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# Functional cure and long-term survival in multiple myeloma: how to challenge the previously impossible

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# Functional cure and long-term survival in multiple myeloma: how to challenge the previously impossible

## Running title: Functional cure in Multiple Myeloma

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**Data sharing statement:** The data that support the findings of this review are available from the corresponding authors (ME, MM) upon reasonable request**.**

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**Abstract**

Multiple myeloma (MM) is a heterogeneous disease with survival ranging from months to decades. The goal of ‘cure’ remains elusive for most patients, but has been shown to be possible, with durable remission and a transition to a plateau phase (analogous to monoclonal gammopathy of uncertain significance/smoldering Myeloma (MGUS/SMM)). Two representative cases set the stage to illustrate how this might be possible and what still needs to be determined to achieve functional disease control over a prolonged period. Several developments have emerged, such as improved diagnostics including the definitions and use of SLiM-CRAB criteria and MRD with whole genome-/single-cell-sequencing as well as other correlates to better understand disease biology. These advances enable earlier detection, more accurate risk stratification and improved personalized treatment strategies by facilitating analysis of genetic alterations and clonal heterogeneity. Whole genome sequencing may also identify driver mutations and modes of resistance to targets like immunotherapies (IOs) as well as other targeted therapies. Today, induction with a CD38 antibody (CD38mAb), proteasome inhibitor, immunomodulatory drug, and dexamethasone, potentially followed by ASCT and lenalidomide maintenance, can be considered standard of care for transplant-eligible (TE) newly diagnosed (NDMM) patients. Whether prolonged disease control and functional cure can be achieved in non-transplant eligible (NTE) patients is currently emerging as a distinct possibility: data from phase III trials that incorporate a CD38mAb into the treatment of NTE NDMM patients demonstrate impressive MRD negativity rates that appear sustained over several years. While the long-term durability of CAR-Ts, bi-specific antibodies and other IOs are evaluated, several clinical trials are now investigating their role in frontline treatment for TE and NTE patients. These will address whether CAR-Ts will replace ASCT and whether such IOs will represent a truly curative option. We conclude that whilst cure remains elusive, the concept of operational or functional cure provides a new benchmark to strive for and is an emerging area of active and potentially achievable clinical research for MM.

## I. Introduction

Multiple myeloma (MM) is a complex and heterogeneous disease with survival ranging from months to decades from primary diagnosis based on a patient's risk profile.[1] However, the ultimate goal of achieving „cure“ remains elusive for almost all patients. Use of the term "cure" for some cancer entities is being debated in view of the increasing survival rates in various cancers and the development of survivorship care as an essential component of hematology/oncology. Some hematologists/oncologists prefer to use "long-term survivor" instead of "cured patient" (and although patients prefer "cured", practitioners may consider this as impossible in some settings). From conditional survival (CS) analyses, it has been shown that the risk for death from cancer is highest in the initial years after diagnosis, decreases progressively, until a time at which the risk becomes negligible, and surviving patients reach a life expectancy that may match the sex- and age-matched general population.[2–4] Thus, CS is defined as the probability of a patient surviving an additional 5 (or 10) years after already surviving a given number of years.[2–4] Today, increasing survival is expected for various cancers as a result of personalized treatments based on our better understanding of the biology and potential response to more effective therapies. Therefore, A) cancer patients can be defined as "cured", when their life expectancy is the same as that of a sex- and age-matched general population. B) The biologic characterization of a tumor and its site, stage, and disease-free interval are variables that influence the correct applicability of the word "cured". C) Considering the social implications of cancer, the word "cured" in certain societies and cultural contexts could also facilitate the return of cancer patients to their personal and professional life after cancer by reducing the risk of work and insurance discrimination.[5] This article will provide an overview of the current landscape of MM treatment, the concept of achieving cure in MM, and the historical perspectives that have shaped our understanding of MM treatment to date.

## II. Data collection and methods

The author panel reviewed available evidence published in randomized clinical studies, meta-analysis, systematic reviews, observational studies, meetings and case reports. The Medline, Embase and Cochrane bibliographic databases were searched from manuscript conception to June 12, 2023. Potentially eligible studies written in English were sought with a combination of search terms (Suppl. Fig. 1). Search terms were "multiple myeloma", "cure", "operational cure", "minimal residual disease" and "long-term remission". To estimate frequencies of patients attaining 'cure' or 'operational cure', the outpatient clinic of the University of Freiburg (UKF) was methodically assessed as described in Tables 1A+B. Long-term remission or "cure" was defined as stringent complete response $\geq$5 years (sCR), with no antimyeloma therapy, no symptoms and good quality of life (QoL). Likewise, "operational cure" was assessed for/assigned to those patients in smoldering multiple myeloma (SMM) states for $\geq$5 years, asymptomatic with no CRAB symptoms, but immunofixation positive (IF+), without anti-MM treatment and with a good quality of life (Table 1B).

The term “SMM” refers to the definitions in European Myeloma Network (EMN) papers,[6,7] where indeed after successful treatment transformation from active myeloma to smoldering or almost non-existing myeloma, but with detection of the disease, was described. Representative patients were selected as case examples of cure and operational cure (Table 2). Moreover, due to the >1 ½ year enduring discussion between the 4 authors of this paper regarding “cured” and “long-term remission” MM patients, this is being assessed (not only via CS analyses,[2–4] but i.e. in the Alcyone-, Maia- or Cassiopeia-studies). If our definitions of “cured” or “long-term remission” MM patients are used, notably true plateaus do evolve (personal communication). We therefore consider this review of few but truly cured or in long-term remission-remaining patients of value to advance these and subsequent analyses.

Between 01/2022 and 6/2023, the paper draft was generated in the course of three-monthly meetings of the authors as representatives of the German Multiple Myeloma study groups (DSMM/GMMG), EMN and International Myeloma Working Group (IMWG).

**Case presentation – towards functional cure**

A 46-year-old woman was diagnosed with MM in June 2004. At the time of diagnosis, she had an IgG (32g/l) lambda (λ-Serum Free Light Chains (SFLCs): 400mg/l) subtype, ISS/R-ISS of I, standard-risk (SR) cytogenetics and bone marrow (BM) infiltration by monoclonal plasma cells (PCs) of 10%. Imaging (whole-body computed tomography (WB-CT)) showed a large extramedullary (EM) mass in the pelvis measuring 7cm in largest diameter. The Revised-Myeloma Comorbidity Index (R-MCI) score[8–10] was 2/9, indicating that she was fit for intensive treatment. Due to the large EM myeloma lesion in the pelvis, a BM infiltration of PCs of 10%, positive immunofixation (IF+), and elevated IgG and λ–SFLCs at initial diagnosis (ID), we had excluded the diagnosis of ‘solitary plasmocytoma of the pelvis and high-dose local radiotherapy as local treatment’. We thoroughly discussed this patient with the directors of the GMMG/DSMM study groups (Profs. Drs. Goldschmidt + Einsele), and due to the non-solitary nature of this IgGλ–MM had decided for systemic treatment. In 2004, the patient was enrolled in the German MM study V (DSMM-V study),[11] received a chemotherapy-based induction (idarubicin-dexamethasone), stem cell mobilization and subsequent tandem autologous stem cell transplantation (ASCT). The patient did not receive any novel agents during induction, consolidation or maintenance. The treatment was successful and the patient achieved a stringent complete remission (sCR) by February 2005 and has remained in sCR for over 16 years since achieving this milestone. The patient's risk factors for MM recurrence were relatively low. She had a SR cytogenetics profile, ISS/R-ISS of both I and a low BM infiltration. The patient's age of 46 years at the time of diagnosis was also favorable. Additionally, the patient's large EM mass in the pelvis was successfully treated with the ASCT approach. Albeit we cannot completely exclude a similarly favorable result with high-dose radiation, the BM infiltration and well-secreting IgGλ-nature of her disease did seem to exclude this. While the

definition of cure in MM is still debated, this patient's prolonged remission is a strong indication that she may have achieved a functional cure from her disease. Other selected and represented patients in long-term remission are summarized in Table 1A.

**Case presentation – Long-term disease control**

While the sustained absence of any kind of measurable disease activity is a pre-requisite for curing MM, some patients experience persistence of a very low level of detectable MM cells while either on or off treatment but remain in deep response for even decades. Disease activity in the respective patients resembles rather a monoclonal gammopathy of undetermined significance (MGUS) or low-risk SMM than overt MM requiring therapy, and is sometimes referred to as plateau phase. The term '*operational or functional cure'* has been introduced to describe such MGUS- or SMM-like behavior after successful induction therapy.[12] Definitions and typical features of cure, operational cure and incurable MM are displayed in Table 2.

The following history of a 52-year-old male who was diagnosed with MM in June 2003 represents a classical case for operational cure. His clinical characteristics included an IgG kappa (κ) subtype (IgG 60g/l, κ-SFLC: 650mg/l), an ISS/R-ISS score of I, and SR cytogenetics. The initial BM biopsy revealed an infiltration rate of 50%. No renal impairment was prevalent. The patient's R-MCI score was 2/9, indicating that he was fit to undergo ASCT. He was enrolled in the DSMM-V study and received tandem-ASCT without maintenance therapy. Ever since the completion of the second ASCT, residual monoclonal protein in the serum indicative of disease activity could be detected. Nevertheless, the patient has been in long-term remission with no evidence of disease progression. In this case, the patient has been in a state of sustained very good partial response (VGPR) for 20 years since his initial diagnosis. While the patient has low detectable levels of monoclonal protein, he does not have any clinical symptoms or end-organ damage. Other representative patients in 'operational or functional cure' are summarized in Table 1B.

Both cases demonstrate that even in the era before novel agents and molecular diagnostics, functional cure could be achieved for a very limited subset of patients. In our review, we summarize the changes in diagnostics and treatment of patients with MM in the last two decades that support the thesis that in the relatively near future, we will or are already achieving a higher proportion of deeper and durable long-term disease control in newly diagnosed MM (NDMM) patients.

**III. Historical perspectives**

The history of MM diagnostics and treatment dates back to the 19th century, when it was first described by Henry Bence Jones in 1850s as a distinct entity characterized by the presence of abnormal proteins in urine.[13] Despite the early discovery of monoclonal proteins in patients with bone destruction, hypercalcemia, anemia and renal insufficiency, MM remained a uniformly fatal disease with very limited treatment options until the late 1960s and early 1970s.

In the early days of MM treatment, the goal was primarily palliative, focused on managing symptoms such as bone pain and hypercalcemia. The only available treatments at the time were radiation therapy and high-dose corticosteroids, which provided temporary relief but failed to improve overall survival (OS). In the 1960s, the introduction of melphalan and prednisone (MP) combination therapy introduced a new era of MM treatment.[14] This regimen provided more durable responses and improved survival, making MP the standard of care for decades.

Despite these advances, the goal of MM treatment remained focused on symptom control, but provided little hope of achieving cure. However, the development of novel agents in the 1990s and 2000s marked a turning point in MM treatment. Thalidomide, a drug with anti-angiogenic properties, was found to induce responses in heavily pretreated MM patients,[15] leading to its approval in 1998. This was followed by the development of bortezomib and lenalidomide, which further expanded treatment options for MM patients. With the advent of these first-generation novel therapies, the goal of MM treatment shifted from palliation to symptom control to an increasing focus on achieving much deeper responses and prolonging survival. The earlier introduction of high-dose therapy and ASCT in the 1980s and 1990s also contributed to this shift in treatment goals.[16] ASCT was found to improve response rates and prolong survival in selected patients, and it became a standard part of MM treatment for many years in younger patients, although its role is now rapidly evolving, with the option of delayed ASCT being preferred as well as even deferred in selected patients.

However, the ultimate goal of achieving cure remained elusive. Despite significant progress in MM treatment, only a small percentage of patients achieve long-term disease-free survival.[17] This led to the development of new treatment strategies aimed at achieving deeper and more durable responses. The concept of measurable residual disease (MRD) negativity emerged as a key goal of MM treatment, with studies showing that patients who achieved MRD negativity had improved outcomes (Fig. 1).[18] Thus, cured and/or long-term remission MM patients do as yet occur with rarer incidence rates than for prostate, breast or colorectal cancer.[5] Although cure and/or long-term remission occurs less frequently for MM than for other cancers, it remains important to detect via CS analyses or definitions as introduced here. Since Germany (and other countries worldwide) suffer from “post Covid” conditions, “release of hospital capacities” – as described in the last part of our review – gains more and more attention in our society. Thus, next to the patients’ personal interest, there has been a general growing interest in the concept of operational cure in MM in recent years. This refers to patients who have achieved durable remission without ongoing therapy, even if they may still have residual disease. While true cure may remain rare, the concept of operational cure provides a new benchmark for MM treatment and is an area of active research (Tables 1A+B + Table 2).

## IV. Advances in diagnosis and prognosis

### Changes in diagnostic criteria and prognostic indicators

Advances in diagnosis and prognosis have brought about significant improvements for early detection and prognostication in MM, increasing the chances of achieving potential long-term disease control and/or functional cure. Several developments have emerged, including changes in diagnostic criteria such as the introduction of the SLiM-CRAB criteria,[19] integration of prognostic indicators like MRD assessment,[20] whole genome sequencing, and novel single-cell sequencing techniques to study the underlying disease biology.[21,22] These advances have revolutionized the field by enabling earlier detection, more accurate risk stratification, and personalized treatment strategies, ultimately enhancing the prospects of achieving long-term remission and potentially curing MM (Table 2).

One notable advancement in the diagnosis of MM was the introduction of the SLiM-CRAB criteria by the IMWG in 2014. The traditional CRAB criteria, which include hypercalcemia, renal insufficiency, anemia and bone lesions, were initially used to identify patients with active disease requiring treatment. However, they often failed to capture early-stage myeloma or rapidly evolving disease, which could delay the initiation of appropriate therapy. The SLiM-CRAB criteria address this issue by incorporating additional parameters, such as the presence of clonal BMPCs ≥60%, involved/uninvolved SFLC ratio ≥100, or >1 focal lesion on magnetic resonance imaging (MRI) or positron emission computed tomography (PET/CT). These criteria enable the identification of asymptomatic patients at higher risk of progression and facilitate early intervention, leading to improved outcomes.[23]

**Implications of early detection and prognostication for achieving functional cure**

Another crucial aspect of achieving cure in MM is accurate prognostication. MRD assessment has emerged as a treatment goal for NDMM and relapsed disease. Highly sensitive techniques, such as next-generation flow cytometry or next-generation sequencing, can detect residual malignant PCs and provide valuable information about disease burden and treatment response. MRD negativity, meaning the absence of detectable disease, has been associated with better outcomes and prolonged progression-free survival (PFS) and OS. By utilizing MRD assessment, clinicians can tailor treatment strategies based on individual response, intensifying therapy for patients with persistent MRD positivity or de-escalating treatment for those achieving deep MRD negativity. This personalized approach may significantly improve the chances of achieving functional cure in MM. Representative current trials implementing MRD-testing in treatment decision-making are summarized in Table 3.

Furthermore, advances in sequencing technologies, such as affordable whole genome sequencing and multi-omic single-cell assessment of malignant PCs as well as non-malignant cells of the surrounding microenvironment, have transformed our understanding of the molecular landscape of MM.[24–26] These techniques allow for comprehensive analysis of the genetic alterations and clonal heterogeneity present within the tumor cells. Whole genome sequencing provides a detailed view of the entire DNA sequence of a patient's tumor, enabling the identification of potential driver

mutations, therapeutic targets but also modes of resistance to targeted therapies like CAR-T cells and personalized treatment approaches. Single-cell sequencing takes this analysis a step further by characterizing the genetic and phenotypic heterogeneity within individual tumor cells. These advanced genomic techniques have revealed important insights into disease progression, treatment resistance and mechanisms of relapse. By deciphering the underlying genetic complexity of MM, clinicians can develop targeted therapies and personalized treatment regimens that address the unique molecular characteristics of each patient's disease to eradicate MRD. By using single cell and whole genome sequencing approaches, modes of resistance to anti-B cell maturation antigen (BCMA) CAR-T cells[27,28] as well as predicting the response to T cell engaging therapies have been successfully studied (Table 4 + Fig. 2).[29] As yet, nevertheless, personalized/tumor agnostic approaches in MM have largely failed: in a recent paper by Andreozzi et al,[30] survival intervals were comparable in the agnostic ("molecular-oriented", MO) vs. physician's choice groups. Weakness of this study was the limited number of patients treated with the MO approach, and other challenges in MM such as the high mutational load, PC heterogeneity and absence of unifying driver events.[31] Widespread biomolecular techniques and improvement of precision medicine treatment algorithms could nevertheless improve selection for precision medicine in MM, a vision that personalized- or molecularly-driven cancer experts thrive to also achieve in MM.[31]

In addition to enhancing early detection and prognostication, these advances have also paved the way for further development of novel therapeutic approaches in MM. Precision medicine, which focuses on tailoring treatment to an individual's unique genetic profile, has gained significant momentum with the integration of genomic technologies. The identification of specific genetic alterations and dysregulated pathways in myeloma cells has allowed the development of targeted therapies aimed at disrupting these mechanisms. For example, the BRAF V600E mutation that can be detected in patients with therapeutic opportunity,[32,33] as well as several others, including the novel peptide drug conjugate melflufen[34] or the potent CELMoD mezigndomide.[35]

**V. Treatment strategies for potentially achieving cure**

Although the approval of every new agent for the treatment of NDMM challenges the continued role of ASCT, delineating transplant-eligible (TE) from transplant-ineligible (NTE) patients remains an important step to define first-line therapy in MM. The latest studies comparing novel agent-based three drug regimens alone or in combination with ASCT and continued maintenance until progression still favor ASCT, especially with regard to PFS benefit.[36,37] Importantly, however, to date, no OS benefit has been shown in these large, randomized studies with mature follow-up when compared to delaying transplant and/or keeping it in reserve. However, including a CD38mAb during induction therapy has led to unprecedented rates of deep remissions before and after ASCT.[38–41] Currently, the results from trials investigating quadruplet induction regimens alone (i.e. Cepheus: NCT03652064) or in combination with ASCT (i.e. ISKIA: NCT04483739 and Perseus: NCT3710603, Table 3) are available and confirm the benefit of this approach.[42,43] Therefore,

induction therapy with a CD38mAb in combination with a proteasome inhibitor, immunomodulatory drug and dexamethasone followed by ASCT and lenalidomide maintenance can be considered a standard of care for most TE NDMM patients today. The high rates of sustained MRD-negativity following such an intensive treatment regimen - especially in SR patients – legitimizes optimism towards a higher functional cure fraction compared to previous reports in TE patients before the introduction of quadruplet induction regimens. There are currently several ongoing trials recruiting NDMM patients that implement intensive frontline therapies and MRD testing aiming at functional curing at least SR patients (Table 3). Whether or not functional cure can also be achieved in NTE patients is currently also under consideration. Data from the MAIA and ALCYONE phase III clinical trials that incorporated daratumumab into treatment of NTE, newly diagnosed patients demonstrated encouraging MRD negativity rates even in frail patients.[44–48] However, longer follow-up is needed to show whether subgroups of patients enrolled in novel frontline trials with CD38mAbs can achieve long-term, sustained complete remission and hence potential functional cure.

**Novel therapies and combination approaches with potential for cure**

While ASCT has been a valuable option for eligible patients, most patients with NDMM are deemed NTE due to various factors. However, recent advances in immunotherapy, specifically chimeric antigen receptor (CAR)-T cell therapy and bispecific antibodies, offer promising alternatives that may revolutionize the treatment landscape for myeloma patients, including those who are unable to undergo ASCT. Several clinical trials investigating BCMA-targeted CAR-T cells have demonstrated promising outcomes.[49–55] Early-phase studies have reported deep and durable responses, even in heavily pretreated patients with relapsed or refractory myeloma (RRMM). Remarkably, some patients achieved sustained MRD negativity.[51] While the long-term durability of CAR-T cell therapy in myeloma is still being evaluated, emerging evidence suggests it could provide a potential curative option, also for NTE patients. Currently, there are several clinical trials investigating the role of CAR-T cell therapy in frontline treatment for TE and NTE patients. These trials will not only answer the question, whether CAR-T cell therapy will replace ASCT, but will also provide evidence whether CAR-T cell therapy represents a curative option in MM. Despite the significant advances of CAR-T cell therapy, there are several unanswered questions that need to be addressed in the future: Besides clinical factors that need to be defined to identify patients who might profit the most from CAR-T cell therapy, there are also socioeconomic challenges that require thorough assessment. The respective issues are connected to the limited availability of manufacturing slots, the substantial costs and financial toxicities for individuals and health care systems as well as regional and racial disparities when it comes to access to CAR-T cell therapy or other higher-priced therapy options.[56–59] Even if CAR-T treatments do provide a potentially curative option for MM patients, only a relatively small number of privileged patients in certain regions of the world with well-resourced health care jurisdictions can afford to derive benefit from this important innovation as of now.[56,58,59]

Bispecific antibodies represent another novel therapeutic approach that holds significant potential in MM treatment. A major advantage compared to CAR T cellular-based therapies include the immediate “off-the-shelf” availability and the broader availability outside tertiary centers, although they remain costly and still require additional hospitalization for step-up dosing that can last several weeks. These engineered molecules simultaneously bind to tumor-associated antigens, such as BCMA, GPRC5D or FcRH5 on MM cells and CD3 on T cells, facilitating the formation of a cytotoxic immune synapse.[60] By bridging cancer cells and immune cells, bispecific antibodies enhance the immune system’s ability to target and eliminate malignant PCs. Early clinical trials showing unprecedented rates of long-lasting and deep remissions in triple-class exposed RRMM patients, have led to the approval of teclistamab and talquetamab by the Food and Drug Administration (FDA) as well as the European Medicines Agency and others to be expected soon.[61,62] Ongoing trials are now investigating bispecific antibodies in combination with established anti-myeloma drugs in earlier lines. Preliminary experiences from these respective clinical trials and the unprecedented rates of MRD negative remission in heavily pretreated RRMM patients support optimism regarding effectiveness in earlier disease. Unanswered questions regarding the application of bispecific antibodies exist towards the optimal treatment duration, intensity and the prevention of severe side effects, especially including the high rate of life-threatening infections.[63] These points need to be addressed to definitively include bispecific antibodies in curative treatment strategies, since a patient who is still under continuous treatment and susceptible to potentially fatal side effects such as overwhelming infection cannot reasonably be considered cured. New strategies, including fixed duration of treatment, that are accompanied by a thorough program to mitigate infectious complications as one example, are clearly warranted.

## VI. Patient factors and barriers to cure

### Age, fitness, and other factors that impact treatment

While advancements in diagnostic, prognostic and treatment options have improved outcomes for many patients, individual characteristics can impact the effectiveness of therapies and the overall chances to achieve cure. Advanced age is often associated with poorer outcomes in MM.[64] Older patients may have comorbidities and reduced physiological reserves, making them more susceptible to treatment-related toxicities and complications.[10,64] However, it is important to note that chronological age alone should not dictate treatment decisions as shown in numerous pro- and retrospective analyses of both ASCT and non-ASCT patients. A study by Straka et al.[65] randomized patients up to the age of 70 years to no induction but upfront Mel-140 tandem-ASCT vs. standard induction-tandem-ASCT. Various aspects of the study were noteworthy, such as the number of patients (n=434) being included, their more advanced age for tandem-ASCT (60-70 years), double transplant approach, and short treatment duration (7.7 months with induction and 4.6 months without induction). On an intention-to-treat basis, median PFS with vs. without induction were comparable with 21.4 and 20.0 months, respectively (p=0.36). Patients aged $\geq$65 years (55%) did

not have an inferior outcome. Patients with low-risk cytogenetics (absence of del17p13, t(4;14) and 1q21 gains) showed a favorable OS. In another study from Germany presented by Straka at the annual meeting of the American Society of Hematology in 2022, 348 patients between the age of 60-75 years were randomly assigned to either continuous treatment with lenalidomide/dexamethasone (Rd) or a 3 cycle Rd induction therapy followed by reduced-intensity (Mel-140) single or tandem-ASCT and lenalidomide maintenance.[66] While there were no significant differences in PFS and OS after a median follow-up of 68 months, an encouraging median OS of 87 and 96 months were observed, respectively, highlighting that even before the introduction of anti-CD38 antibodies, elderly patients had a meaningful likelihood of experiencing long-term remission. These data also demonstrate that in certain patient subgroups the clinical benefit from the addition of intensive chemotherapy and ASCT may be limited. A similar observation was made in the DETERMINATION study, where African American patients failed to achieve the same PFS gain as others, and appeared to do better with ASCT being kept in reserve.[67] Therefore, the overall health status, other pathobiological conditions, and functional age of patients should always be considered.[67] To objectify biological health, several scoring systems to quantify fitness and frailty in MM have been established.[10,64,68,69] While frail patients are usually not considered transplant-eligible, the introduction of CD38mAbs led to improved outcomes in this difficult to treat population[70,71] which usually represents the largest portion of patients treated outside of clinical trials and tertiary centers, given that the median age of diagnosis in MM is approximately 70 years.[72] Future studies will show, whether functional cure can only be achieved in fit patients or if adaptive and/or adoptive immunotherapy such as CAR-T cells and bispecific antibodies may provide similar functionally curative options for elderly and/or frailer patients.[73] Furthermore, psychological and social support can significantly impact a patient's ability to cope with the challenges of MM treatment.[74] Patients with robust support networks, exercise and fitness training,[69,75,76] and access to psychological support services often experience improved treatment adherence, better quality of life (QoL) and potentially better treatment outcomes.[77] Additionally, patients who are embedded in a stronger social support system might gain better access to novel therapies, including clinical trials, not least through the encouragement, advocacy and support of caring family and friends.

**The role of supportive care in achieving cure**

With the increasing number of available agents to treat MM and the higher rates of deep, long-lasting remissions, supportive care remains vitally important in the management of MM, especially with the aim of long-term control and/or functional cure of the disease. Historically, symptom management such as alleviating bone pain, addressing side effects like peripheral neuropathy (PN) and improving bone health with bisphosphonates or receptor activator of nucleus factor beta ligand (RANKL) antibodies are at the center of supportive care in MM.[78] To ensure that patients re-enter their normal life after the diagnosis and potentially curative treatment, additional areas need to be addressed. Supportives should include psychological counseling, exercise programs,

psychotherapy, support groups, and relaxation techniques to address physical fitness, emotional distress, anxiety, depression and fears associated with the disease. Additionally, the importance of diet on general health and the effect on deep remission and follow-up treatment has been recognized in recent years.[79] Beneficial effects of plant-based diets have been shown in NDMM[80] and fasting diets may be associated with improved immune function in cancer patients making this an important and exciting area of study in MM.[81] Maintaining adequate nutrition is crucial for optimizing treatment outcomes and supporting the body's ability to tolerate therapy. Nutritional counseling and support from dietitians can help address dietary deficiencies, manage treatment-related changes in taste or appetite, and provide guidance on maintaining a healthy diet during and after treatment.

Preventing infections and managing them optimally is another highly crucial aspect of supportive care in the journey of any MM patient and particularly towards the goal of potential functional cure for MM.[63] Patients with MM are particularly susceptible to infections due to immune system dysfunction caused by the disease itself and treatment-related immunosuppression. Prophylactic measures, such as antimicrobial and antiviral agents as well as vaccinations following treatments are mandatory (such as in the first six months following ASCT or CAR-T cell therapy to reduce the risk of infections and their associated complications).[63] Additionally, intravenous immunoglobulin (IVIG) substitution therapy should be considered in most cases,[82] especially in patients treated with CAR-T cell therapy and bispecific antibodies. IVIG, derived from pooled human plasma, contains antibodies that provide passive immunity against various infectious agents. For myeloma patients with hypogammaglobulinemia (e.g. IgG <400mg/dl) or recurrent severe infections, IVIG should be administered monthly and typically over at least six months to supplement deficient antibodies and reduce the risk of infections .

Ideally, these respective safety measures are implemented during the first months following a potentially curative treatment and then discontinued after recovery of the patient’s immune system. However, long-term data on immune reconstitution following CAR-T cell therapy and discontinuation of bispecific antibodies after achieving a deep and sustained remission are currently undergoing study and further data will be required before definitive recommendations can be made.

## VII. Future strategies and directions

### Advances in genomics and personalized medicine

Deciphering the human genome accounted for costs of approximately one million US dollars in 2007. Currently, these costs have decreased to several hundred US dollars per patient. Furthermore, novel single cell multi-omic analyses have been developed to study tens of thousands of malignant myeloma cells and non-malignant individual cells to better characterize an individual’s immune system. These developments are leading to a better understanding of outcome with novel immunotherapies to reveal modes of resistance to treatment. Examples are the pretherapeutic T cell landscape that is connected to response to bispecific antibodies[29] and the biallelic loss of antigens

like BCMA on MM cells.[27,28] Additionally, the respective genetic information may be used in the future for personalized treatment decisions based upon these findings. Examples include the targeting of BRAF V600E mutation as well as the effectiveness of BCL2 inhibitors in patients with high BCL2 expression in malignant PCs as often but not exclusively observed in patients harboring a (11;14) chromosomal abnormality.[83] However, malignant PCs are not homogeneously distributed within the patient. Therefore, the emerging concept of spatial genomic heterogeneity needs to be addressed,[84–87] especially when aiming at eradicating MRD and potentially curing patients with MM.[88] As personalized approaches continue to evolve, the ability to translate clinical trial findings to real world practice is likely to improve.[89]

**Implications of achieving cure in MM for healthcare systems and society as a whole**

Implementing the goal of cure into myeloma care has obvious implications for our healthcare systems and for society in addition to profound implications for each MM patient. The incidence and prevalence of MM has significantly increased over the last several decades.[90] Given the improved diagnostic and therapeutic options now available, changes in strategy from the past to the future aim for functional cure as summarized in the Table 4.

Patients are now diagnosed earlier and survive longer with the disease compared to the past.[23] However, current treatments are applied until progression which supposes a significant burden on healthcare resource utilization. The vision of curing MM patients with and ultimately achieving a fixed duration of treatment would not only alleviate side effects but would also be more cost effective compared to continuing the application with multiple lines of therapy. In addition to this cost reduction, curing myeloma would also have implications for healthcare resource allocation. Currently, MM requires long term treatment and management which also places a substantial burden on healthcare providers. Achieving functional cure of MM would redirect these resources potentially to other areas of need so easing the demands on hospital resources and reducing the needs for ongoing treatment. Furthermore, when an individual encounters MM this can lead to reduced productivity and possible unemployment due to treatment-related side effects and physical limitations.[4,69,91] Ultimately fostering a cure for MM would empower patients and the community, and instill positivity, so inspiring others with not least a reinforcement of belief in the value of medical science, and its potential for overcoming great and seemingly impossible challenges.

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**Table 1A. Multiple myeloma (MM) examples of patients achieving long-term remission and cure (University of Freiburg, UKF)**

Definition of 'cure': sCR ≥5years, Ø therapy, Ø symptoms/SLIM-CRAB, IF:-, QoL: good. Frequency search outpt clinics$_{UKF,\ 1.1.2023\text{-}31.3.2023}$: n=190 MM pts: 5 CR (5/190=2.6%)

| # | Age ID | m/f | ID MM | Risks (ISS, CC, BM, RI, R-MCI) | MM-therapy | ASCT: Y/N | Maintenance: Y/N | Remission duration |
|---|---|---|---|---|---|---|---|---|
| 1 | 46 | f | 6/2004 | IgGl, ISS/R-ISS I, SR, 10%, large EM MM pelvis (7cm), Ø RI, R-MCI: 2/9=fit | R->DSMMV+Tandem-Tx | Y: Tan-Mel200 | N | sCR since 2/2005 = +18y |
| 2 | 45 | m | 10/2009 | IgAl, ISS/R-ISS I, SR, 20%, Ø RI, R-MCI: 2/9=fit | DSMMXII: RAD, CE+Tandem-Tx | Y: Tan-Mel200 | Y: R | sCR since 6/2010 = +13y |
| 3 | 52 | f | 12/2010 | IgGk, ISS/R-ISS II, SR, 80%, Ø RI, R-MCI: 2/9=fit | VCD, IEV, Tx | Y: Mel200 | N | sCR since 9/2011 = +12y |
| 4 | 46 | m | 4/2012 | IgGk, ISS/R-ISS I, SR, 30%, Ø RI, R-MCI: 4/9=interm. | VCD, EVC, Tx | Y: Mel200 | N | sCR since 9/2012 = +11y |
| 5 | 74 | f | 6/2017 | k-LC, ISS/R-ISS I, unfavorable (1q,del20p), 40%, Ø RI, R-MCI: 5/9=interm. | VRd, CE, Tx | Y: Mel140 | Y: Vd | sCR since 6/2018 = +5y |
| ∑<br>**Median/ Mean (range)** | **46 / 52 (45-74)** | **f: 3, m: 2** | **2004-2017** | **ISS/R-ISS I: 4, II: 5, SR: 4**<br>**BM: 30 / 40 (10-80)**<br>**Ø RI: 5**<br>**R-MCI: 2 / 3 (2-5)** | **Tx: 5** | **Tandem-Tx: 2** | **Maintenance: 2** | **12 / 12 y (5-18)** |

**Abbreviations and definitions**: sCR: stringent complete remission, Ø: no; IF: immunofixation serum and urine; QoL: quality of life; oupt: outpatient clinic at university of Freiburg; pts/pt: patients/patient; ID: initial diagnosis; m/f: male/female; ISS: international staging system; CC: cytogenetics (FISH); BM: bone marrow infiltration of plasma cells; R-MCI: revised myeloma comorbidity index; ASCT: autologous stem cell transplantation; Y/N: yes/no; EM: extramedullary site of MM lesion; RI: renal impairment; DSMM: German MM study group Würzburg; Tan=Tandem; y: years; DSMMV: idarubicin-dexamethasone-induction with tandem-Tx in TE NDMM; RAD: lenalidomide, adriamycin, dexamethasone; CE: cyclophosphamide/etoposide; R: lenalidomide; VCD: bortezomib, cyclophosphamide, dexamethasone, IEV/EVC: ifosphamide, epirubicine, etoposide; Mel140/200: melphalan-conditioning; VRd: bortezomib, lenalidomide, dexamethasone; Tx: ASCT; +: ongoing; ∑: summary of cases with median/mean provided (whenever appropriate)

**Table 1B. Multiple myeloma (MM) examples of patients achieving states of smoldering disease (SMM) (University of Freiburg, UKF)**
Definition SMM-transformation ≥5years, VGPR, Ø therapy, Ø symptoms/SLIM-CRAB, IF:+, good QoL. Frequency search outpt clinics$_{UKF,\ 1.1.2023\text{-}31.3.2023}$: n=190 MM pts: 7 in long-term VGPR (7/190=3.7%)

| # | Age ID | m/f | ID MM | Risks (ISS, CC, BM, RI, R-MCI) | MM-therapy | ASCT: Y/N | Maintenance: Y/N | Remission duration |
|---|---|---|---|---|---|---|---|---|
| 1 | 52 | m | 6/2003 | IgGk, ISS/R-ISS I, SR, 50%, Ø RI, R-MCI: 2/9=fit | DSMMV, IEV+Tandem-Tx | Y: Tan-Mel200 | N | VGPR; SMM since 2/2004 = +19y |
| 2 | 65 | m | 6/2010 | IgGk, ISS/R-ISS I, SR, 20%, Ø RI, R-MCI: 3/9=fit | DSMMXII: RAD, CE+Tandem-Tx | Y: Tan-Mel200 | Y: R | VGPR; SMM since 4/2011 = +12y |
| 3 | 49 | f | 4/2018 | k-LC, ISS/R-ISS II, SR, 70%, RI, R-MCI: 3/9=fit | VCD, C, Tx | Y: Mel140 | Y: Vd | VGPR; SMM since 9/2018 = +5y |
| 4 | 71 | f | 7/2014 | k-LC, ISS/R-ISS III/II, unfavorable, 20%, RI, R-MCI: 5/9=interm. | VCD, CE, Tx | Y: Mel140 | Y: Vd | VGPR; SMM since 11/2014 = +8y |
| 5 | 56 | m | 6/2017 | IgGk, ISS/R-ISS II, unfav. (del1p, del16q), 90%, RI, R-MCI: 3/9=fit. | VCD, CE, Tx | Y: Mel200 | Y: Vd | VGPR; SMM since 8/2017 = +6y |
| 6 | 45 | m | 2/2008 | IgAl, ISS/R-ISS I, SR, 20%, Ø RI, R-MCI: 5/9=interm. | DSMM XI: VCD, IEV, Tx | Y: Tan-Mel200 | Y: R | VGPR; SMM since 12/2014 = +8y |
| 7 | 41 | f | 6/2008 | IgGl, ISS/R-ISS I, SR, 40%, Ø RI, R-MCI: 2/9, SPM (BC->CR) | DSMM XI: VCD, IEV, Tx | Y: Tan-Mel200 | Y: R | VGPR; SMM since 12/2014 = +8y |
| **∑ Median/ Mean (range)** | **52 / 54 (42-71)** | **f: 3, m: 4** | **2003-2018** | **ISS/R-ISS I: 4, II: 3, SR: 5 BM: 40 / 40 (20-90) Ø RI: 4 R-MCI: 3 / 3 (2-5)** | **Tx: 7** | **Tandem-Tx: 4** | **Maintenance: 6** | **8 / 9 (5-19)** |

**Abbreviations and definitions**: VGPR: very good partical reponse, Ø: no; IF: immunofixation serum and urine; QoL: quality of life; oupt: outpatient clinic at university of Freiburg; pts/pt: patients/patient; ID: initial diagnosis; m/f: male/female; ISS: international staging system; CC: cytogenetics (FISH); BM: bone marrow infiltration of plasma cells; R-MCI: revised myeloma comorbidity index; ASCT: autologous stem cell transplantation; Y/N: yes/no; EM: extramedullary site of MM lesion; RI: renal impairment; DSMM: German MM study group Würzburg; Tan=Tandem; y: years; RAD: lenalidomide, adriamycin, dexamethasone; CE: cyclophosphamide/etoposide; R: lenalidomide; VCD: bortezomib, cyclophosphamide, dexamethasone, IEV/EVC: ifosphamide, epirubicine, etoposide/ cyclophosphamide, epirubicine, etoposide; Mel140/200: melphalan-conditioning; VRd: bortezomib, lenalidomide, dexamethasone; Tx: ASCT; +: ongoing; ∑: summary of cases with median/mean provided

**Table 2. Cure and functional cure and transformation in smoldering multiple myeloma (SMM) state definitions**

| Relevant parameters | Cure >5-10 years | 'Operational cure' | Incurable |
|---|---|---|---|
| ***Definition*** | Considered less often (<10%), Sustained BM MRD- (NGS, NGF $10^{-5}$ – $10^{-6}$ levels) and imaging- (MRI, PET) for at least 1y | In younger pts, receiving most active 3-4 agent therapy (PI+ImiD+CD38ab), in combination with ASCT, followed by maintenance<br>In older pts receiving CD38ab-based therapies and w novel immunotherapies<br>Minimal levels of MRD remain + | Considered typical for most (>90%) MM pts |
| ***Patient constitution*** | Fit pts | Younger and older | Frail |
| ***Cytogenetics and disease stages*** | SR<br>ISS I/II rather than ISS/R-ISS: III | Both ISS/R-ISS: I-III | HR cytogenetics, especially del(17p)<br>ISS/R-ISS: III |
| ***Stages of MM disease when therapy is initiated*** | Treat at an earlier stage: SLIM-CRAB + HR SMM states | Treat with SLIM-CRAB | Treat with severe and multiple CRAB symptoms (i.e. 4/4), dense BM infiltration and unresolving organ impairment |
| ***Therapy modalities*** | With ASCT, tandem-ASCT, allo-SCT, possibly CAR-Ts+BITES upfront | With ASCT + novel agent therapies | Unable to endure multiagent MM therapy |
| ***Lines of therapy*** | Most likely possible to be achieved with first- than later-line treatment | With first-line and later relapse? | With successive relapses |
| ***Obtained response*** | Achievement of sustained CR, IF-, MRD- | CR and VGPR, MRD may remain + | Only achievement of SD or PD or entirely non-responsive MM |
| ***Symptoms evolving and QoL*** | Sustained relief of MM symptoms ad QoL ↑ | Improved or stable MM symptoms and QoL → | No relief of MM symptoms and QoL ↓ |

**A Abbreviations:** BM: bone marrow, MRD: minimal residual disease, NGS/NGF: next generation sequencing/-Flow, MRI: magnetic resonance imaging, PET-CT: positron emission tomography-computed tomography, y: year, SR: standard-risk, HR: high-risk, ISS: international staging system; ASCT: autologous stem cell transplantation; allo-SCT: allogeneic stem cell transplantation, CARTs: chimeric antigen receptor T cells; BITEs: bispecific antibodies; CR: complete response, IF: immunofixation negative, QoL. Quality of life, PI: proteasome inhibitor, ImiD: immunemodulatory drugs, CD38ab: CD38-antibody; VGPR: very good partial response; SD: stable disease; PD: progressive disease.

**Table 3. Selected trials of those adapting multiple myeloma treatment according to MRD**

| Trial | # of pts | Primary endpoint | Treatment | MRD assessment + sensitivity | Treatment modification | Treatment restarting upon MRD+ |
|---|---|---|---|---|---|---|
| MIDAS (ph3) (NCT-4934475) | 716 | MRD- after cons | Isa-KRd induction and then randomization based on MRD | NGS (clonoSEQ) $10^{-5}$ | ASCT vs. not upon MRD achievement | N/A |
| PERSEUS (ph3) (NCT-3710603) | 690 | PFS | VRd vs. D-VRD + ASCT, Rm vs. DRm | NGS (clonoSEQ) $10^{-5}$ | MRD- pts will stop D after sustained MRD- | D restart at recurrence of MRD |
| AURIGA (ph3) (NCT-3901963) | 214 | MRD conversion at 12 ms | DRm vs Rm post ASCT | NGS (clonoSEQ) $10^{-5}$ | >VGPR + MRD+ must haves for study entry | N/A |
| DRAMMATIC (ph3) (NCT-4071457) | 1100 | OS | DRm vs Rm post ASCT | NGS (clonoSEQ) $10^{-5}$ | Each arm (D-R + R) randomly assigned to cont. vs. MRD-driven cessation of m in MRD- pts | N/A |
| OPTIMUM (ph3) (NCT-3941860) | 510 | OS, change in FACT TOI score | Rm+Ixa vs R-placebo post ASCT | NGS (clonoSEQ) $10^{-5}$ | Must have MRD+ disease prior to Rm | MRD+ pts randomly assigned to Rm+Ixa or Rm+placebo |
| University Michigan (ph3) (NCT-4140162) | 50 | MRD negativity after induction | DRd -> D-VRd cons (only in MRD+) -> DRm -> Rm | NGS (clonoSEQ) $10^{-5}$ | D-VRd cons in MRD+ pts | N/A |
| MASTER (ph3) (NCT-3224507) | 123 | MRD negativity after cons | D-KRd -> ASCT -> D-KRd cons (0-8 cycles depending on MRD)->Rm | NGS (clonoSEQ) $10^{-5}$ | Treatment stop after 2 cons MRD- evaluations | D restarted at recurrence of MRD |

**Abbreviations and definitions**:
pts: patients; ph3: phase 3 trial; PFS: progression free survival; Isa: Isatuximab, MRD: minimal residual disease, NGS: next generation sequencing, ASCT: autologous stem cell transplantation, N/A: not applicable, progression free survival, OS: overall survival, Rm: lenalidomide-, DRm: Daratumumab-lenalidomide-maintenance, m: maintenance, Rm+Ixa: Lenalidomide-Ixazomib maintenance, cons: consolidation;

kindly adapted from: Mateos, Nooka, Larson. Am Soc Clin Oncol Educ Book. 2022 Apr:42:1-12[92]

**Table 4. Possible changes in multiple myeloma: past, present, future and implications that may allow prolonged remission and possible cure**

| **MM parameters** | | **Past** | **Present** | **Future** | **Implications** |
|---|---|---|---|---|---|
| ***MM diagnostics*** | *Staging system* | Durie&Salmon | ISS -> R-ISS + SLIM-CRAB | Inclusion of molecular-determined risks | Allowing earlier MM treatment start |
| | *Disease burden measurement* | M-gradient,<br>X-ray examination of the bone | M-gradient quantification,<br>Sensitive imaging (WB-CT, -MRI, PET-CT),<br>Mass spect,<br>Circulating PCs, tumor-DNA in PB + BM<br>MRD in PB + BM,<br>Molecular diagnostics (WGS) | Further refined imaging<br>Deeper MRD<br>PB diagnostics<br>WGS | Disease burden detected earlier -> treatment advanced quicker |
| ***Treatment-related factors*** | *Treatment start* | With symptoms, i.e. CRAB | SLIM-CRAB,<br>In studies: HR-SMM | ? | Less „ice-berg“ to be diminished |
| | *Therapy duration* | For 4-6 cycles | Until progression | Defined treatment stops | With longer treatment -> deeper + prolonged remission induction<br>Stop treatment in cured patients |
| | *Therapy options* | limited | Many options, combination partners, numerous clinical trials, IO: moAb, ADC, BITES, CARTs, quadruplets and “5-agent combos” | Cure combos ? | Almost limitless treatment options |
| | *Therapeutic goal* | Symptoms control, MM-stabilization or decrease | In young+fit: CR + as deep and prolonged remission as possible<br>In elderly and unfit: disease control | Cure options in both young and elderly | |
| | *Therapy lines* | Less often: beyond 3 | 6-10 not uncommon | Cure or chronic disease transformation | |
| | *Relapse -> start of retreatment* | With CRAB=MM symptom reoccurrence | With serological progression | With MRD reversal from - -> +? | Less disease burden needing to dwindle |
| ***Patient-related factors*** | *Patient constitution* | Fit-pts: being treated<br>Unfit: BSC | Fit and unfit pts defined with treatment options for both | Unfit pts made fit again? | |
| | *Transplant limits* | <60-65 years | ≥70 years, if tested fit | Transplants deceasing? | |
| ***Outreach approaches*** | *Center-related* | Center-focused MM treatment | International exchanges, comprehensive cancer centers, IMWG/EMN consortia | Entire worldwide exchange | |
| ***Prognosis*** | *Changes in PFS + OS* | 3-5 years | 8-10 years | >10 years -> cure | Much better prognosis |

**Abbreviations:** WB-CT. whole body computed tomography, MRI: magnetic resonance imaging, PET-CT: positron emission tomography-computed tomography, mass spect: mass spectrometry (MS), PC: plasma cells, PB: peripheral blood, BM: bone marrow, HR-SMM: high-risk smoldering multiple myeloma, IO: immune oncology therapies: moAb: monoclonal antibodies, ADC: antibody drug conjugates, BITEs: bispecific antibodies, CARTs: chimeric antigen receptor T cells, pts: patients, PFS: progression free survival, OS: overall survival, EMN/IMWG: European Myeloma Network/International Myeloma Working Group

**Figures 1-3:**

**Fig. 1**. Correlation of depth of response and survival

**Fig. 2**. Strategies to attain cure or operational cure in multiple myeloma

**Fig. 3**. Future strategies to achieve cure in 1-10% of multiple myeloma patients

Fig. 1.

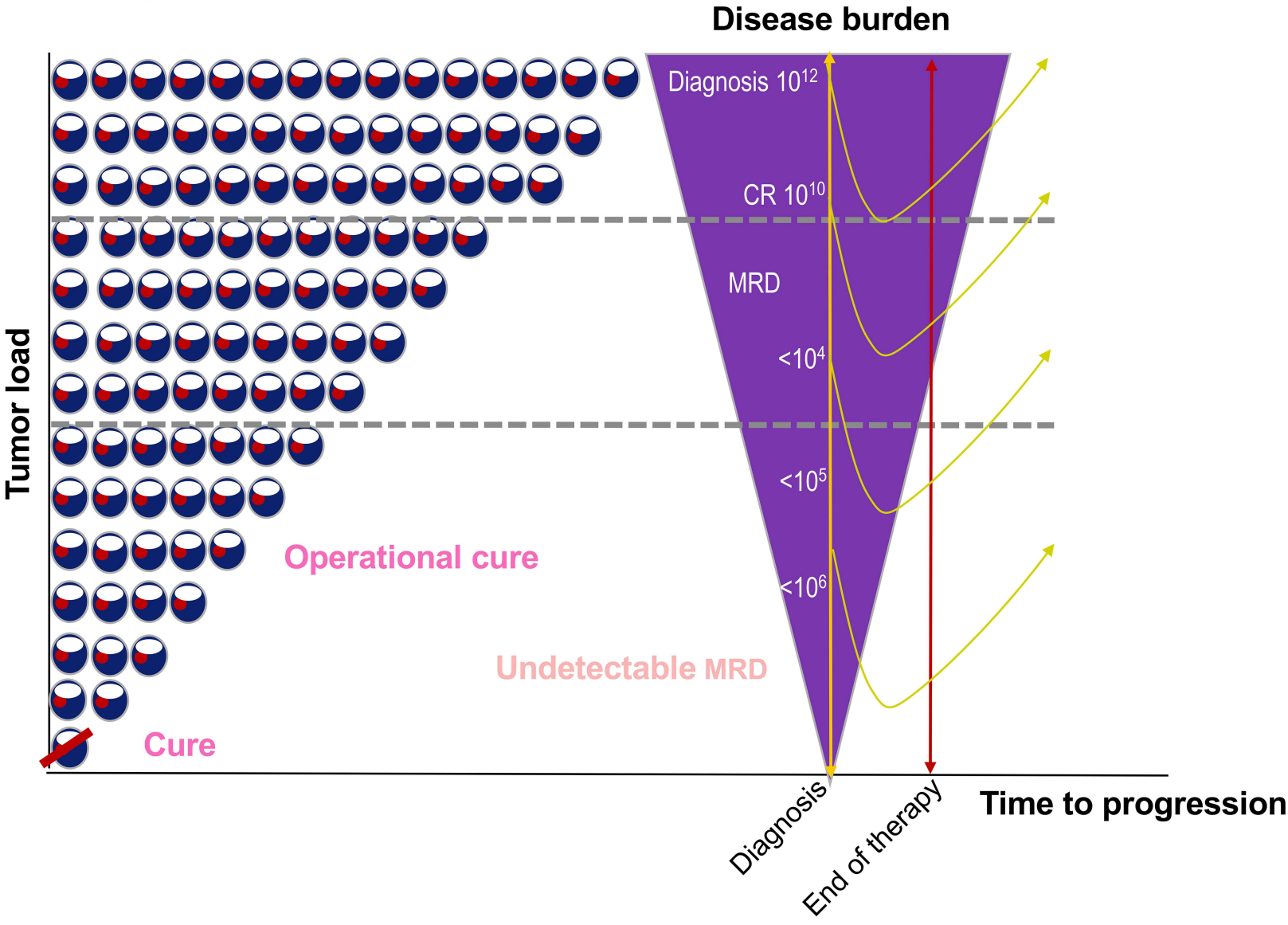
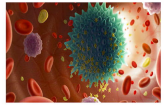

Disease burden
Diagnosis $10^{12}$
CR $10^{10}$
MRD
$<10^4$
$<10^5$
$<10^6$
Tumor load
Operational cure
Undetectable MRD
Cure
Diagnosis
End of therapy
Time to progression

Fig. 2.

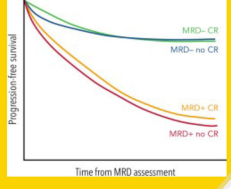
**Patient-related factors**
- Efficient tumor burden reduction
- MM-symptom control
- Tolerable side effects
- Stabilization or improvement of QoL

**Optimize patient management during treatment**
- Bone+infectious propylaxis
- Nursing support
- Self-support interventions
- Patient advocacy groups
- Physical interventions / fitness training

**Avoid resistance mechanisms**
- Combination therapy
- Novel target combos



**MRD assessment**
- Aim for sustained MRD$^-$ in BM+via imaging
- Tailor treatment with sustained MRD$^-$ >1y




**Improving T cell response and hematopoietic regeneration**
- Novel immunotherapy approaches (ITA) in clinical trials
- ASCT, Tandem-SCT, allo-SCT in trials vs. ITA
- Growth factor support
- Vaccinations

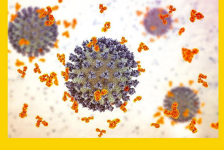
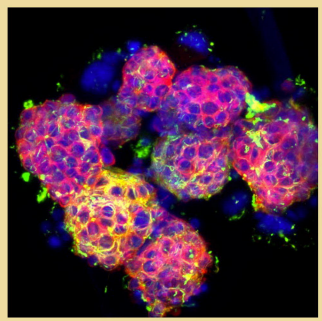


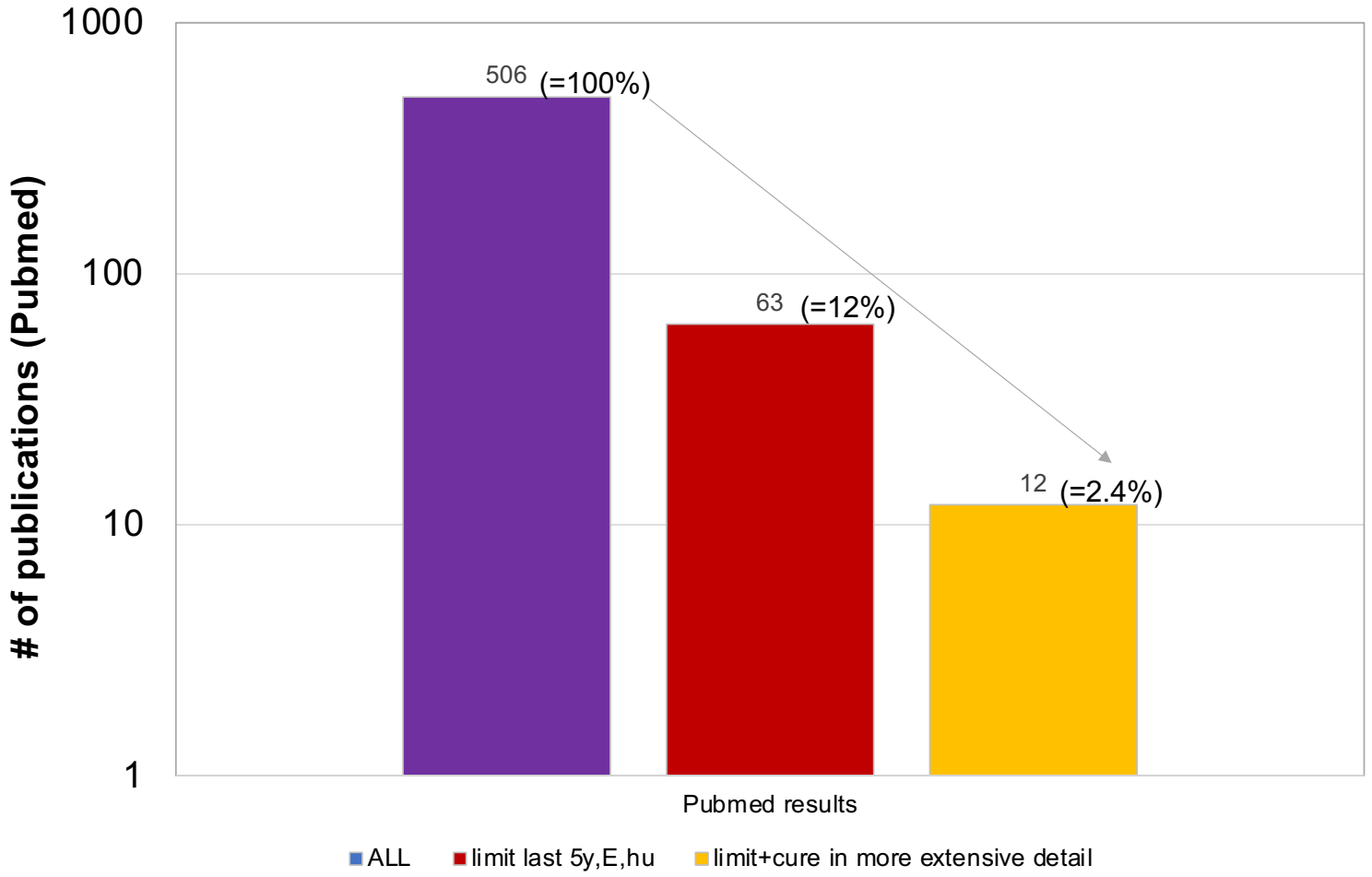
Fig. 3.


Transform to chronic disease
or cure

Irradicate disease as much as possible, forsee side effects,
preserve QoL



Understand MM biology, genetics, microenvironment, immune surveillance, response, resistance




**Suppl. Fig. 1.** Literature search „Cure + MM“ -> review process (Pubmed search „Cure AND MM“)