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Evolution of the Classification and Management of Smoldering Multiple Myeloma

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Abstract

The evolving molecular landscape of Smoldering Multiple Myeloma (SMM) has underscored its complex nature and the urgent need for more refined diagnostic and treatment strategies. With an increased risk of progression to Multiple Myeloma (MM), it has become important to identify patients at the highest risk of progression for interception strategies. Risk evaluation has been a constantly moving target with rapidly changing approaches to classification being based predominantly based on imaging and biochemical data thus far. More recently, advances in whole genome sequencing and a deeper understanding of SMM's biology have led to the recognition of genomic variants impacting its evolutionary trajectory to MM. Genomic analysis and molecular models are delivering ongoing contributions towards predicting the risk of progression and bringing about a pivotal shift toward precision medicine. Conversely, these advances have also facilitated the recognition of lower-risk subtypes, which may guide a less interventional and more health management approach to its care. This nuanced approach highlights the dual promise of genomic insights: tailoring interventions to intercept disease progression and potentially to achieve a cure while avoiding the overtreatment of patients less likely to progress. We review ongoing clinical trials dedicated to optimizing therapy for high-risk SMM, showcasing a concerted effort to identify precision treatment strategies. Through a blend of wide-ranging clinical trials and the exploration of genomic-based risk classification, the SMM management paradigm is poised for transformation, aiming to extend progression-free survival and ultimately, to improve patient survival.

Keywords: Multiple myeloma, SMM, Smoldering multiple myeloma

Classification of Smoldering Multiple Myeloma

SMM is a pre-cancerous condition that has the potential to develop into an invasive cancer phase that requires therapy, MM. Both monoclonal gammopathy of undetermined significance (MGUS) and SMM are asymptomatic clonal precursor plasma cell disorders; however, SMM is distinguished from MGUS for clinical reasons, primarily due to its increased risk of progression to symptomatic MM. Thus, SMM occupies the intermediate space between MGUS and MM, delineating a continuum of clonal plasma cell disorders that are asymptomatic precursors to MM. MGUS typically progresses to MM at an annual rate of 1.5%, while SMM presents a heightened annual progression risk of 10% [1]. The disease presents variably, with some patients having a 63.1% 2-year risk of progression to MM, while others follow a more MGUS-like trajectory with a 3.8% progression risk within the same timeframe [2]. While some patients diagnosed with SMM may eventually transition to MM necessitating therapeutic intervention, others may remain stable without progression effectively having a natural history analogous to MGUS, and thus never needing treatment.

First identified over 40 years ago, the disease entity of SMM described the clinical path of patients fitting MM's diagnostic criteria without showing progression. These individuals had a serum M-protein level of ≥ 3 g/dL and bone marrow plasma cells (BMPC) ≥10%, yet they exhibited no end-organ damage nor needed myeloma-directed therapy for a minimum of five years [3]. Since then, many efforts have been made to classify SMM [4-6]. In 2003, The International Myeloma Working Group (IMWG) published a consensus guideline defining SMM as an

entity with clonal BMPC ≥ 10%, and/or serum M-protein ≥ 3 g/dL, and without myeloma-related end-organ damage [5]. In 2007, a model was developed by the Spanish PETHEMA group that used two independent prognostic risk factors, ≥ 95% aberrant plasma cells (aPCs)/BMPC and immunoparesis [7] to predict progression-free survival (PFS). Additional factors have been investigated since then including M-protein levels, BMPC percentage, and a free light chain (FLC) ratio, that have led to the definition of distinct risk groups highlighting the heterogeneous composition of disease subsets making up SMM [7-9]. In particular, the term ultra-high-risk SMM was coined for patients with a FLC ratio of 100 or higher or BPMC ≥ 60% or >1 focal bone lesions on MRI that had a risk of progression to MM of less than two years from diagnosis [10-13]. This led to the reclassification of SMM in 2014 by the IMWG that redefined ultra-high-risk SMM into MM [14] that included a group with an 80% 2-year MM progression risk.

Despite reclassification, SMM still showed marked variability in its progression to MM. This led to the creation of the Mayo Clinic's 2/20/20 model in 2018, which incorporates a FLC ratio >20, M-protein >2g/dL, and BMPC>20%, that serves as a clinical predictor of progression risk [15]. Validated by the IMWG in 2020, this model showed a 2-year MM progression risk of 6.2%, 17.9%, and 44.2% for low, intermediate, and high-risk groups, respectively. It introduced a scoring system factoring in cytogenetic abnormalities, categorizing patients into low, low/intermediate, intermediate, and high-risk, with respective 2-year progression risks of 3.8%, 26%, 51%, and 73% [2]. However, similar to the other models, this model is static and predicates the treatment decision for an individual patient on outcomes measured at a diagnosis. In addition, the reproducibility of the FLC ratio exhibits wide variance [16]. Importantly, patients deemed low or intermediate risk may still progress quickly and could benefit from early intervention, highlighting the necessity to enhance the understanding of biological characteristics, prognostic models, and treatment strategies.

Biology of Plasma Cell Development

Differentiation from a B-cell lineage progenitors in the bone marrow, to a plasma cell has a vital role in producing diverse antibodies for the humoral immune response, **Figure 1**. Key to antibody variability are V(D)J gene recombination in a precursor and somatic hypermutation in the germinal center (GC) [17]. Early in B-cell development, V(D)J recombination occurs at the immunoglobulin (Ig) heavy chain DNA locus, initiated by the activation of recombination activating genes (RAGs), generating primary antibody diversity, mainly via the classical non-homologous end joining pathway [18].

Upon leaving the bone marrow, B-cells, after encountering their cognate antigen B-cells move to the GC of the secondary lymphoid organs [17]. In the GC they undergo somatic hypermutation (SHM) and class switch recombination (CSR) that is facilitated by the enzyme activation-induced cytidine deaminase (AID), which deaminates cytosine in DNA and RNA, leading to somatic mutations and DNA breaks [19]. Errors in IgH CSR contribute to IgH translocations, often seen in plasma

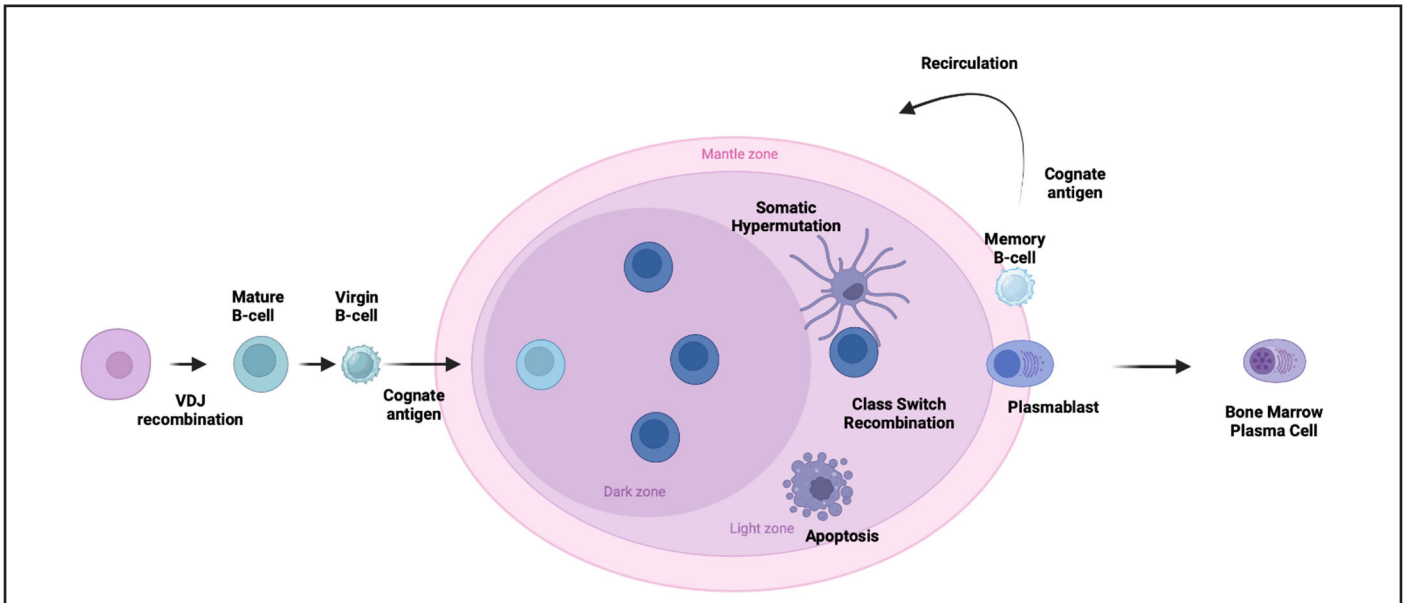

Figure 1. Biology of plasma cell development. Plasma cell development is initiated when B cells recognize their cognate antigens through their receptors, a process facilitated by V(D)J recombination, somatic hypermutation and class switch recombination. Upon activation, B cells undergo clonal expansion, with some differentiating into plasma cells. These plasma cells specialize in producing antibodies tailored to specific pathogens. They migrate to infection sites to release antibodies, marking pathogens for destruction. Despite their short lifespan, the immune system maintains sustained antibody production through a subset of long-lived plasma cells, ensuring enduring immunity.

cell dyscrasias, activating oncogenes including CCND1, NSD2, and MAF, which, along with specific aneuploidies like amp 1q and del17p, have prognostic importance and can be factored into prognostic models [20,21]. Recent investigations have demonstrated that APOBEC3, a cytidine deaminase, possesses the capacity to deaminate cytosine in viral genomes and is predominantly expressed in plasma cells and CD10+ B cells and an aberrant APOBEC3 activity has also been implicated in mutational signatures in MM [22,23].

During the molecular evolution of myeloma precursor to MM that requires therapy, a pre-malignant clone is thought to be immortalized through a series of genetic events in the germinal center, before relocating to the bone marrow where it undergoes clonal expansion, diversification, and selection within a number of heterogenous ecosystems [24,25]. Next-generation sequencing (NGS), including whole-genome sequencing (WGS), has been used to generate a detailed analysis of the evolution of myeloma genome and has shown branching evolutionary patterns and punctuated evolution with sudden catastrophic molecular events that can deregulate multiple genes, leading to rapid phenotypic shifts and progression [26-28].

Genomic Sequencing and Classifications

A paired WGS done on SMM and MM samples at progression found SMM genomic profiles resembled MM, including the abnormalities 1q, del13q, hypodiploidy, and IGH translocations [29]. The study identified two progression models of SMM to MM. A non-branching model with sub-clonal structure preservation and a median TTP of 5.5 months. And a branching model consistent with Darwinian evolution and a median TTP of 23 months. Both SMM and MM samples demonstrated AID and APOBEC's impact on mutations, with off target AID generating regions of kataegis, indicating a role in early pathogenic stages and alterations driven by an APOBEC signature being seen later. A further study extended this first analysis including MGUS, SMM, and MM samples and examined genomic differences between them [29,30]. They discovered that stable, non-progressing myeloma precursors typically emerge later in life and lack myeloma-defining genomic events such as chromothripsis, templated insertions, mutations in key genes, aneuploidy, and APOBEC signatures, differentiating them from cases advancing to MM. Further, a study from Dutta et al. used WGS to study the transition from MGUS, SMM, and MM, observing 7-8 subclones on average and emphasized the role of RAS/MAPK mutations—present in 40% at MGUS/SMM and rising to 70% at MM. RAS mutations were found at low variant allele frequencies within sub-clonal populations, suggesting their early presence and evolution during the disease [31].

In 2021 we reported on sequential WGS on samples from patients with SMM who subsequently developed MM [32]. Our findings revealed that SMM is characterized by a lower frequency of *NRAS* and *TENT5C* mutations, diminished APOBEC mutational signatures, and fewer adverse cytogenetic deletions, such as del(1p), del(14q), del(16q), and del(17p), in comparison to MM. Additionally, mutations in *KRAS* were correlated with a reduced TTP. We noted an increase in tumor sub-clonal complexity at least one year prior to progression from SMM to MM, with branching clonal evolution emerging as the predominant pattern of progression. These observations may underscore their contributory roles as drivers in the transition to MM and can be used as "myeloma-defining" events in this setting.

In a 2020 study, using WGS to examine the progression from SMM to MM, Bustoros et al. found MYC aberrations, MAPK pathway mutations, and DNA repair pathway alterations were linked to adverse outcome median TTP of 8.4, 14.4, and 15.6 months, respectively [33]. By the Mayo 2018 model, high-risk patients with these genetic changes showed a significantly lower TTP of 1.2 years. In their validation cohort, patients deemed low-risk by the Mayo 2018 model without high-risk genomic alterations did not progress. Enrichment of APOBEC mutational signatures in progressing patients and a strong genetic resemblance between SMM and MM was observed, indicating most driver mutations appear in the SMM stage, despite sub-clonal variations over time. A follow-up study in 2022 employed clustering analysis on 42 driver genetic alterations to categorize SMM into six distinct subtypes [34]. These encompassed three high-risk subtypes: Hyperdiploid-like 2 (HL2) with multiple arm-level deletions and the t(14;20) IgH translocation, and mutations in MAPK and DNA repair; Hyperdiploid-like 3 (HL3) featuring *KRAS* mutations and *MYC* translocations; and Translocation-like 1 (TL1), characterized by t(4;14) and t(14;16) translocations, alongside mutations in genes like *DIS3*, *MAF*, *FGFR3*, *PRKD2*, and *PRDM1*. Two intermediate-risk SMM subtypes, Hyperdiploid-like 1 (HL1) and Hyperdiploid-like 4 (HL4), were identified. HL1 was enriched for mutations in *NRAS*, *TRAF3*, *MAX*, and *FAM46C*, while HL4 featured mutations in *NFKB2* and *KLHL6*, with frequent copy gains in 2p and 1q. The sole low-risk subtype, Translocation-like 2 (TL2), predominantly showed t(11;14), *CCND1* mutations, and gains in chromosome 11. Primary cohort median TTP was 4 years, with a median follow-up of 7.1 years. Both the high-risk (HL2, TL1, HL3) and intermediate-risk (HL1, HL4) genetic subtypes demonstrated a significantly shorter median TTP of 2.6 and 5.2 years, respectively, compared to the low-risk subtype (TL2) with a median TTP of 11 years (2.6 and 5.2 vs. 11 years, respectively, $P < 0.0001$). Notably, within the clinically high-risk group by the Mayo 2018 model, patients also with high-risk genetic subgroups exhibited an increased progression risk, with a hazard ratio (HR) of 3.7. In a combined cohort analysis focusing on patients at a high-risk clinical stage, those with the low-risk genetic subgroup (TL2) showed a higher median TTP of 8.7 years.

Management of SMM

The standard treatment for SMM primarily has involved active observation but this is changing. Recent advances in MM therapy have spurred various clinical trials to evaluate new treatments for SMM. Therapeutic strategies are twofold: one aims to postpone organ damage using low-intensity treatments, and the other seeks to eliminate cancerous cells and sometimes uses more aggressive therapy. Outcome comparisons across these studies are challenging, especially in earlier trials, due to changing classification criteria and ongoing variations in defining high-risk SMM.

The QuiReDex study, a phase 3 trial comparing lenalidomide and dexamethasone (Rd) with lenalidomide maintenance versus observation, is the only clinical trial to date demonstrating an overall survival (OS) benefit in SMM [35]. With a 12.5-year long-term follow-up, it revealed a median TTP of 2.1 years for the observation arm versus 9.5 years for the Rd arm, and an OS of 8.5 years for the observation group. The study's limitations include recruitment before the use of FLC and advanced imaging for MM diagnosis, and the absence of mandatory skeletal imaging, possibly including patients with myeloma bone disease.

The phase 3 ECOG E3A06 study evaluated lenalidomide monotherapy against observation for intermediate to high-risk SMM patients [36]. In the observation group, 24% progressed at 24 months, indicating a possibly less risky cohort than expected, as reflected by the 2018 Mayo risk stratification with 31.9% low-risk, 37.4% intermediate-risk, and 30.8% high-risk SMM. The study showed a 3-year PFS of 91% for lenalidomide versus 66% for observation, with an HR of 0.09 in high-risk patients, signifying PFS benefits primarily for this subset. Unlike the QuiReDex study, ECOG E3A06 included baseline MRI scans of the spine and pelvis to screen out active MM.

Another phase 3 study (ITHACA), will compare an anti-CD38 monoclonal antibody isatuximab plus Rd regimen vs Rd regimen [37]. Safety run-in results with isatuximab plus Rd regimen alone showed - 100% overall response rate (ORR) (23 patients), 30.4% complete response (CR), and 13% stringent CR (sCR). Additional phase 3 studies like DETER-SMM (NCT03937635), will assess Daratumumab plus Rd versus Rd, and AQUILA (NCT03301220), which will compare daratumumab with active monitoring, are still ongoing.

In the phase 2 clinical trial setting, several studies have investigated aggressive therapies aimed at curing high-risk SMM. The GEM-CESAR trial investigated carfilzomib and Rd (KRd) regimen with autologous stem cell transplant (ASCT). At a median follow-up of 65.8 months, 94% of patients maintained PFS and 23% sustained MRD negativity (MRD-ve) 4 years post-ASCT [38]. The ASCENT trial evaluated a 2-year daratumumab and KRd regimen, and reported a high response rate and MRD-ve at a median follow-up of 25.8 months, with the best ORR of 97% and 37% sCR [39]. Additionally, 84% achieved MRD-ve at a median of 6.6 months, with a 3-year PFS of 89.9%, improving upon the 71% MRD-ve in the MANHATTAN trial, which used a similar regimen in newly diagnosed MM [40].

The long-term impact of attaining MRD-ve states remains difficult to fully understand. In a phase 2 study for high-risk SMM, a similar three drug regimen without daratumumab showed 70% sustained MRD-ve over 8 years with a median follow-up of 31.9 months [41]. Another example of an intensive treatment strategy under investigation is in the Immuno-PRISM (NCT05469893), designed to compare Teclistamab (TEC) with Rd arm [42]. At median follow-up of 6 months there was a 100% ORR with 42% achieving CR in the TEC arm, where 8 out of 12 evaluable patients treated with TEC reached a 100% MRD-ve rate at 10^{-6} sensitivity. Additionally, the CAR-PRISM (NCT05767359) trial is assessing upfront CAR-T therapy's potential in high-risk SMM.

Several studies are exploring immunotherapy as a single agent. The phase 2 CENTAURUS trial assessed daratumumab monotherapy's efficacy in intermediate or high-risk SMM using three dosing schedules: intense, intermediate, and short [43]. While it did not meet its co-primary endpoint of a CR over 15%, ORRs of 56.1% were noted in both the intense and intermediate arms and 37.5% in the short arm, over a median follow-up of 85.2 months. The daratumumab monotherapy regimen is also under comparison with observation in the ongoing phase 3 AQUILA study (NCT03301220), with PFS as the primary outcome, expecting results by 2024-2025. If daratumumab shows a PFS benefit, it could potentially lead to the first FDA-approved option for high-risk SMM. Further details on additional clinical trials can be found in **Table 1**.

Building Future Interception Strategies

Our growing understanding of clonal evolution and the impact of genetic changes are improving our ability to predict the likelihood of progression in SMM. Investigating high-risk genetic subtypes within SMM, alongside the existing risk profile defined with clinical parameters might improve its predictive power allowing for the identification of patients at risk of progression akin to what has been done already with ultra-high-risk SMM. Such an approach could pave the way for earlier interception strategies, **Figure 2**. These patients might gain from pre-emptive, aggressive treatment akin to that for myeloma, to forestall severe and possibly irreversible end-organ damage due to progression to overt MM. Also, this might be a setting where we may succeed in achieving cures but randomized evidence supporting this approach is still not available. Currently, assessing the veracity of clinical trial data for the impact of early treatment of SMM is constrained by the varying inclusion criteria used resulting from the evolving classifications and differences in risk assessment. In addition to this there is insufficient long-term outcome data in recent studies which prevents a full understanding

Table 1. Selected Phase 2 and 3 clinical trials in SMM.

Trial Name (The National Clinical Trial number)	Date, Updates (Study start ->projected completion date)	Study Phase	SMM patient inclusion criteria	Intervention	Outcome
QuiReDex. (NCT00480363) [35]	2013, 2016, 2022 (2007->2013)	Phase 3	High-Risk SMM defined by SMM diagnosed <5 years and either: - BMPCs ≥ 10% and IgG level ≥ 3 g/dL, IgA level 2 g/dL, or urinary Bence Jones protein level 1 g per 24 h. - or only 1 of 2 criteria above with ≥ 95% phenotypically aberrant plasma cells in BMPC compartment and immunoparesis (PETHEMA Criteria)	Rd induction for 4 week x9 cycles followed by lenalidomide maintenance for 2 years vs observation	Primary Outcome: TTP (defined as end organ damage, median follow-up 12.5 years) - median TTP to MM 2.1 years observation vs 9.5 years in Rd OS - median OS 8.5 years in abstention arm vs not reached in Rd group
ECOG-ACRIN E3A06. (NCT01169337) [36]	2019 (2011 ->2019)	Phase 3	Intermediate or High-Risk SMM defined by SMM diagnosed <5 years with: - BMPCs ≥10% and abnormal sFLC ratio (<.26 or >1.65)	Lenalidomide vs Observation. Continued until progression, toxicity, or withdrawal.	Primary Outcome: PFS (median follow-up 35 months) - 3-year PFS 91% vs 66% - high-risk SMM by mayo 2018 subgroup – Hazard ratio was .09
DETER-SMM (NCT03937635)	(2019 ->2029)	Phase 3	High-risk SMM diagnosis within past 12 months and two or more following factors: - abnormal FLC i/ui >20 but less than 100 if involved FLC is ≥10 mg/dL - M-protein ≥ 2 gm/dL - >20% BMPC - t(4;14) or del 17p, del 13q or 1q gain	Daratumumab plus Rd vs Rd. Both treatments up to 24 cycles.	Primary Outcome: OS, functional assessment score (pending results)
ITHACA (NCT04270409) [46]	2021,2022 (2020->2033)	Phase 3	SMM within 5 years and HR-SMM defined by the Mayo '20-2-20' and/or updated PETHEMA model criteria. (2 met mayo clinical model criteria 13 pts met PETHEMA model criteria)	Isatuximab +Rd vs Rd. Isatuximab once weekly then biweekly plus Rd for 24 cycles followed by isatuximab monotherapy for 12 cycles for total 36 cycles	Primary Outcome: Safety, Cmax of isatuximab, PFS (preliminary median follow-up 19.4 months, median duration of treatment exposure was 19.7 months) - ORR 100% (23 patients), CR 30.4%, sCR 13%, VGPR 30.4%

AQUILA (NCT03301220)	(2017 ->2025)	Phase 3	Confirmed diagnosis of SMM for <5 years, factors indicating high-risk of progression to MM (clonal bone BMPCs ≥ 10% and ≥ 1 of the following: serum M protein ≥ 30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved Ig isotypes, serum involved:uninvolved FLC ratio ≥ 8 to < 100, or clonal BMPCs >50% to <60% with measurable disease)	Daratumumab vs active monitoring (Q1W dara Cycle 1 and 2, Q2W dara cycle 3-6, and Q4W dara until 39 cycles up to 36 months)	Primary Outcome: PFS (pending results)
CENTAURUS (NCT02316106) [43,47]	2017, 2018, 2020, 2023 (2015 ->2023)	Phase 2	Intermediate or High-Risk SMM defined as SMM diagnosed <5 years with ≥10% and <60% BMPC and - M-protein ≥ 3 g/dL (≥ 2 g/dL or IgA) - Urine M protein > 500 mg per 24 hours - FLC ratio >8 if M protein 1-3 g/dL - involved FLC ≥ 100 (if FLC ratio between 8-99)	Daratumumab: - Intense (Q1Wx8, Q2x8, Q4x8, Q8x8) - Intermediate (Q1Wx8 and Q8Wx19) - Short (Q1Wx8)	Primary Outcome: CR rate (median follow-up 85.2 months) - Intense arm – 4.9% -Intermediate arm 12.2% - Short arm - 0% 84 months -OS - Intense arm – 81.3% - Intermediate arm – 89.5% - Short arm – 88.1% PFS (reported in 2020 paper, median treatment follow-up 25.8 months). 24-month PFS rate - Intense arm – 90% - Intermediate arm – 82% - Short arm – 75% 24-month biochemical PFS rate - Intense arm – 84.3% - Intermediate arm 70.2% - Short arm 31.5%
GEM-CESAR (NCT02415413) [38]	2019, 2022 (2015->2027)	Phase 2	The high-risk SMM was defined by the presence of both ≥ PC 10% and MC ≥ 3g/dL (2008 Mayo) or if only one criterion was present, pts must >95% of aberrant PCs within the total PCs BM compartment by immunophenotyping plus immunoparesis (PETHEMA criteria).	Induction KRd x 6. Melphalan conditioning and ASCT. KRd x 2 consolidation. Rd x 2-year maintenance	Primary Outcome: Sustained MRD-MFC post induction and ASCT (median follow-up 65.8 months) - 23% maintained MRD-ve 4 years after ASCT and 2 years after finalizing protocol PFS - 94% PFS at median f/up 65.8 months - Biological PFS at 5 years 72%

ASCENT (NCT03289299) [39]	2020, 2022 (2018 ->2031)	Phase 2	High-risk defined by the Mayo 20/2/20 model or IMWG risk-stratification score ≥ 9	Dara-KRDx6 induction Dara-KRDx6 consolidation DRx12 maintenance	Primary Outcome: Stringent CR rate (median follow-up 25.8 months) - The best overall response rate was 97%, with 37% sCR. - 84% patients became marrow MRD-ve at a median of 6.6 months - Median PFS not reached. PFS at 3 years was 89.9%.
Kazandjian et al. (NCT01572480) [41]	2021 (2012->2025)	Phase 2	Diagnosis of high-risk SMM based on the Mayo Clinic, Spanish, and/or Rajkumar, Mateos, and Landgren criteria.	KRd x8 cycles induction followed by 24 cycles of lenalidomide maintenance	Primary Outcome: MRD-CR (median Follow-up 31.9 months) - The MRD-ve CR rate was 70.4%. - The 8-year probability of being free from progression to multiple myeloma was 91.2%
ISAMAR Manasanch et al. (NCT02960555) [48]	2019, 2023 (2017->2025)	Phase 2	High-risk SMM: Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL or urinary monoclonal protein ≥ 500 mg per 24 hours and/or clonal bone marrow plasma cells 10-60% AND PETHEMA criteria	Isatuximab monotherapy up to 30 cycles without lenalidomide (stage 1) and with lenalidomide maintenance (stage 2)	Primary Outcome: ORR (median follow-up time not sated). - The study met its primary endpoint of ORR ≥ 70% after 6 cycles of therapy. - For stage 1, median PFS was 49.3 months; median OS not reached at a median f/u of 49 months. - Stage 2 ORR 89% - Stage 2 median PFS/OS is not reached.
E-PRISM (NCT02279394) [49]	2016, 2018 (2014->2022)	Phase 2	High-risk SMM per Mayo or Spanish criteria as per below: Bone marrow clonal plasma cells ≥10% and <60% and any one or more of the following: - Serum M protein ≥ 3.0 g/dL, IgA SMM, Serum involved/uninvolved FLC ratio ≥ 8 (but less than 100), Progressive increase in M protein level, BMPC 50-60%. Abnormal plasma cell (PC) immunophenotype (95% of BMPCs are clonal) and reduction of one or more uninvolved immunoglobulin isotypes. t (4;14) or del 17p or 1q gain. Increased circulating PCs. MRI with diffuse abnormalities or 1 focal lesion. PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction Increase in serum monoclonal protein by ≥ 25% on two successive evaluations within a 6-month period	Elotuzumab + Rd x8 cycles followed by elotuzumab + Rd 9-24 cycles	Primary Outcome: PFS at 2 years (median follow-up not stated, prelim follow-up ~2-3 year into the study accrual until 2018 abstract) - ORR 84%, CR 6% to date of abstract - no progression to overt MM to date of abstract

B-PRISM (NCT04775550) [50]	2022 (2021 ->2029)	Phase 2	High-risk SMM per Mayo 2018 "20-2-20" model and other previously established criteria including Mayo 2008 criteria, presence of immunoparesis, evolving type of SMM, and high risk FISH.	Daratumumab + bortezomib and Rd total of 24 cycles (2 years).	Primary Outcome: MRD-ve at 2 years (preliminary median follow-up 6 months) - MRD evaluable 8 out of 16 patients with MRD-ve rate 50% and 25% at threshold 10-5 and 10-6. - ORR 90%, 25% CR
Nadeem et al. (NCT02916771) [51]	2019, 2021, (10/2016->4/2025)	Phase 2	BMPCs ≥ 10% and <60% and any one or more of the following: - Serum M protein ≥ 3.0 g/dL, IgA SMM, Serum involved/uninvolved FLC ratio ≥ 8 (but less than 100), Progressive increase in M protein level, Bone marrow clonal plasma cells 50-60%. Abnormal PC immunophenotype (95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes. t (4;14) or del 17p or 1q gain. Increased circulating plasma cells. MRI with diffuse abnormalities or 1 focal lesion. Urine monoclonal light chain excretion ≥ 500 mg/24 hours. PET-CT with one focal lesion with increased uptake without underlying osteolytic bone destruction.	Ixazomib plus Rd x 9 cycles followed by ixazomib and lenalidomide x 15 cycles for total of 24-month period	Primary Outcome: PFS 2 years (preliminary median follow-up duration not noted, median cycle completed 24) - ORR in participants who completed at least 2 cycles of treatment was 90.9% (CR, 21.8%; VGPR, 18.2%; PR, 50.9%) - ORR in patients who completed the induction phase (≥ 9 cycles) was 92.3% with 40% deep remissions including 23.1% CR and 19.2% VGPR
Immuno-PRISM (NCT05469893) [42]	2023 (2022->2030)	Phase 2	High-risk SMM per 2018 Mayo criteria or ≥ 10% BMPC and at least one of following: - evolving monoclonal protein - evolving change in hemoglobin - progression involved light chain increase on two successive evaluations - Abnormal Plasma Cell immunophenotype (≥ 95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotype. - High risk cytogenetics defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain	Rd vs Teclistamab	Primary Outcome: CR rate (preliminary median follow-up 6 months) TEC arm - ORR 100%, CR 42% Rd arm. MRD-ve at 106 in 100% of patients - ORR 66%, no CR to date - of 12 patients in TEC cohort, 1 grade 3 infection (resolved), 1 grade 3 pancreatitis (resolved), 75% with CRS (all grade 1 except 2 grade 2 requiring tocilizumab (all resolved)

CAR-PRISM (NCT05767359)	(2023 – 2040)	Phase 2	High-risk SMM per 2018 Mayo criteria or ≥ 10% BMPC and at least one of following: - evolving monoclonal protein - evolving change in hemoglobin - progression involved light chain increase >10% over 6 months along with LC ratio>8 - Abnormal Plasma Cell immunophenotype (≥ 95% of BMPCs are clonal) and reduction of ≥ 1 uninvolved immunoglobulin isotype. - High risk cytogenetics defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain	2 safety run-in phases in a standard 3 + 3 design. Stem cell collection on-site post-apheresis. Cyclophosphamide and fludarabine in pre-determined doses 1 x daily for 3 consecutive days. Hospitalization to receive Cilta-cel in per-determined dose per protocol 1 x daily for 3 consecutive days. Follow-up for 3 years post-treatment and up to 15 years. Expansion cohort of 14 participants will be enrolled after safety run-in phases	Primary Outcome: Incidence of dose limiting Toxicities (DLT), Nature of DLT, Incidence of adverse events. (pending results)
HO147SMM (NCT03673826)	(2018–>2028)	Phase 2	Patients must have high-risk SMM based on the Mayo Clinic and/or the PETHEMA criteria	KRd vs Rd KRd x 9 cycles followed by extended lenalidomide for 24 cycles vs Rd (Rd x 4 cycles followed by extended lenalidomide for 24 cycles)	Primary Outcome: PFS (pending results)
NCT04776395	(2021 ->2025)	Phase 2	Intermediate- or high-risk SMM as confirmed by at least one of the following factors either at screening or within 28 days of screening: Bone marrow clonal plasma cells ≥ 20% confirmed on either screening bone marrow biopsy or by outside pathology <5 years from initiation of study drug. Abnormal serum FLC ratio > 20 by serum FLC assay. Serum monoclonal protein ≥ 2 g/dL. Subject must have been diagnosed with SMM ≤ 5 years from initiation of study drug	Iberdomide and dexamethasone vs iberdomide monotherapy. Both until toxicity or progression.	Primary Outcome: ORR (pending results)

NCT05014646	(2022->2024)	Phase 2	High-risk SMM, as defined below: The presence of ≥ 2 of the following risk factors: BMPC% >20% Serum M-protein >2 g/dL Free light chain ratio (FLCr) >20. A diagnosis of high-risk SMM must have been made within the last 3 years. Patients must identify as African-American OR European-American	Ieflunomide PO QD on days 1-28. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.	Primary Outcome: PFS, incidence of adverse events (pending results)
REVIVE (NCT06100237)	(2023->2029)	Phase 2	High-risk by the PETHEMA criteria (immunoparesis and ≥ 95% aberrant bone marrow plasma cells (aBMPCs) by flow) and/or Mayo Clinic (20/2/20) criteria and/or have clonal BMPCs ≥ 10% with any one or more of the following criteria: Serum M protein ≥ 3 g/dL Immunoglobulin A (IgA) SMM Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes Serum involved/uninvolved FLC ratio ≥ 8 (but <100) Progressive increase in M-protein level (evolving type of SMM; increase in serum M-protein by ≥ 25% on 2 successive evaluations within a 6-month period) Clonal BMPC 50%-59%. Abnormal PC immunophenotype (≥ 95% of BMPCs are clonal) and reduction of ≥ 1 uninvolved immunoglobulin isotype(s) Chromosomal abnormalities specifically translocation of chromosomes 4 or 14 (t(4;14)) or deletion of the short arm of chromosome 17 del(17p)) or gain of the long arm of chromosome 1 (1q gain) found in ≥ 5% of cells Increased circulating PCs (PCs >5 x 106/L and/or >5% PCs per 100 peripheral blood mononuclear cells (PBMCs) MRI with diffuse abnormalities or 1 focal lesion, AND/OR PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction.	Teclistamab-Daratumumab OR Talquetamab-Daratumumab. Injection per discretion of treating physician.	Primary Outcome: MRD-ve as measured by flow cytometry (pending results)

NCT04933539	(2022->2032)	Phase 2	Mayo Clinic 2018 criteria, PATHEMA criteria, or Rajkumar, Landgren, Mateos may also be used to define high-risk disease, namely clonal bone marrow plasma cells ≥ 10% AND any one or more of the following: Serum M protein ≥ 30 g/L, IgA SMM, Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes, Serum involved/ uninvolved FLC ratio ≥ 8 (but <100), Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥ 25% on 2 successive evaluations within a 6-month period), Clonal BMPCs 50%-60%, Abnormal PC immunophenotype (95% of BMPCs are clonal) and reduction of ≥ 1 uninvolved immunoglobulin isotypes, t(4;14) or del(17p) or 1q gain, Increased circulating PCs, MRI with diffuse abnormalities or 1 focal lesion, AND/OR PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction	Subcutaneous Daratumumab, Once Weekly Carfilzomib, and Dexamethasone (DKd). Dexamethasone PO/IV (for Cycles 1-4: Dexamethasone 40 mg IV/PO on days 1, 8, 15, 22; for Cycles =5: Dexamethasone 20 mg IV/PO on days 1, 8, 15, 22); for up to 12 cycles Carfilzomib IV (for Cycles 1-2: 20 mg/m2 IV on day 1, 56 mg/m2 IV on days 8, 15; Cycles =2: 56/ m2 IV on days 1, 8, 15); for up to 12 cycles Daratumumab SC 1800 mg (Cycles 1-2: Days 1, 8, 15, 22; Cycles 3-6: Days 1, 15; Cycles =7: Days 1 of the 28-day cycle); up to 36 cycles total	Primary Outcome: Response Rate (pending results)

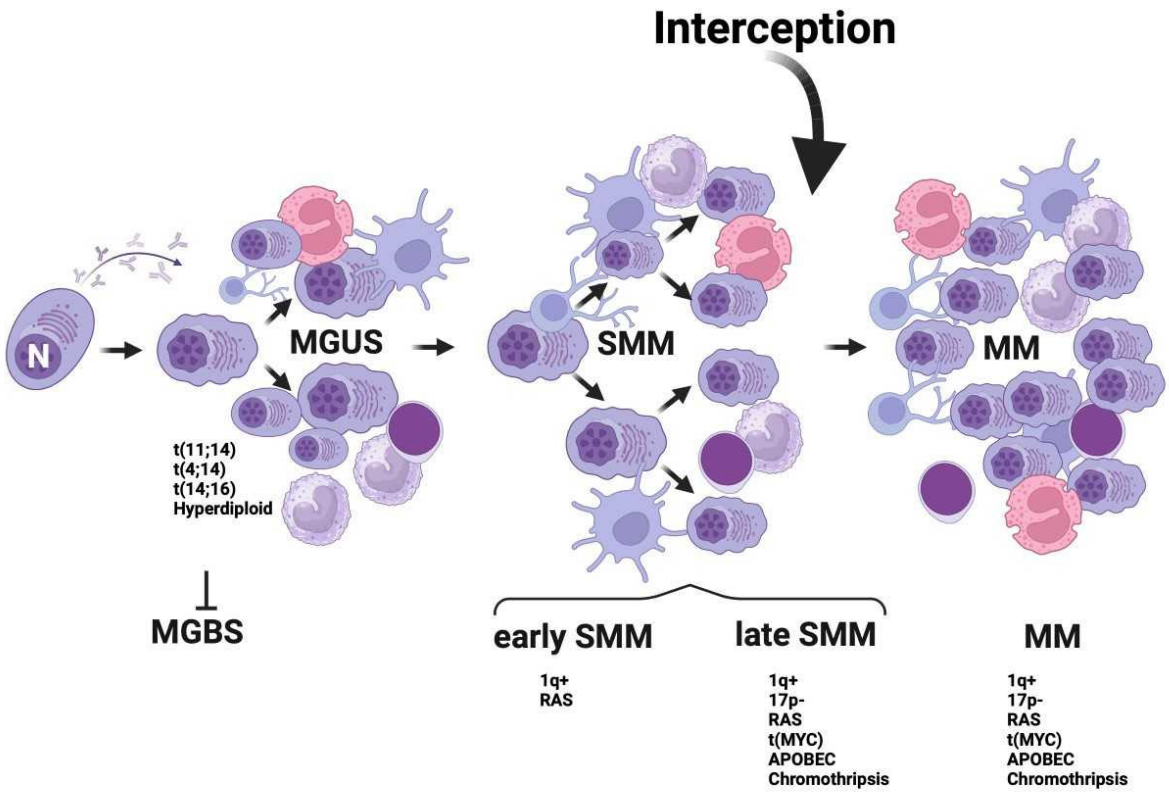

Figure 2. Interception strategy to prevent Multiple Myeloma progression. Hypodiploidy and translocations such as t(11:14) typically exhibit clonality, implying early occurrence in disease progression. Conversely, mutational patterns linked to chromothripsis, *RAS* mutations, and *MYC* translocations often show varied clonal distributions, suggesting later emergence in the disease trajectory. Enhanced exploration to delineate the disease progression timeline and improved risk assessment through genetic subtype analysis could inform clinical decision-making regarding the timing of intervention prior to MM progression. MGBS: Monoclonal Gammopathy of Benign Significance.

of whether the therapeutic targeting of high-risk genomic subsets could improve cure rates. Future clinical trial results incorporating longer-term data will play a pivotal role in discerning whether early intervention targeting high-risk SMM using more intensive therapies can yield enhanced and enduring cure rates. Equally important during this process will be the application of close monitoring and assessment of the early and late side effect profiles of early intervention. This evaluation should be conducted alongside measuring long-term outcomes to holistically determine the overall net benefit of early intervention compared to the potential harm of overtreatment. Additionally, studies such as the ongoing SPOTLIGHT trial (NCT06212323) is evaluating the use of diffusion-weighted whole-body MRI as a method for the early detection of myeloma bone disease as an alternative to early intervention for patients with high-risk SMM.

Caution is necessary when considering aggressive treatments for patients with asymptomatic SMM without precise risk stratification. This approach can lead to unnecessary adverse outcomes, especially with therapies known for significant side effects, such as CAR-T cell therapy and bispecific therapies, which are currently approved for relapsed MM cases. Nevertheless, existing genomic subtype data may play a crucial role not only in pinpointing higher-risk subtypes but also in distinguishing lower-risk subtypes that might justify observation, despite falling within clinically defined high-risk SMM categories. For example, the low-risk genetic subtype group TL2, characterized by t(11;14) and gain in chromosome 11 demonstrated a significantly longer median progression time of 11 years [34]. TL2 subtype, even within a high-risk clinical stage as per Mayo criteria, presents a lower median TTP of 8.7 years, suggesting a nuanced approach to managing SMM based on genetic risk stratification.

In addition, genomic models may not only be helpful for determining treatment threshold and time but may also give us guidance on specific types of therapy regimens as well if it incurs treatment variance or opens up new avenues for targeted treatment rooted in biology and evolution of the cancer cell. This treatment variance based on genomic subtype can already can be seen in MM [44]. However,

genomic models currently do not fully take account of the complexity of the bone marrow microenvironment and the significance of immune evasion in the development and spread of the disease. Recent research has explored single-cell RNA sequencing of bone marrow cells to uncover immune alterations [45]. Enhanced comprehension of early immune events and changes that precipitate MM progression may also facilitate more refined stratification of risk and in combination with genomic models may guide the development of selective therapeutic options.

In summary, despite ongoing efforts to improve classification and in the development of risk models for SMM, it remains a heterogeneous disease with difficulty in accurately differentiating between indolent and aggressive phenotypes. However, with improving advances in genetic testing and understanding SMM's biology, we look forward to better identification of high-risk subtypes, guiding treatments to prevent progression to full-blown myeloma while avoiding unnecessary treatment for low-risk patients. Ongoing clinical trials aim to improve treatment for high-risk SMM, utilizing precise strategies tailored to individual patients. Overall, the synthesis of genomic insight and clinical innovation heralds a new era in SMM management, where personalized genomic-based classification could significantly improve the predictability of the disease's trajectory and guide treatment options.

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