM	Raje, Wang, & Nooka 2012-ongoing
BI-505 (human antibody binding to ICAM-1 [CD54])	Phase II, single-arm, open-label trial Aim: to investigate the effect of BI-505 on tumor burden	10	BioInvent International AB Hansson 2013-ongoing
Daratumumab (anti-CD38)	Phase II, randomized, open-label trial Aim: to evaluate three Daratumumab dosing schedules in SMM	120 SMM	Janssen Research & Development 2014-ongoing
Elotuzumab and Lenalidomide ± Dexamethasone (Elo/Len/Dex vs Elo/Len)	Phase II, randomized, open-label trial Aim: to evaluate proportion of patients who are progression free at 2 years; time from therapy to progression	82 High Risk SMM	Ghobrial 2014-ongoing
Low-dose Bortezomib	Phase II, single-arm, open-label trial	17 SMM	Zangari 2009-ongoing

Type of therapy	Clinical trial and design	Number of patients	Ref.
	Aim: to evaluate the bone anabolic effect of Bortezomib in SMM and effect of Bortezomib on natural history of smoldering myeloma		
IPH2101, a human monoclonal anti-KIR antibody	Phase II, randomized multicenter, open-label trial Aim: to study the anti-tumor activity, safety, and pharmacology of two dose regimens in patients with SMM	30 SMM	Munshi 2010-2013 (completed)
Lenalidomide and Dexamethasone versus Observation	Phase III, randomized, open-label trial Aim: to evaluate when Len and Dex treatment extend time to progression to symptomatic multiple myeloma	120 high risk SMM	PETHEMA Foundation 2007-2013 (completed)
Polyphenon E, an extract of green tea	Phase II, single-arm, open-label trial Aim: sustained M-protein reduction of > 25% from baseline	8 monoclonal gammopathy of undermined significance and SMM	Zonder 2009-ongoing

BMS: Bristol-Myers squibb; SMM: Smoldering multiple myeloma; ZLD: Zoledronate