

**Should patients with high risk smoldering myeloma receive treatment? [YES]**

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Almost 35 years ago, based on the description of 6 patients, Greipp and Kyle coined the term smoldering multiple myeloma (SMM). Subsequently, several parallel definitions and concepts were introduced including indolent myeloma (Alexanian et al), evolving multiple myeloma (Blade et al.), and Durie Salomon stage I disease (Durie et al.). To consolidate overlapping definitions, in 2003, the International Myeloma Working Group developed a consensus definition for SMM (serum M-protein  $\geq 3$  g/L and/or  $\geq 10\%$  monoclonal plasma cells in the bone marrow, in the absence of end organ damage related to myeloma). The past few years, studies have been developed to identify SMM patients at high versus low risk of transformation to multiple myeloma. The Mayo Clinic and the Spanish PETHEMA study group have developed clinical risk scores showing that 1/3 of SMM patients on average take less than 2 years to develop multiple myeloma.

The first randomized clinical trial focusing on SMM was published in 1993 (Hjort et al.). In that study, the investigators randomized patients (referred to as “indolent multiple myeloma stage I patients”) to initial versus deferred Melphalan + Prednisone therapy. No statistical difference was found for progression-free survival (PFS) or overall survival (OS). Later several smaller studies have been developed; some of them suggesting that early therapy may be beneficial. In 2013, a randomized multi-center phase III study focusing on high-risk SMM reported that Revlimid + Dexamethasone was associated with a better PFS and OS than observation (Mateos et al.). Currently, a range of ongoing studies are investigating the role of various 1-, 2-, and 3-drug combinations for patients with high-risk SMM.

This debate presentation will discuss available data supporting initiation of treatment for patients with high-risk SMM. Also it will discuss major gaps in our understanding of this topic, as well as opportunities to improve survival and ultimately find an established cure.