Aus dem Lehrstuhl
für Innere Medizin III
Prof. Dr. Wolfgang Herr
der Fakultät für Medizin
der Universität Regensburg

Biomodulatory Therapy in Multiple Myeloma – Clinical Phase I/II Trial

Inaugural – Dissertation
zur Erlangung des Doktorgrades
der Medizin

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1. Deutsche Zusammenfassung

Die langfristige Kontrolle des refraktären/rezidivierten multiplen Myeloms (RRMM) stellt für zielgerichtete Therapien immer noch eine Herausforderung dar. In der vorliegenden Arbeit wurde ein neuartigen Ansatz zur Reprogrammierung der Myelom-Homöostase untersucht, um das Wachstum von RRMM-Zellen zu verlangsamen.

In der multizentrischen prospektiven Phase-I/II-Studie für RRMM wurde eine metronomische Vierfach-Kombinationstherapie mit Pioglitazon, Dexamethason, niedrig dosiertem Treosulfan und Lenalidomid verabreicht, unabhängig von einer vorherigen immunmodulatorischen Therapie (IMiD-Therapie). Für Phase II wurde eine Lenalidomid-Dosis von 15 mg/d in Phase I als sicher eingestuft und in Phase II eingesetzt. Insgesamt wurden 47 Patienten mit einem Durchschnittsalter von 63 Jahren (47 bis 77) in die Phase I/II aufgenommen. Die mediane Nachbeobachtungszeit betrug 33,4 Monate, die mediane Anzahl der vorangegangenen Therapien 4 (2 bis 10) und die mediane Behandlungsdauer 4,7 Monate (0,2 bis 57,1).

Die objektive Ansprechrate (ORR) betrug 57,4 % (95 % CI: 42,2 bis 71,7) mit einer kompletten Remission (complete remission, CR) (2,1 %), 9 sehr guten Teilremissionen (very good partial response, VGPR) (20,5 %) und 15 Teilremissionen (partial response, PR) (34,1 %). 15 Patienten erreichten stabile Erkrankungen (stable disease, SD) (34,1%), was zu einer Krankheitskontrollrate (disease control rate, DCR) von 91,5% (95% CI: 79,6 bis 97,6) führte. Das mediane Gesamtüberleben (overall survival, OS) und das progressionsfreie Überleben (progression-free survival, PFS) betrugen 39,2 Monate (95% CI: 21,0 bis 56,2) bzw. 8,3 Monate (95% CI: 4,6 bis 16,6). Eine vorangegangene IMiD-Therapie hatte keinen negativen Einfluss auf das OS (p=0,93). Die häufigsten Nebenwirkungen (adverse events, AEs) aller Grade während des Behandlungszeitraums waren Anämie (34, 72,3 %), Neutropenie (31, 66 %) und Thrombozytopenie (26, 55,3 %). Infektionen der Grade 3 und 4 traten bei 14 Patienten (29,8%) auf.

Bei RRMM reduziert eine konzertierte Myelom-Gewebe-Reprogrammierung wirksam die Myelom-Belastung und kontrolliert das erneute Wachstum des Myeloms bei tolerierbarer Toxizität. (ClinicalTrials.gov-Kennung: NCT01010243)

Gründe für das Therapiedesign

Trotz der Fortschritte in der Behandlung durchlaufen Patienten mit multiplem Myelom (MM) häufig die Standardtherapien wie Proteasominhibitoren (PIs), immunmodulatorische Medikamente (IMiDs) und monoklonale Antikörper (mAbs) gegen CD38.

Die 92 verschiedenen Therapieschemata, die in der LocoMMotion-Studie (1) zusammengefasst sind, zeigen, dass es in der Praxis keine einheitliche Standardbehandlung für stark vorbehandelte, dreifach exponierte Patienten mit RRMM gibt, was zu schlechten Behandlungsergebnissen führt. Dies unterstreicht den Bedarf an neuen Behandlungen mit neuartigen Wirkmechanismen.
Die derzeit verfügbaren Behandlungsansätze des RRMM werden durch Chemotherapie-gekoppelte mAbs, bispezifische Antikörper und CAR-T-Zellen, die auf Myelom-assoziierte Epitope gerichtet sind, erweitert, oder sie zielen auf spezifische genetische Aberrationen wie bcl2 mit Venetoclax oder BRAFV600E mit BRAF/MEK-Inhibitoren.
Experimentelle Studien an Myelom- und Stromazellen von Patienten geben Aufschluss über das räumlich diversifizierte Myelomgewebe und die Heterogenität der Myelomzellen, einschließlich der Tumorstruktur in fokalen Läsionen. Die Heterogenität der Myelomzellnischen, die molekulargenetische und genetische Heterogenität, die Vielfalt der Zellkompartimente mit Einfluss auf das Myelomwachstum sowie die primär vorhandenen und sekundär sich entwickelnden heterogenen Resistenzmechanismen gegen zielgerichtete Therapien regen dazu an, das Therapieportfolio mit anderen pathophysiologischen Überlegungen und therapeutischen Intentionen weiterzuentwickeln (2, 3).

Anakoinosis, also das Verfahren, das die Biomodulation des Tumorgewebes erleichtert, fördert die Umprogrammierung und Zellrekrutierung im Tumorgewebe, was letztlich zur Plastizität des Tumors in Bezug auf den therapeutischen Effekt der verabreichten Substanzen beiträgt (4). Tumor-assoziierte Kommunikationslinien, die tumortypspezifische Kommunikationsprotokolle zwischen verschiedenen Tumorzellkompartimenten bilden, sollen entsprechende therapeutische Ziele von Editing-Techniken sein (5). Das Editing-Verfahren greift auf Kommunikationslinien zurück, die tumorspezifische Funktionen und phänotypische Plastizität etablieren (5).

Die phänotypische Plastizität von Myelomen besteht aus sich zeitlich und räumlich entwickelnden autonomen und nicht-autonomen Prozessen der Tumorzellen. Sie ist nicht allein durch genetische oder molekulargenetische Aberrationen zu erklären, vor allem, wenn Treibermutationen fehlen, wie bei den meisten Neoplasien. Der Reprogrammierungsprozess wird als Anakoinose oder Biomodulation bezeichnet.

Wirkstoffsynergismus und Anakoinose

Um den Tumorphänotyp bei rezidivierten oder refraktären (r/r) Neoplasien therapeutisch zu erreichen, sind zwei wesentliche Therapieelemente für die Wirksamkeit im Gewebe verantwortlich: eine niedrig dosierte metronomische Chemotherapie und eine duale oder, wie hier im Falle des RRMM, dreifache Transkriptionsmodulation. Alle Therapieelemente haben eine geringe oder gar keine Einzelwirkstoffaktivität, insbesondere wenn man die deutlich reduzierten Dosierungen der metronomischen Chemotherapie berücksichtigt.

Welchen Beitrag leisten einzelne Medikamente ohne signifikante Monoaktivität zu Ansätzen der Tumorgewebebearbeitung?

Arzneimittelinteraktionen können vielfältig sein. Steel et al. führten den Begriff "Coalism" für Medikamente ein, die allein nicht aktiv sind, die jedoch in "Kooperation" aktiv sind, wenn die kombinierte Wirkung auf eine Reihe von biologischen Systemen gerichtet ist (6, 7). Dies gilt zum Beispiel für Pioglitazon. Im nächsten Schritt sind die biologischen Systeme und ihre Zielprofile, die für die Reprogrammierung von Krebsmerkmalen zur Verfügung stehen, von zentralem Interesse.

Die Anakoinose oder Biomodulation, die die therapeutisch beabsichtigte kommunikative Umprogrammierung von Tumorgeweben beschreibt, umreißt ein neuartiges systemtherapeutisches Behandlungsparadigma zur Krebsbekämpfung. Sie beschreibt die therapeutische Freisetzung und Nutzung tumorspezifischer Phänotypen zur Kontrolle von r/r-Metastasen durch Umprogrammierung von Krebsmerkmalen, hier des Multiplen Myeloms, und die "Normalisierung" der gestörten Homöostase von Tumorgeweben. Bestimmend für das qualitative Ergebnis der pro-anakoinotischen Therapie sind die ausgewählten Medikamente, die spezifischen Muster pro-anakoinotischer kommunikativer Gewebenetzwerke auf der Tumorseite und der homöostatische Ausgleich von Krebsmerkmalen (4).

Noch unzureichend erforscht sind die tumorspezifischen Netzwerkcharakteristika, die die „Hallmarks“ des Multiplen Myeloms koordinieren und die systembiologischen Voraussetzungen zur Entschlüsselung der Myelom-spezifischen Phänotypen. Daher ist es nur möglich, die bisher bekannten Wirkprinzipien der Anakoinose zu beschreiben. Hierzu zählen die quantitative und qualitative Veränderungen des Tumorphänotyps, die Entzündungskontrolle, Differenzierungsinduktion, und klinische Outcome-Parameter, wie langfristige Krankheitskontrolle oder komplette Remission (CR) bei metastasierten r/r-Neoplasien (5).

Es hat sich gezeigt, dass Tumorgewebe-Editing-Konzepte die Ausbreitung von Metastasen, die Neubesiedlung von Krebs und die erworbene Resistenz von Tumorzellen (metastatic spread, cancer repopulation and acquired tumor cell resistance, M-CRAC) wirksam eindämmen oder beseitigen können, indem sie tumorassoziierte Merkmale umlenken, die das Wachstum dämpfen und alternative Muster des Tumorzelltods bei r/r-Tumorerkrankungen induzieren. So können klinische Versuche mit Editing-Konzepten eine langfristige Tumorkontrolle, ein objektives Ansprechen oder sogar ein vollständiges klinisches Ansprechen (clinical completer response, cCR) bewirken (8).

Bei r/r Hodgkin-Lymphomen und metastasierten Melanomen konnte gezeigt werden, dass das Gewebe-Editing die Wiederherstellung der IMiD-Empfindlichkeit fördern kann (5).

Wir haben auf dieser Grundlage eine Studie für RRMM konzipiert, in der wir die Hypothese aufstellten, dass die IMiD-Resistenz durch Myelom-Gewebe-Editing-Ansätze überwunden werden kann und dass das multiple Myelom wieder empfindlich auf die IMiD-Therapie reagieren kann. Dies konnte durch die Fortsetzung der IMiD-Therapie während des therapeutischen Gewebe-Editings gemäß dem Studienprotokoll nachgewiesen werden.

2. Abstract

Long-term control of refractory/relapsed multiple myeloma (RRMM) is still challenging for myeloma cell-directed therapies. We investigated a novel approach reprogramming myeloma homeostasis for attenuating MM cell growth.

The multicenter prospective phase I/II trial for r/rMM implemented metronomic quadruple combination therapy with pioglitazone, dexamethasone, low dose treosulfan, and lenalidomide, irrespective of previous IMiD therapy. For phase II, a lenalidomide dose of 15mg/d was deemed safe in phase I and employed in phase II. Altogether 47 patients with a median age of 63 years (range 47 to 77) were included in phase I/II. The median follow-up was 33.4 months, the median number of prior therapies 4 (range 2 to 10), and the median treatment duration 4.7 months (range 0.2 to 57.1).

Objective response rate (ORR) was 57.4% (95% CI: 42.2 to 71.7) with one complete remission (2.1%), 9 very good partial remissions (20.5%), 15 partial remissions (34.1%). 15 patients achieved stable diseases (34.1%), resulting in a disease control rate (DCR) of 91.5% (95% CI: 79.6 to 97.6). Median overall (OS) and progression-free survival (PFS) were 39.2 months (95% CI: 21.0 to 56.2) and 8.3 months (95% CI: 4.6 to 16.6), respectively. Previous IMiD therapy did not impact negatively on OS (p=0.93). Most common all-grade AEs during the treatment period

were anemia n= 34, (72.3%), neutropenia n=31 (66%) and thrombocytopenia n=26 (55.3%). Grade 3 and 4 infections occurred in 14 patients (29.8%).
In r/rMM, a concertedly myeloma tissue reprogramming, tissue 'editing' therapy, efficaciously reduces myeloma burden and controls myeloma regrowth at tolerable toxicity. (ClinicalTrials.gov Identifier: NCT01010243)

Rational for the therapy design

Despite treatment advances, patients with multiple myeloma (MM) often progress through standard drug classes including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs).
The 92 different regimens summarized in the LocoMMotion review (1) demonstrate a lack of clear real-life standard of care (SOC) for heavily pretreated, triple-class exposed patients with RRMM in real-world practice and result in poor outcomes. This supports a need for new treatments with novel mechanisms of action.
The currently available treatment approaches successfully advance treatment in relapsed or refractory multiple myeloma (RRMM) with chemotherapy coupled mAbs, bispecific antibodies and CAR-T-cells directed to myeloma-associated epitopes or aim at targeting specific genetic aberrations, bcl2 with venetoclax or BRAFV600E-mutated multiple myeloma with BRAF/MEK inhibitors.
Experimental studies on myeloma and stroma cells from patients reveal insights into the spatially diversified myeloma tissue, the heterogeneity of myeloma cells, including the subclonal structure in focal lesions. Heterogeneity of myeloma cell niches, molecular-genetic and genetic heterogeneity, the diversity of cell compartments with impact on myeloma growth, primarily present and secondarily developing heterogeneous resistance mechanisms to targeted therapies stimulate to advance the therapy portfolio with basically different operative pathophysiologic considerations and therapeutic intensions (2, 3).

The operational procedure facilitating tumor tissue editing, i.e., anakoinosis, promotes therapy-initiated reprogramming and cell recruitment in tumor tissues, that finally contributes to the tumors' plasticity in therapeutic intention (4). Tumor-associated supervising communication lines, that cumulatively constitute tumor-type specific communication protocols among different tumor cell compartments are supposed to be respective therapeutic targets of editing techniques (5). The editing procedure takes recourse on communication lines establishing tumor-specific

functions and phenotypic plasticity. Extend and quality of tumor systems' plasticity reflects evolutionary systems states, developmental and medical histories of tumor diseases (5). Myelomas' phenotypic plasticity is constituted by timely and spatially developing tumor cell autonomous and non-autonomous processes and cannot be described by genetic or molecular genetic aberrations only, particularly, if driver mutations are absent, as in most neoplasias. The reprogramming process is termed anakoinosis in anticipation of future descriptions of communicative lines describing the molecular background of the respective pharmacologic interactions on the tissue level in more detail.

Drug synergism and anakoinosis

For unlocking tumor phenotypes in relapsed or refractory (r/r) neoplasias, two major therapy elements are necessary for tissue editing: low dose metronomic chemotherapy and dual or triple transcriptional modulation, in case of RRMM triple modulation. All therapy elements have poor or no single agent activity, particularly when considering the scheduled dose reductions of metronomic chemotherapy.

How do single drugs without significant monoactivity contribute to tumor tissue editing approaches?

Drug interactions may be considered in a traditional way. Steel et al. introduced the term 'coalism' for drugs that are not active alone, or active in 'cooperation' if the combined effect is directed on a range of biologic systems (6, 7). This applies for pioglitazone. In the next step, the targeted biologic systems, and their target profiles that are available for reprogramming hallmarks of cancer, are of pivotal interest.

Anakoinosis, describing the therapeutically intended communicative reprogramming of tumor tissues, outlines a novel systems-therapeutic anticancer treatment paradigm, the therapeutic unlocking and exploitation of tumor specific phenotypes for controlling r/r metastatic disease by reprogramming cancer, here multiple myeloma hallmarks and 'normalizing' dysbalanced tumor tissue homeostasis. The selected editing techniques, on tumor site the specific patterns of pro-anakoinotically druggable communicative tissue networks, and homeostatically balancing of cancer hallmarks, are determining the qualitative outcome of pro-anakoinotic reprogramming techniques (4).

Still insufficiently evaluated are the tumor-specific network characteristics coordinating multiple myeloma hallmarks, the key parameters determining the specific relevance of distinct hallmarks in the systems context, and the systems-biologic prerequisites how to specifically unlock the multiple myeloma-promoting phenotypes. Therefore, it is only possible to draw on an effect-based description of anakoinosis, that records quantitative and qualitative changes in tumor phenotypes, here inflammation control, differentiation induction, and clinical outcome parameters, such as long-term disease control or complete remission (CR) in metastatic r/r neoplasias (5).

Tumor tissue editing approaches turned out to efficaciously control or resolve metastatic spread, cancer repopulation and acquired tumor cell resistance (M-CRAC) by redirecting cancer associated hallmarks into biologic hallmarks attenuating tumor growth and induction of alternative patterns of tumor cell death in r/r tumor disease. As shown, clinical trials using editing approaches may induce long-term tumor control, objective response or even clinical complete response (cCR) (8).

Reconstitution of IMiD sensitivity and edited non-oncogene addiction

Data from r/r Hodgkin's lymphoma and metastatic melanoma have shown that tissue editing may facilitate edited non-oncogene addiction for mTOR (5).
We designed a study for RRMM, hypothesizing that IMiD resistance might be overcome by myeloma tissue editing approaches, and that multiple myeloma may regain sensitivity to IMiD therapy as may be shown by continuation of IMiD therapy during therapeutic tissue editing according to study protocol.

3. Theoretical Background

3.1 Main Characteristics of Multiple Myeloma

3.1.1 Epidemiology, Clinical Appearance and Survival Prognosis

Multiple myeloma is characterized by the malignant proliferation of fully differentiated plasma cells, which produce either monoclonal immunoglobulins or, less frequently, monoclonal free light chains (9). The subtypes of multiple myeloma are defined by the immunoglobulin they produce: Most common are IgG-myeloma with 60% of all myelomas, followed by IgA-myeloma (20%), light-chain myeloma (15%), IgD-myeloma (1%) and non-secretory myeloma which do not produce any immunoglobulins or light chains (10).

Regarding the western population, multiple myeloma has an incidence of 5/100,000 individuals, thus it is the second most common hematological malignancy in adults in the western world. With a median age at diagnosis of 69–70 years, it is more common in elderly patients, even though it can already occur at the age of 40 years. Most myeloma develop from a monoclonal gammopathy of undetermined significance ("MGUS"), which means there is an M-Gradient in electrophoresis without typical symptoms for multiple myeloma, with a rate of progression of 0,5-1% (9) (10). At the time of initial diagnosis, patients present with various symptoms: Most common conditions are bone pain, pathologic fractures, hypercalcemia, renal failure, anemia and severe bacterial infections.

Bone pain and pathologic fractures result from an increased RANK-L (receptor activator of NF-κB Ligand) expression and a reduced OPG (osteoprotegerin) expression in the bone marrow, which leads to the typical osteolytic lesions. The enhanced depletion of bone tissue also explains the increased serum calcium levels since calcium is being set free during this process, which can lead to nausea, dizziness and polyuria.

Infections are caused by the decreased bone marrow function based on the suppression of granulopoiesis, as well as by secondary immunoglobulin deficiency.

Anemia is caused multifactorial: On the one side, hematopoiesis is also decreased by the bone marrow infiltration of plasma cells, on the other side a decreased production of erythropoietin, increased IL-6 (interleukin 6) levels and an inappropriate utilization of iron contribute to decreased hemoglobin levels.

Renal failure often results from a so called cast-nephropathy, which is caused by the accumulation of Bence-Jones-proteins in the renal tubules, or can be the result of a hypercalcemia (11).

Survival prognosis and progression-free survival depend on multiple factors: not only the age and the comorbidities of the single patient play an important role, but also the cytogenetic subtype affects the outcome. For details on molecular and genetic mechanisms, see chapter 3.1.3. Although multiple myeloma is still not curable and is reappearing after initial therapy in almost all patients, in the last few years a doubling of the overall survival of myeloma patients from 3-4 to 6-8 years was achieved. This might be explained by the development of novel therapeutic

options, but also by the fact that even elderly patients can now be treated with therapeutic drugs that are less toxic than conventional therapies (11)(12). Nevertheless, due to the fact that for multiple myeloma we need long-term therapies, there is a big necessity for new therapies with long time progression-free survival and low toxicities.

3.1.2 Hallmarks of Cancer and Multiple Myeloma

In 2000, Hanahan and Weinberg published a paper in which they postulated six "Hallmarks of Cancer" named tissue invasion and metastasis, limitless replicative potential, sustained angiogenesis, evading apoptosis, self-sufficiency in growth signals and insensitivity to anti-growth signals (13). They updated their theory in 2011, adding deregulation of cellular energetics and invulnerability of cancer cells as two more hallmarks of cancer (14).

Hanahan and Weinberg propose that many or all tumor entities, including multiple myeloma, acquire these properties through an evolutionary process of conversion from normal cells to malignant cell types, which enables their growth as well as the spreading to distant metastatic sites.

Newer evidence suggests that malignant neoplasias such as multiple myeloma acquire those hallmarks by various mechanisms. One crucial mechanism is the interaction between tumor cells and tumor microenvironment including, amongst others, immune cells, bone marrow stem cells and stroma cells. The tumor microenvironment contributes significantly to pathogenesis of multiple myeloma (15), but also to treatment resistance. It is hypothesized that a subset of malignant cells is protected by the tumor microenvironment and survive the therapy result as minimal residual disease. Over the time, resistant myeloma phenotypes develop. They may cause disease recurrence and are less responsive to therapies (16). For details about tumor microenvironment and communicative reprogramming of the interaction between myeloma and the bone marrow microenvironment, see chapter 3.3.1.

Self-sufficiency in growth signals as a main hallmark of cancer means that tumor cells can proliferate independent from extrinsic growth signals by altering several parts of signal transducing. The three strategies Hanahan and Weinberg suggest for that mechanism include the alteration of extracellular growth signals, of transcellular transducers of those signals, and of intracellular circuits that translate growth signals into actual growth (17). For example, the EGF-R (epidermal growth factor receptor) or the production of PDGF (platelet derived growth factor)

and TGFα (transforming growth factor α) is upregulated in several tumor entities (18) (19). By this alteration of physiological processes the tumor cells can force themselves to grow less dependent from stroma cell influence (17).
One crucial pathway for self-sufficiency in growth factors specifically in multiple myeloma is signal transducer and activation of transcription 3 (STAT3) signaling. STAT3 is a cytoplasmatic transcription factor that regulates various biological functions like cell proliferation and survival, stemness, inflammation and immune responses. Through activation via interleukin-6 (IL-6), STAT3 is sustaining myeloma cell survival and proliferation by upregulating genes like B-cell lymphoma 3 (BCL3), B-cell lymphoma 6 (BCL6) and, among others, oncogenes JUN and JUNB (20). STAT3 also regulates tumor microenvironment, e.g. bone barrow milieu in multiple myeloma. Bone marrow stromal cells secrete IL-6, leading to STAT3-regulated overexpression of myeloid leukemia cell differentiation protein 1 (Mcl-1) and consequently inhibition of apoptosis (21).
The constitutive activation of JAK/STAT3 by tumor-derived factors prevents differentiation of immature myeloid cells into dendritic cells, resulting in a compromised function of dendritic cells with a lower amount of myeloma-specific cytotoxic T-lymphocytes (22, 23). Thus, STAT3 compromises to tumor-associated immunosuppression exerted by myeloma cells and bone marrow microenvironment.
Additionally, the interaction between CD28 on plasma cells and CD80/86 on dendritic cells promotes plasma cell survival by enhancing IL-6 production and by CD28-mediated downstream prosurvival signaling (24, 25).

Quite similar to the independence of growth signals, there are some ways that make tumor cells insensitive to anti-growth signals. On the one hand, cells can be arrested in the G0-state where the cell cycle is stopped. The second possibility is the induction of a postmitotic and differentiated state where cells do not proliferate anymore. The most frequent antiproliferative agent is the pRb (retinoblastoma protein) and the two related proteins p107 and p130 which repress proliferation by affecting the cell cycle. If pRb or part of its pathway is disrupted, for example by a mutation in TGFß (transforming growth factor β), which normally prevents pRb from phosphorylation and so from inactivation, this may lead to an excessive proliferation of cells (17) (26).

By evading apoptosis, cells with damaged desoxyribonuclein acid (DNA) that would normally be forced to die can survive and spread their oncogenic gene configuration. This might be

substantiated either by apoptotic sensors such as interleukin 3 (IL-3) or Fas-receptor, or by apoptotic effectors that include cytochrome c or caspase-8 and -9 (27) (28). The most common proapoptotic mutation involves the p53 tumor suppressor gene which usually monitors DNA damages (29). The empowerment of anti-apoptotic processes seems to be a major characteristic of tumor cells, allowing them to proliferate despite the damaging of important DNA sections (17). For escaping from the offense of immunologic cells and other effectors of the immune system, tumor cells have to disable these immunologic features. How this works is not exactly known, but it is shown that cancer cells can paralyze cytotoxic t-cells and natural killer cells (nk-cells) by secreting for example TGF-ß (30) or by recruiting inflammatory cells that suppress immunologic functions (31) (32). Invulnerability of myeloma cells and evading apoptosis is also mediated by T-cells reacting to antigens presented by major histocompatibility complex (MHC) I. Tumor-infiltrating lymphocytes affect the progression from benign to malignant states by altering the tumor environment and also codetermine the response to immunomodulatory drugs (33). One crucial component of myeloma development is the escape from immune surveillance. Resistance to immune effector function is a main driver of progression from benign precursor states as smoldering myeloma or monoclonal gammopathy of unknown significance (MGUS) to multiple myeloma (34). There is some evidence stating that myeloid-derived suppressor cells (MDSCs) accumulate in the bone marrow of myeloma patients (35) and are associated with the formation of blood vessels and growth of osteoclasts (36). Interaction between plasma cells and regulatory T cells via CTLA-4 supports the maintenance of long-lived plasma cells (37). The cross talk among regulatory T cells, dendritic cells and malignant plasma cells might be a trigger for myeloma development within the bone marrow (38).

Macrophages usually are responsible for pathogen elimination and tissue repair. In tumors such as multiple myeloma, the ratio of anti-tumorigenic M1-macrophages and pro-tumorigenic M2-macrophages is altered favoring M2-macrophages (39). T-cell function is inhibited in myeloma cells by impairing proliferation and cytokine secretion (40), forming another part of a tumor-promoting microenvironment. Proliferation and function of regulatory T-cells, whose expansion has a negative impact on survival (41), are narrowed by immunomodulatory drugs such as pomalidomide or lenalidomide (42).

In addition, tumors can settle distant metastases. Therefore, they disengage from the regular cell formation and migrate to metastatic sites. Of course, metastatic cells depend on all other hallmarks just as the primary tumor cells do. But in addition, they alter the adhesion on the surrounding

tissue as well as the activation of extracellular proteases. Some important targeting structures of alteration include integrin and cell adhesion molecules (CAMs). In the CAM family, E-cadherin plays the most important role. Usually, it is needed by the cells to couple to other cells, thereby transmitting anti-growth signals. Lacking these signals, tumor cells can proceed with invasion and metastasis (43). Other common mutations include nerve cell adhesion molecule (N-CAM) adhesive properties and shifts in integrin isoforms (17).
In the field of proteases, upregulation of protease genes and downregulation of inhibitors leads to a higher number of active proteases which dissolve the extracellular matrix and thus enable tumor cells to invade the surrounding tissue as well as blood vessel walls and epithelial surfaces, allowing the tumor cells to spread to metastatic sites (17) (44).
There are several mechanisms of tissue invasion proven for multiple myeloma, from which the deregulation of homeostasis between osteoblasts and osteoclasts seems to be a very important one (45). Myeloma cells activate molecular cascades increasing the secretion of receptor activator of nuclear factor kappa b ligand (RANKL) and decreasing the secretion of osteoprotegerin (46, 47), which leads to an increased bone degradation by activation of osteoclasts. In addition, osteoblasts are inhibited by downregulating the Wingless (Wnt) and dickkopf-1 (DKK1) pathway, resulting in a reduced osteoblast recruitment, reduced osteoblast differentiation and reduced activation (48, 49).
The key drivers for the mentioned metabolic changes often are dictated by oncogenes activated by chromosomal aberrations and epigenetic alterations (50). For details on molecular and genetic mechanisms of myeloma development see chapter 3.1.3.

The number of cells is not only determined by the number of cells dying, but also by the rate of proliferation, so that tumor cells must acquire limitless replicative potential for tumor progression, i.e. an impairment in autophagy. Autophagy is a conserved self-digestive process, degrading cytoplasmic contents in the lysosome (51). Autophagy, amongst others, plays a critical role in innate and adaptive immunity. In cancer cells, it has oncogenic as well as tumor-suppressive effects and is not fully understood (52). Plasma cells have high autophagic activities and might, by allowing limitless replicative potential, play a general role in plasma cell oncogenesis (51).

Usually, cells can perform a defined number of doubling before they arrest in a postmitotic state named senescence, where they are unable to proliferate. When some of these cells succeed to escape from this state, they reach a phase called crisis where the cells usually die. But if a few of

them emerge from the crisis state, they gain unlimited replicative potential, a process called immortalization (14). Malignant cells then can continue proliferation, not least because of an upregulation of telomerase, which results in an elongation of the telomeres of the chromosomes and so again promotes tumor growth (53)(17).

Another important hallmark is the sustained angiogenesis which provides the tumor with nutrients and energy. The mechanisms inducing angiogenesis include receptors at the endothelial cell surface and their ligands; furthermore it is evident that integrins and adhesion molecules are involved in this process (17).The tumors can either increase their production of proangiogenetic signals such as vascular epithelial growth factor (VEGF) or fibroblast growth factor (FGF), or they repress inhibitors of angiogenesis such as thrombospondin-1 or interferon ß (IFNß), both by altering their gene transcription (54) (55). Additionally, proteases can determine the availability of angiogenetic factors by releasing or blocking them (17).

Based on altered metabolic pathways, myeloma cells can deregulate their cellular energetics (56). Usually, in the presence of oxygen, glycolysis is followed by the procession of pyruvate to CO_2 in the mitochondria. In tumor cells, even if enough oxygen is provided, the glycolysis is preferred and only a few fractions of the resulting pyruvate is used in mitochondria, an effect called Warburg-effect (57) (58). This might seem confusing because the adenosine triphosphate (ATP) output is much lower in this way and tumors need a lot of energy for growth and surviving, but for compensating this energy “wasting”, tumors upregulate the expression of glucose transporter 1 (GLUT-1) and glycolytic enzymes (59), resulting in an increased uptake of glucose into tumor cells (60) and enhanced oxidative phosphorylation (61). The metabolic products such as lactate are exported and generate a pro-tumorigenic microenvironment (62), resulting in tumor growth and progression.

All the hallmarks mentioned above are a display of two fundamental underlying enabling characteristics, which can also be seen in multiple myeloma: genome instability and mutation, and tumor-promoting inflammation (14).
As already explained, tumor growth can be promoted by mutations in tumor suppressor genes or in protooncogenes, but also non-mutational mechanisms can lead to a selective advantage for several cell clones: DNA methylation and histone acetylation can alter activation or inactivation of genes (63). Despite the sophisticated monitoring systems that detect DNA damage, tumor cells

succeed in acquiring several mutations by an increased sensitivity to mutagenic agents, or by damages in the genomic monitoring systems (14).
The presence of inflammatory reactions in tumor sites is already known a long time. Usually we thought this would be an expression of the immune systems trial to eradicate tumor cells, but there is some evidence that somehow an opposite effect may occur: tumor-associated inflammation can amplify tumorigenesis and can lead to the acquisition of the necessary hallmarks for tumor progression, and on top, inflammatory cells can release mutagenic agents such as reactive oxygen species and IL-6, which fuel mutation and tumor progression (64) (65).

All those hallmarks represent important mechanisms of tumor development, as well as in multiple myeloma and in various other tumor entities, yet we cannot explain every detail of tumor behavior. Instead, we need to alter the fundamental underlying pathways of communication, forcing the tumor cells to re-establish physiological functions such as apoptosis and evading the hallmark processes not by targeting only one hallmark, but by altering master regulators of communication with the aim to suppress tumor growth and progression, and to lower the amount of tumor cells.

Our multicenter prospective phase I/II trial for RRMM aims at reprogramming myeloma-associated inflammation, at re-establishing immunosurveillance and at altering myeloma metabolism.

3.1.3 Molecular and Genetic Mechanisms of Myeloma Development

Multiple myeloma evolves through premalignant phases characterized by genomic abnormalities and genome instabilities as a main driver of tumorigenesis. Genomic instability is a pivotal mechanism of myeloma development which drives disease evolution (66). Although genetic instability is also detected in the precursor states of MGUS and smoldering myeloma, the genetic landscape between those entities varies (66) and for development of malignancy, a sequence of genomic alterations is required. Key secondary events leading to disease progression seem to be copy number variations involving MYC and somatic mutations affecting MAPK, NF-κB and DNA-repair pathways (67).

Mutations are divided into primary and secondary mutations (68) that result in many different numeric and structural aberrations (9) (69).

According to its primary mutation, multiple myeloma can be divided into hyperdiploid myeloma and myeloma with translocations. Most frequent, reciprocal translocations are leading to an oncogene being controlled by the immunoglobulin enhancer gene on chromosome 14q31. Common translocation partners for chromosome 14 are chromosomes 4, 6, 11, 16 and 20. Hyperdiploid myeloma presents with multiple trisomies of chromosomes 3, 5, 7, 9 11, 15, 19 and 21.

Secondary mutations in multiple myeloma include changes in transcription factors MYC, NRAS, KRAS or BRAF which all lead to an activation of NFkB, and deletions of chromosome 17p (68) (70).

It is proven that the type of chromosomal aberration has an impact on survival prognosis and relapse possibility: The loss of 17p13 and the translocations t(4;14) and t(4;16) are related to a poor prognosis, whereas the ones with t(11;14) and t(6;14) have a better prognosis concerning survival and progression. Patients without detectable translocations have an intermediate prognosis (70).

So for understanding multiple myeloma, we also need to consider the signaling pathways that are up- or downregulated, such as NF-κB, RAS/RAF/MEK/ERK, PI3K/Act/mTOR and Jak/Stat3 (71).

NF-κB signaling pathway is influencing various targets in cell cycle such as cell proliferation, survival, differentiation and immune response. Depending on different subtypes of NK-κB forming dimers, it can stimulate or repress transcription processes, but also influences post-translational regulatory loops (72). Physiologically, NF-κB molecules are hold back in the cytoplasm by inhibitory proteins called IκB. Multiple myeloma cells can be stimulated by cytokines secreted by bone marrow stem cells or by myeloma cells themselves, so that inhibitor of kappa B alpha (IκB) is degraded and NF-κB can stimulate the transcription of several proteins influencing cell cycle progression, antiapoptosis and cell adhesion (71), in summary leading to tumor growth and progression.

RAS mutations occur in approximately 23% of newly diagnosed multiple myeloma and in 45% of relapsed multiple myeloma (73). Deregulation of the RAS/RAF/MEK/ERK pathway, for example by mutations, amplifications and translocations in receptor or kinase genes or by increased cytokine levels of for example insulin like growth factor (IGF) or vascular endothelial growth factor (VEGF), affects cell growth, malignant transformation, drug resistance, senescence and aging (74). For senescence, see chapter 3.1.2.

The PI3K/Act/mTOR pathway can be activated by cytokines as IGF, IL6, VEGF or IL-

1β and is often upregulated in various cancer types including multiple myeloma, which leads to increased growth and survive of tumor cells (71)(75). These cytokines activate surface receptors which transduce the activation signal over PI3K to Act. Although the classical mutations in PI3K or in tumor suppressor PTEN that usually stimulate the PI3K/Act/mTOR pathway are absent in multiple myeloma (76)(77), this pathway is still upregulated and triggered by cytokines as IL-6 (78).

Jak/Stat3 is also stimulated by IL-6. When cytokines as IL-6 bind to an extracellular receptor, this is transduced to intracellular signaling activating a Janus kinase (JAK), which then activates transcription factors (STAT). This pathway is essential for immune response and infection control, so that it does not only play a role in tumor development, but also in autoimmunity and several inherent immunodeficiency syndromes (79).

The transcription factor MYC is an established oncogene which is not only deregulated in multiple myeloma, but in the majority of human cancers (80, 81). Its dysregulation in hematological neoplasia is often a result of chromosomal translocations (50). Strucutral variants of MYC can be identified in 42% of newly diagnosed multiple myeloma (82).

As mentioned above, IL-6 stimulates various pathways, and it is known to be essential in tumor growth, proliferation, and survival of multiple myeloma. It impacts the abovementioned Ras/Raf/Mek/Erk, PI3K/Act/mTOR and Jak/Stat3 pathways (83)(84). It can either be secreted by the myeloma cells themselves or by bone marrow stem cells. IL-6 not only forces tumor growth, but also facilitates resistance to dexamethasone treatment, so that dexamethasone induced apoptosis is limited (85). Furthermore, IL-6 stimulates the generation of Th17 cells, but inhibits regulatory t-cells, which might lead to a proinflammatory tumor microenvironment, forcing tumor cells to grow (86)(84).

Despite its big impact on tumor development, IL-6 also seems to stimulate osteoclastic differentiation (87), which might be essential in multiple myeloma regarding osteolytic bone disease.

3.2 Current Therapeutic Options for Multiple Myeloma

Cure in RRMM remains difficult to achieve. Therefore, a main strategy concept seems to be long-term disease control, also called ‘functional cure’, an aim that seems to come within reach (88).

3.2.1 Staging Systems and Indications for Treatment

There is a huge number of quite different treatment modalities for multiple myeloma, from which the best fitting one for the individual patient must be selected. Not all stages of multiple myeloma require treatment, we rather need to check for the tumor stage and for organ damage resulting from the underlying disease.

For multiple myeloma, two staging systems are used in clinical practice: the international staging system (ISS)-classification and the staging system of Durie and Salmon (89). In addition, the CRAB-criteria are used to determine the need for therapeutic intervention.
The ISS staging system requires only two markers: the serum albumin and the $ß_2$-microglobuine, which is a tumor marker reflecting the mass of the tumor. The stages are defined as shown in Table 1.

ISS Stage	Criteria
I	Serum $ß_2$-microglobulin < 3,5 mg/l and serum albumin ≥ 3,5g/dl
II	Not ISS stage I or III
III	Serum $ß_2$-microglobulin ≥ 5,5 mg/l

Table 1: ISS staging criteria for multiple myeloma

The distribution of patients into these three groups is validated by significant differences in the median survival between the groups: According to the data published in the original paper that introduced the ISS staging system, patients with ISS stage I had a median survival of 62 months, whereas in stage II the median survival was 44 months and in stage III only 29 months (90)(91). In 2015, Palumbo et al. released the reversed R-ISS criteria, which combine ISS staging system with the detection of chromosomal abnormalities and LDH value to give a more reliable prognosis regarding overall survival and progression free survival (90).

According to the German guidelines for multiple myeloma, the ISS staging system is state of the art, but there is another common system that is still used in clinical practice: The staging system according to Durie and Salmon uses the extent of bone lesions, the hemoglobin level, the serum calcium and the M-component levels in serum and urine to give information about tumor mass and response possibility (92). The staging criteria are listed in Table 2.

Durie and Salmon Stage	Criteria	Myeloma cell mass
I	All of the following criteria: • Hemoglobin >10g/dl • Serum calcium ≤12mg/dl • Radiological normal bone structure or solitary plasmacytoma only • Low M-component production rates: - IgG <5g/dl - IgA <3g/dl - Urine light-chain M-component on electrophoresis <4g/24hrs	Low
II	Not Durie and Salmon Stage I or III	Intermediate
III	One or more of the following: • Hemoglobin <8,5g/dl • Serum calcium >12mg/dl • Advanced lytic bone lesions • High M-component production rates - IgG >7g/dl - IgA >5g/dl - Urine light chain M-component on electrophoresis >12g/24hrs	High
Subclassification		
A		Normal renal function: serum creatinine < 2,0mg/dl
B		Abnormal renal function: serum creatinine ≥2,0 mg/dl

Table 2: Staging system according to Durie and Salmon (92)

In addition to these staging systems, the CRAB-criteria, respectively the newer SLiM-CRAB-criteria, are used to determine the need for a therapeutic intervention (see Table 3). If a patient shows one or more of the criteria listed in Table 3, or symptoms like pain, hyperviscosity syndrome, B-symptoms or recurrent severe infections, the IMWG (international myeloma working group) recommends to supply therapy (93). The following chapter shows an overview of therapeutic options, their indications and their limitation.

Criteria	Definition
CRAB-Criteria	
Hypercalcemia (C)	Serum calcium >2,75mmol/l or >0,25mmol/l over highest normal level
Renal failure (R)	Creatinine ≥2,0mg/dl or GFR <40ml/min
Anemia (A)	Hemoglobin <10,0g/l or ≥2,0g/l under lowest normal level
Bone disease (B)	Prove of at least one bone lesion in imaging
SLiM-Criteria	
Bone marrow infiltration (S; sixty percent bone marrow plasma cells)	Clonal plasma cells in bone marrow >60%
Light chain ratio (Li)	Free light chain ratio in serum >100 (involved/not involved free light chains)
Magnetic resonance imaging (M)	More than one focal lesion on MRI imaging

Table 3: SLiM-CRAB Criteria (93) (94); GFR = glomerular filtration rate

3.2.2 Peripheral Blood Stem Cell Transplantation

Autologous stem cell Transplantation has evolved from a second- or third-line therapy to first line therapy in transplant eligible patients. The standard transplant protocol includes induction therapy with bortezomib and dexamethasone, perhaps combined with lenalidomide, cyclophosphamide or thalidomide, followed by high-dose chemotherapy with melphalan and stem cell collection. Subsequently, a maintenance therapy for example with bortezomib or lenalidomide is needed (93). For initial treatment in eligible patients, this therapy regimen is superior to systemic treatment, but cannot be performed in patients with serious comorbidities (95)(96)(97).

In contrast to autologous stem cell transplantation, the status of allogenic stem cell transplantation remains controversial for multiple myeloma patients (98). Often only chronic GvHD may control

myeloma regrowth (99). Due to transplant-associated complications and mortality, even with reduced intensity conditioning, and the missing evidence of survival benefit, allogenic stem cell transplantation is currently recommended for use in clinical trials (100). CAR-T cell therapies could replace autologous stem cell transplantation (88, 101).

3.2.3 Systemic Treatments for Multiple Myeloma

First-line therapies according to the German guidelines for multiple myeloma include several combinations of drugs of different entities. Established drugs for first line therapy are thalidomide, lenalidomide, pomalidomide, bortezomib, ixazomib, panobinostat, belantamab mafodotin, selinexor, bendamustin, cyclophosphamide, doxorubicin or melphalan which are usually administered as a combination therapy of two or three substances and a steroid, namely dexamethasone or prednisone. Newer options are monoclonal antibodies (mAbs) or B-cell maturation antigen chimeric antigen receptor (CAR) T cells (102). For details, see the section below.

Despite treatment advances, patients with multiple myeloma (MM) often progress through standard drug classes including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (mAbs). The following pages shall give an overview over the current main substances for treating multiple myeloma. The data on the use of therapy regimen as first/second/third line therapy are based on the German guidelines for multiple myeloma.

Nitrogen lost derivates: One group of therapeutic agents are nitrogen lost derivates (103). Some substances such as bendamustine or melphalan can be used in myeloma therapy. Bendamustine and melphalane are alkylating agents, but in combination with prednisone bendamustine has higher rates of complete remission (CR)s and a longer time to progression than melphalane (104)(93). The latter is often used as high-dose chemotherapy in autologous stem cell transplantation, as explained in the chapter above (93).

Proteasome inhibitors: Very effective is the group of the proteasome inhibitors, from which bortezomib is the most commonly used one. It can be given as monotherapy or in combination with dexamethasone and perhaps a third agent like daratumumab, lenalidomide, melphalan and others and is part of most first line therapies, either with or without stem cell transplantation (93). Further proteasome inhibitors are Carfilzomib, which has higher rates of remissions and a longer

progression free survival (PFS) and overall survival (OS) in second line than bortezomib (2), and ixazomib, which is orally applicable (93).

Alkylating agents: Cyclophosphamide is an alkylating agent which is in clinical use for over 40 years (105). It does have monoactivity, but is mostly used in combination with bortezomib and dexamethasone (93), which is also a first line therapeutic option.

Monoclonal antibodies: There are also several kinds of antibodies which can be used to treat multiple myeloma, like daratumumab, elotuzumab and isatuximab. Trials using monoclonal antibodies (mAbs) in first line are on the way worldwide. Daratumumab is a monoclonal antibody targeting CD38 that can be used as monotherapy or combined with dexamethasone and bortezomib or lenalidomide (93). In combination with bortezomib, lenalidomide and dexamethasone (VRd), daratumumab has shown a reduced risk of disease progression or death compared to VRd alone (progression-free survival 84,3 vs. 67.7%) in transplant-eligible myeloma patients (106) and is recommended as a potential first line therapy in Germany (102).
Another antibody recommended for multiple myeloma is elotuzumab, which is an Anti-surface antigen CD139 (SLAMF7)-antibody. SLAMF7 is a glycoprotein expressed by NK-cells, but also by more than 95% of the bone marrow myeloma cells, so elotuzumab can target myeloma cells selectively without severe damage of healthy tissue, but also stimulates NK-cells and thereby the antibody dependent cell-mediated cytotoxicity. Combining elotuzumab with lenalidomide/dexamethasone leads to a higher rate of remission and an increase in progression free survival and overall survival (107).

Antibodies linked with cytotoxic agents: Belantamab-Mafodotin is a drug-antibody-conjugate which combines the B-cell maturation antigen (BCMA)-antibody Belantamab with the microtubule inhibitor monomethyl auristatin F (MMAF). It is used in refractory or relapsed multiple myeloma as fourth line therapy (108).

Cytotoxic agents: Doxorubicin is an anthracycline, which actually is an antibiotic agent, but also has cytotoxic effects in cancer treatment (109). It is mostly used in combination with bortezomib and dexamethasone (93).

Histone deacetylase inhibitors: Panobinostat is a histone deacetylase inhibitor, which is also used in combination with bortezomib and dexamethasone. In this combination, it leads to a longer progression free survival, but not overall survival (110)(93).

B-cell maturation antigen chimeric antigen receptor (CAR) T cells: CAR-T cells emerged as a promising treatment option during the last years. To generate CAR-T cells, polyclonal T cells are collected from the patient's blood and are genetically engineered. A gene encoding a T cell receptor specific for a known tumor antigen is inserted and the cells are re-administered to the patient (111). Idecabatagene vicleucocel (ide-cel) is a B-cell maturation antigen-directed CAR-T cell-therapy which is also used for relapsed or refractory myeloma. Clinical trials showed an extended progression-free survival in patients with RRMM treated with CAR-T cells, compared to standard therapy. Notably, 95% of these patients had daratumumab-refractory disease (112). Cytokine release syndrome is a main adverse event recognized in up to 80% of patients, but can nowadays be adequately diagnosed and therapied (113). Another common adverse event is hematological toxicity (114). Nevertheless, CAR-T cells are highly effective even in heavily pretreated patients with myeloma refractory to proteasome inhibitors, immunomodulatory agents and CD38-antibodies, but also in earlier treatment lines (115).

XPO-1-Inhibitors: Another new therapy is Selinexor, an XPO-1 inhibitor. It forces nuclear accumulation and activation of tumor suppressor proteins and inhibits nuclear factor κB and is used in patients with multiple myeloma, who had at least four previous therapies (116).

Glucocorticoids: A substance which is part of almost all drug treatment regimens for multiple myeloma, also used in our study, is dexamethasone, a steroid and one of the most effective monotherapies, but also part of nearly all double or triple combinations. It can be applied as high dose therapy or in lower dosages (93). The latter has shown to be safer and so leads to a higher 12 months survival rate than high dose dexamethasone, so that low dose therapy is now therapy of choice (117) (93). Other steroids used for treating multiple myeloma are prednisone or prednisolone, which are often combined with melphalan. This combination is even more effective when bortezomib is added, so that overall survival and progression free survival are increased (118) (119).

IMiDs: Another group of drugs called immunomodulatory drugs (IMiDs) is used in our MM03-study. The three established agents are lenalidomide, pomalidomide and thalidomide, from which thalidomide was the first one to be synthesized. They can be used in double-or triple therapies or, as lenalidomide, for maintenance after autologous stem cell transplantation, where it can significantly extend progression free survival and overall survival (120). For further information about steroids and IMiDs, see chapter 3.3.2.

Combination therapies in > 2nd line: Combined therapies are clinical routine for RRMM and improve progression-free survival. Nowadays, third line therapies are mostly based on immunomodulatory drugs (IMiDs). The most frequent combinations used in third line in Germany are Lenalidomide + Carfilzomib + Dexamethasone as well as Lenalidomide + Daratumumab + Dexamethasone or Daratumumab + Bortezomib + Dexamethasone (121). An overview about the efficacy of approved combinational therapies based on the German guidelines and current research is listed in in Table 4.

Therapy	**PFS**	**Overall response (OR)**	**Adverse events (AEs)**
Lenalidomide + Carfilzomib + Dexamethasone	26.3 months (median PFS)	87.1%	83.7% (grade 3 or higher), especially hypokalemia and fatigue
Lenalidomide + Ixazomib + Dexamethason	20.6 months (median PFS)	78%	Rash (36%), peripheral neuropathy (27%), Thrombocytopenia Grade III or IV (12%) (122)
Lenalidomide + Daratumumab + Dexamethasone	83.2% (12 months PFS), not reached (median PFS)	92.9%	Neutropenia (59.4%), Diarrhea (42.8%), Anaemia (31.1%) (123)
Lenalidomide + Elotuzumab + Dexamethasone	18.4 months (median PFS)	76.7%	Infections (33.9%), Neutropenia (18.5%), Anaemia (15.4%) (124)

Pomalidomide + Bortezomib + Dexamethasone	11.2 months (median PFS)	82.2%	Peripheral sensory neuropathy (48%), Neutropenia (46%), Thrombocytopenia (37%) (125)
Pomalidomide + Daratumumab + Dexamethasone	12.4 months (median PFS)	69%	Neutropenia (71%), Infections (65%), Anaemia (37%) (126)
Pomalidomide + Isatuximab + Dexamethasone	11.5 months (median PFS)	63%	Anaemia (99%), Neutropenia (86%), Thrombocytopenia (84%) (127)
Pomalidomide + Elotuzumab + Dexamethasone	10.3 months (median PFS)	53%	Neutropenia (13%), Anaemia (10%), Hypergylcemia (8%) (128)
Pomalidomide + Cyclophosphamide + Dexamethasone	9.5 months (median PFS)	64.7%	Anemia (54.6%), neutropenia (51.5%), thrombocytopenia (48.5%)
Bortezomibe + Daratumumab + Dexamethasone	60.7% (12 months PFS), not reached in follow up (median PFS)	82.9%	Thrombocytopenia (45.3%), Anaemia (14.4%), Neutropenia (12.8%) (129)
Bortezomib + Panobinostat + Dexamethasone	5.4 months (median PFS)	34.5%	Diarrhea (70.9%), Thrombocytopenia (65.5%), Anaemia (47.3%) (130)
Carfilzomib + Daratumumab + Dexamethasone	74% (12 month PFS), not reached (median PFS)	84%	Respiratory tract infections (77%), Thrombocytopenia (37%), Anaemia (16%) (131)

Carfilzomib + Isatuximab + Dexamethasone	Not reached in follow up (median PFS)	87%	Respiratory tract infections (83%), infusion-related reaction (46%), hypertension (37%) (132)
Carfilzomib + Cyclophosphamide + Dexamethasone	19.1 months (median PFS)	70%	Respiratory tract infection (29%), anemia (28.8%), neutropenia (24.7%)
Thalidomide + Elotuzumab + Dexamethasone	3.9 months (median PFS)	38%	Lymphopenia (50%), asthenia (35%), anemia (20%)
Ixazomib + Cyclophosphamide + Dexamethasone	14.2 months (median PFS)	48%	Diarrhea (33%), nausea (24%), thrombocytopenia (22%)

Table 4: Efficacy and safety of approved triple-therapies for second- and later line treatment of refractory or relapsed multiple myeloma in Germany (129, 133, 128, 131, 132, 125, 122–124, 126, 127, 130, 134–138)

Biomodulatory therapy approaches such as the combination of elotuzumab, pomalidomide and dexamethasone showed comparable progression free survival rates and safety profile as other established therapies. Median PFS and overall response were lower for thalidomide + elotuzumab + dexamethasone, but patients were heavily pretreated with a median of three previous therapies and safety parameters were comparable to other therapies (137).

Metronomic chemotherapy: For patients with RRMM and severe complications like heart failure, lung function impairment, coronary heart disease, pleural effusion or ECOG performance score of 3 or more, metronomic chemotherapy with continuous low-dose cyclophosphamide plus prednisone is a possible option with lower side effects. In 32% of the enrolled patients, complications even improved during cyclophosphamide therapy and allowed additional application of bortezomib, lenalidomide, thalidomide or ixazomib (139).
Metronomic administration of cyclophosphamide combined with low-dose corticosteroids even showed similar efficacy to carfilzomib monotherapy in heavily pretreated patients with RRMM

and reached a median overall survival of 10 months in patients treated with a median of five prior therapies (140). Combined with ixazomib and dexamethasone, cyclophosphamide showed favorable efficacy for patients with RRMM and 1-3 prior therapies, resulting in a median overall survival of 14.2 months and a relatively low rate of hematological side effects (141).

Alternatively, CAR-T cells are a promising option for RRMM with a pooled overall response rate of 77% and a median progression-free survival of 8 months. Main serious adverse events are, as mentioned above, cytokine release syndrome and neurologic toxicities with 14% and 13% respectively (142).

3.2.4 Radiotherapy

In plasma cell disorders, radiotherapy is used adjunctive as well as for primary treatment. In multiple myeloma it is mostly used as palliative treatment for patients with symptomatic lesions, either skeletal or in soft tissue, from which bone pain is the most frequent observed symptom (143) (144). Although radiotherapy in multiple myeloma is a palliative approach, it is quite effective and widely spread, so that almost 40% of myeloma patients require radiotherapy at some time at their course of disease (145).

3.2.5 Surgical Intervention

As multiple myeloma is a systemic disease, surgical intervention cannot primarily be performed. Instead, it is necessary when secondary problems such as pathological fractures for example of the spine occur, or when the patient develops severe osteonecrosis due to bisphosphonate treatment (9)(93). Only for the subgroup of solitary plasmacytoma surgery combined with radiotherapy can have a benefit (146). For bisphosphonate treatment see chapter 3.2.6.

3.2.6 Treatment of Bone Disease

Osteolytic lesions are a hallmark of multiple myeloma affecting the majority of myeloma patients. It results from enhanced bone resorption driven by osteoclast activation and can cause spinal cord compression and pathologic fractures (147).

Bisphosphonates such as pamidronate and zoledronic acid are well known therapies for osteoporosis as well as for myeloma. Molecularly, they are related to inorganic pyrophosphates and have a high affinity to calcium. Therefore, they target areas of high bone resorption and

restrict osteoclast activity. They treat and prevent bone disease-related osteolytic lesions (148) and mediate calcium levels, but bear the risk of osteonecrosis of the jaw and renal toxicity (147). Alternatively to bisphosphonates, denosumab is a monoclonal antibody that targets RANKL and thereby inhibits osteoclast-mediated bone resorption and osteoclastogenesis. Denosumab showed superiority to zoledronic acid in delaying the time to the first skeletal-related event. It has similar rates of osteonecrosis of the jaw, but can be administered independent of renal function (149).

3.3 Targeting Myelomas' Phenotypic Plasticity: The Novel Therapy Concept for RRMM

3.3.1 Concept

"Anakoinosis" is the ancient Greek term for "communication". Every cell must communicate for surviving and growing, but also for dying, and so do tumor cells.

Current cancer treatment approaches aim at specific targeting structures of tumor cells, especially at inducing apoptosis, but do not consider the holistic communication network in which tumor cells are living and growing. Aiming at one single target structure may not seem useful because it can always only target parts of specific tumor entities, but not the general underlying mechanism of tumor development (4). We also know that tumor cells mutate frequently during their evolution, so that some targeting structures are present in the original tumor, but may not be detectable any more for example in metastatic sites (150).

A tumor develops when homeostatic processes between tumor and stroma cells are recessively setting. Subsequent events develop context dependent in a specific cellular environment (151). The recessive phenotype of tumor cells is well proven by preclinical tests: for example, tumor cells are behaving completely different in embryonic stroma than in their original stroma tissue (152).

As a consequence, a goal may be to target the underlying communication structures of tumor evolution with the aim of communicatively reprogramming tumor cells, forcing them into apoptotic processes (8). Communicatively reprogramming by using biomodulatory therapy means the alteration of complex signaling pathways such as Notch or Wnt (153)(154)(155) aiming at forcing the tumor cells into apoptosis, or at least into arrest of growth and proliferation. The renouncement of affecting single therapeutic targets in tumor therapy in favor of remodeling communicative pathways in tumors and their microenvironment is called "anakoinosis", "modular therapy" or "biomodulatory therapy" (156) and aims at remodeling tumor communication between tumor cells but also with their environment. Thus, we might better target tumor-associated stress response and communicative context of neoplastic cells and adjacent stroma.

Malignancies develop specific molecular patterns to deal with neoplasia-specific stress responses to finally maintain survival and neoplasia-specific hallmarks of cancer. Metronomic, (very) low-dose chemotherapy therapeutically promotes a continuous pattern of stress responses in neoplastic cells irrespectively of the histologic origin (5). Clinical data reveal that metronomic chemotherapy even at very low doses limits tumor tissue plasticity by limiting stress response, probably decreasing phenotypic heterogeneity of tumor cell niches. Tissue stress generally induces a tighter phenotype (5).

Alteration of MM stress response with low dose metronomic chemotherapy is prerequisite for the therapeutically efficacious establishment of triple transcriptional modulation with nuclear receptor agonists, PPARα/γ agonist plus dexamethasone, showing no or poor monoactivity in RRMM, e.g., pioglitazone and dexamethasone at low doses.

Pre-clinically valuable nuclear receptor crosstalks have been observed between glucocorticoid and mineralocorticoid receptors in MM. Mineralocorticoids may boost glucocorticoid-induced killing of multiple myeloma cells in vitro (157).

Therefore, we use agents that may not have therapeutical effects when given as a single therapy, but which, when combined, affect multiple levels of tumor biology (158).

With the paradigmatic new approach of biomodulatory therapy, we aim at correcting tumor and tissue homeostasis. Modifying gene expression or tissue homeostasis can even induce complete remission in early relapsed acute myelocytic leukemia (AML) (159, 160).

For inducing anakoinosis, we use biomodulatory therapies consisting of different therapeutics, like low dose metronomic chemotherapy, but also repurpose drugs like glitazones, dexamethasone or cyclooxygenase 2 (COX-2) inhibitors, in some cases combined with established tumor therapies. For drugs used to induce anakoinosis see chapter 3.3.2. As a result, we can not only achieve tumor response in multiple myeloma, but also in many other tumor entities (see chapter 3.3.3).

3.3.2 Drugs Used in Biomodulatory Therapy Schedules

For inducing anakoinosis, there are several groups of drugs available that can be used and combined to induce phenotypical reprogramming of RRMM, i.e., so called MM editing approaches, a term used in analogy to genetic tissue editing: epigenetically and transcriptionally acting substances, metabolic modulators, demethylating agents, metronomic low-dose chemotherapy and drugs that act on protein level, may be combined with classical targeted therapy

(150) (153). They are often used metronomically (161), e.g. continuously applied at low doses, so less toxicity occurs.

Agonists of nuclear receptors: Epigenetically and transcriptionally acting substances are for example all-trans retinoic acid (ATRA), glitazones and corticosteroids. They can be used to change nuclear transcription and so gene expression with the result of altering for example cell proliferation and metabolism (150). For intensifying this effect, in our study we used dual transcription modulation with low dose dexamethasone and pioglitazone, which is a peroxisome proliferator-activated receptor gamma (PPARα/γ)-agonist.
PPARγ is a subtype of the peroxisome proliferator-activated receptors (PPAR). The PPARs are ligand-activated nuclear hormone receptors belonging to the steroid receptor superfamily (162). They are mainly involved in metabolic processes like lipid and glucose homeostasis. For example, pioglitazone is formerly known as an antidiabetic drug, but is also involved in regulating inflammation-driven growth of myeloma cells by lowering the production of IL-6 in bone marrow stem cells (163), which was the reason for us to use it as an antimyeloma agent.

Glitazones and IMiDs: Glitazones can reprogram T-lymphocytes and adipocytes involved in myeloma progression, can suppress osteoblastogenesis and enhance osteoclastogenesis (164–166, 4). Considering tissue communication, glitazones modulate communication lines which are essential for myeloma growth, such as Wnt signaling, MAPK, PI3K/Akt pathway, NF-κB and STAT3 signaling as well as exosomes, extracellular matrix and metabolites involved in tissue communication (167–171).
Wnt/β-catenin/CD44 signaling is epigenetically dysregulated in multiple myeloma and is linked to progression and aggression levels (172). The overexpression of CD44 was found to be a Wnt transcriptional target in lenalidomide resistance models (172). Classical targeted therapies aim at of blocking Wnt/β-catenin/CD44 signaling, but instead, pioglitazone attenuates Wnt/β-catenin signaling with its reprogramming profile, so CD44 is downregulated and the Wnt-driven CRBN, a required IMiD target, is regulated (173–175, 172). Aberrant CRBN DNA methylation was uncovered as a mechanism of IMiD resistance in multiple myeloma recently and predicts IMiD response (176).
Activated Wnt signaling promotes protein synthesis, such as PDK and MCT-1, and therefore, involves target genes of beta-catenin and angiogenesis (174). PPARγ agonists can downregulate

MCT-1 (177), so we suggest further evaluation of pioglitazone and its mechanism of action for overcoming IMiD resistance.

Targeting drug metabolism: Pioglitazone is approved as metabolically active drug in insulin resistant diabetes mellitus and has also metabolic activity in neoplastic cells. Metformin is also a well-known representative of metabolic modulators, which can for example inhibit cell proliferation and migration in glioblastoma by mechanisms such as increasing lactate secretion and lowering oxygen consumption (178)(179). But also the mechanistic target of rapamycin (mTOR) pathway, which is often dysregulated in tumor cells, can be a therapeutic target: mTOR is involved in cellular functions such as growth, proliferation, survival and metabolism (180).

The possibilities of targeting a tumor's metabolism are widely spread. There is some evidence that inhibiting glutaminase in tumor cells can block their replication. Tumor cells seem to need glutamine metabolism to cover their need of energy. By allosterically inhibiting glutaminase, cancer cells can be decapacitated from proliferating.
Further possible targets in tumor metabolism are isocitrate dehydrogenase enzymes (IDH1/IDH2) and lipid metabolism, as well as epigenetic remodeling of metabolic pathways (181).

DNA methylation seems to play an important role in tumor progression and in response to therapy since hypermethylation has been linked to therapy resistance and poor prognosis. Demethylating agents, such as azacytidine inhibit DNA methyltransferases (182), are resulting in a hypo-/demethylation of DNA and so in inactivation of mutated genes that promote tumor growth (183).

Low-dose metronomic chemotherapy, for example with cyclophosphamide, methotrexate or treosulfan, has multifold effects on tumor cells. By applying constantly low doses of chemotherapy instead of higher doses with the need to recover before the application of the next dose, adverse effects can be lowered while retaining the therapeutic effect of the drug. Initially, it was thought to only inhibit angiogenesis. This anti-angiogenetic effect still is a major mechanism of action of these drugs, but in addition it has several other synergistic effects in tumor treatment. Metronomic chemotherapy was found to enhance the immune response against cancer cells by down-regulating regulatory t-cells, which otherwise can suppress NK-cells and so lower immune response. In addition, metronomic chemotherapy can induce senescence, therefore detain tumor

cells from proliferation, or tumor dormancy by inducing cell-cycle arrest (184). These pleiotropic effects work synergistically in tumor combating.

Anakoinosis can also be induced on protein level by drugs such as arsentrioxide, IMiDs, COX2-inhibitors with their anti-inflammatory effects and others (153).
An important regulator of several IMiD-related cellular modifications in MM seems to be cereblon (CRBN). CRBN is a protein targeted by IMiDs such as thalidomide, but also lenalidomide and pomalidomide and is required for the efficacy of these drugs. When CRBN is silenced, the gene expression changes induced by IMiDs are dramatically decreased, implicating that CRBN is an important mediator of IMiD-induced tumor modification (185).

IMiDs, such as lenalidomide, which was used in our study, have various effects on tumor cells, especially in multiple myeloma: they can induce myeloma cell death among others by inhibiting cereblon and NFkB (186), activating caspases, increasing pro-apoptotic factors, inhibiting anti-apoptotic factors and inhibiting the PI3K/AKT pathway. Furthermore, they inhibit neoangiogenesis, lower IL-6, RANK-L and cell adhesion molecules, which leads to the detachment of myeloma cells from their bone marrow environment and to downregulation of osteoclastic activity (187) (188) (189). On cellular level, IMiDs stimulate NK-cells and inhibit regulatory T-cells, which in combination with lower levels of tumor necrosis factor (TNF)-α, IL-6 and other cytokines leads to an enhanced immune response against the tumor (188).

3.3.3 Current Research on Anakoinosis Inducing Therapies

There were several papers published during the last years that explore the different aspects of anakoinosis and demonstrate its efficacy and safety:

In 2003, Vogt et al. published a study on six patients with advanced malignant vascular tumors receiving pretreatment with 45mg oral pioglitazone and 25mg oral rofecoxib for 14 days, and subsequently in addition 50mg oral trofosfamide three times daily until tumor progression. They observed mild toxicities (world health organization (WHO) grade 1-2) with no hospitalization needed. Two patients achieved complete remission, one patient had partial response and three patients had a disease stabilization (190).
One year later in 2004, another trial including 45 patients with stage IV melanoma or metastatic soft tissue sarcoma was published, containing the same treatment schedule as in the trial

mentioned above. There were no toxicities WHO grade 3 or higher. The most common adverse events were edema in 20% and hematologic toxicity in 25% of the patients. Complete response or partial response was observed in 13% of patients, and prolonged disease stabilization was observed in 11% (191).

Kattner et al present a case of early relapsed AML after hematopoietic stem cell transplantation that was refractory to azacytidine. The patient received biomodulatory salvage therapy with low dose azacytidine, pioglitazone and all-trans-retinoic acid and achieved complete remission after two cycles. Treatment was ceased after five cycles, and the patient remained in complete remission for another seven months (159).

Six patients with stage IV melanoma were enrolled in a phase I trial with 60mg oral pioglitazone daily, 60mg oral etoricoxib daily plus 50mg oral low dose trofosfamide three times daily and i.v. temsirolimus weekly at two dose levels with 15 mg or 25 mg. Four patients had disease stabilization, one partial response and one mixed response. The PFS was 4-13 months. Grade 4 toxicities did not occur, main grade 3 toxicities were hematotoxicity and edema (192).

In a retrospective analysis, Reichle and Vogt summarized results of several phase II trials on patients with different tumor types: They chose trials on tumors with high vascular density, highly inflammatory tumors and tumors with a known inflammatory component. Enrolled tumor types include among others renal clear cell carcinoma, chemoresistant multivisceral Langerhans cell histiocytosis, melanoma, cholangiocellular carcinoma and hormone-refractory prostate cancer. Median PFS was 2.0-11.5 months, and OS was 8.0-25.6 months. The most frequent toxicity over all trials was hematotoxicity in 6.2% of all patients (193).

In a clinical phase II trial with low-dose chemotherapy with capecitabine, pioglitazone and rofecoxib for treating non-curative hepatocellular carcinoma, 38 patients were enrolled. They first received a two-week lead-in phase with 60mg oral pioglitazone daily and 25mg oral rofecoxib daily. Subsequently, patients received 1g/m^2 oral capecitabine twice a day in addition to pioglitazone and rofecoxib. They were constrained to take this medication without any interruption until disease progression or the need of permanent discontinuation. Due to withdrawal of rofecoxib from the market, it had to be substituted by 60mg oral etoricoxib daily. The median progression-free survival was 2.7 months and the median overall survival was 6.7 months (194).

Thomas et al could show that in five patients with acute myelocytic leukemia and primary chemorefractory disease, treatment with low-dose azathioprine, pioglitazone and all-trans retinoic acid could induce complete molecular remission (195).

For refractory or relapsed classical Hodgkin lymphoma, Ugocsai et al could show good results in three patients with metronomic low dose chemotherapy with treosulfan, everolimus, pioglitazone, etoricoxib and dexamethasone. One patient achieved partial response and fluordesoxyglucose-positrone emission tomography (FDG-PET)-negativity of lung lesions and involved lymph nodes. One more patient achieved FDG-PET-negativity and one patient had mixed response. All of them underwent allogenic stem cell transplantation subsequently and two of them remained in complete remission (196).

In a single arm, open label phase II study, Vogelhuber et al treated 65 patients with castrate refractory prostate cancer with imatinib mesylate, pioglitazone, etoricoxib, treosulfan and dexamethasone. 23 patients were prostate specific antigen (PSA) responders and had a mean PSA decrease from 278.9 ± 784.1 ng/mL at baseline to 8.8 ± 11.6 ng/mL at the final visit (197).

Eleven patients with multi-system Langerhans cell histiocytosis were treated with metronomic low-dose trofosfamide, etoricoxib, pioglitazone and low-dose dexamethasone on a compassionate use basis. Four of them achieved ongoing complete remission, three had partial remission and four had stable disease (198).

Lüke et al treated six patients with relapsed or refractory classic Hodgkin lymphoma with metronomic low dose treosulfan, everolimus, pioglitazone, etoricoxib and low dose dexamethasone. Medication was administered daily from day one. All patients achieved complete remission, four of them after becoming eligible for allogenic stem cell transplantation (199).

In a national, multicenter, prospective, open-label, randomized phase II trial, Heudobler et al treated 37 Patients with squamous and non-squamous non-small cell lung cancer who failed first line chemotherapy with low dose treosulfan, pioglitazone and clarithromycin. The control group was treated with nivolumab. Biomodulatory therapy was inferior in PFS (1.4 vs. 1.6 months, $p = 0.048$), but equal in OS (9.4 vs. 6.9 months, $p = 0.44$) and superior in treatment-related grade 3-5 adverse events (10% vs. 29%) (200).

Current research indicates that biomodulatory therapy can alter tumor communication and thus induce remission or at least reduction of tumor mass in histologically quite different tumor entities. Especially elderly or frail patients or patients with intense previous treatments might profit from the low-dose, less toxic therapeutic concept of biomodulatory therapy.

A central substance of this approach is pioglitazone, a dual PPARα/γ-agonist. As described in chapter 3.3.2, PPARα/γ-receptors are involved in metabolic processes like lipid and glucose homeostasis, but have also shown to mediate inflammation, immune response, proliferative

signaling, cancer metabolism and angiogenesis, which are mainly covered by the hallmarks of cancer (201, 202). New evidence suggests that tumor tissue editing may also be able to control (post-therapeutic) metastatic spread, cancer repopulation and acquired tumor cell resistance (M-CRAC).

M-CRAC-associated disease traits, i.e., metastatic spread, cancer repopulation, and acquired tumor cell resistance as well as genetic and/or molecular-genetic tumor cell heterogeneity, may be clinically separated as a unique post-therapeutic response pattern to systemic tumor therapies based on the clinical finding that M-CRAC may be successfully resolved or attenuated by the introduction of tumor tissue editing techniques designed for the treatment of r/r neoplasias of different histologic origin (5).

Tissue editing targets the myelomas' phenotypic plasticity by therapeutically including simultaneously myeloma and stroma cells in the therapeutic concept. The novel treatment paradigm facilitates to reprogram myeloma-promoting hallmarks, inflammation, decreased immunosurveillance, and myeloma metabolism in therapeutically relevant biologic hallmarks attenuating myeloma growth in RRMM.

In particular, the differentially developing resistance patterns in tumors, originating either from resistant clones during initial tumor growth or from the multifold resistance patterns induced by preceding systemic tumor therapies, describe the therapeutic challenges for establishing M-CRAC control and indicate the necessity for novel therapeutic solutions. The multifaceted M-CRAC disease traits have been intensively studied, e.g., in RRMM (203, 176, 204, 205). The M-CRAC concept summarizes disease traits promoting tumor progression or relapse following any kind of prior systemic therapy, such as chemotherapy, immunotherapy, and targeted therapies with small molecules. M-CRAC is often associated with mixed or organ-specific response patterns to systemic tumor therapy (206, 207).

The novel treatment paradigm 'tumor tissue editing' is adopted to the use of tissue editing technologies for correcting genetic or epigenetic abnormalities in tumor tissues (161, 5). Now, tumor tissue editing methodologies aim at phenotypic, therapeutically relevant editing of tumors. In RRMM, metronomic chemotherapy may induce phenotypic integration of inflammation control by additional transcriptional modulation of the myeloma tissue (5). Exposure of tumor tissues with therapeutic stress in addition to the limited tumor intrinsic management of oncogenic stress for preserving tumor integrity and promotion, or the inhibition of salvage pathways managing the stress response, may induce tumor cell death pathways. Whereas non-tumor cells

compensate for therapeutically induced perturbations, as indicated by the modest toxicity profile of editing trials (5).
Tumor tissue editing techniques finally inhibit the relief of stress in tumor tissue, which neoplastic cells are relying on for survival. This way, tumor tissue editing approaches resolve or attenuate M-CRAC (5).

Tissue editing by administration of low-dose metronomic chemotherapy and transcriptional modulators with or without targeted therapies holds the potential to address M-CRAC in patients wo are refractory to or relapsing after conventional chemotherapies. By targeting drivers of M-CRAC, i.e. the hallmarks of cancer, tissue editing successfully activates tumor cell differentiation, immunomodulation and inflammation control (5).

4 Material and Methods

4.1 Study Design and Endpoints

To determine the efficiency and safety of biomodulatory therapy in patients with relapsed or refractory or progressive multiple myeloma, we investigated a prospective phase I/II, one-arm, one-stage multicenter open label study of lenalidomide in combination with pioglitazone, dexamethasone, and metronomic low-dose chemotherapy with treosulfan as third-line therapy.
The study objective is statistically formulated as a test of the null hypothesis H_0: $p \leq p_0$ versus the alternative hypothesis H_1: $p \geq p_1$. Our null hypothesis is that response to treatment occurs in 30% of patients or less ($p_0 = 0.30$). The target level is $p_1 = 0.50$, which would imply that response to treatment occurs in at least 50% of patients. The latter result would indicate the potential usefulness of our treatment for the selected patient group.
A one-sided, binominal hypothesis with a target significance level $\alpha = 0.10$ and a target power 1-ß = 0.90 was used for analysis. Based on the number of responses the following decisions will be made: If, out of 39 patients, 15 or less responses are observed, then H0 is not rejected. If, out of 39 patients, 16 or more responses are observed, then H0 is rejected. In this case, the study treatment will be considered promising.

We included 8 patients in phase I and 39 patients in phase II, so that in total 47 patients were enrolled in the study. The first patient in phase I was enrolled on October 14, 2009, last patient in phase I on February 2, 2011. The first patient in phase II was enrolled on May 2, 2012, last patient in phase II on December 13, 2016.

Primary endpoint of the phase I part of the study is the occurrence of dose limiting toxicities (DLT)s in the first 4 weeks of treatment. A DLT is defined as any toxicity with common toxicity criteria for adverse events (CTCAE) grade ≥ 3 for which a causal relationship to the administration of lenalidomide, treosulfan, pioglitazone and dexamethasone is assumed. To be evaluable for DLT the patients must have taken at least 80% of the dose of lenalidomide, dexamethasone, pioglitazone and treosulfan or experienced a DLT.

Primary endpoint of the phase II part of the study is the response rate to treatment. A patient is defined as a responder according to the International Myeloma Working Group (IMWG) criteria (208).

Objective response is defined as the best response in the period from the start of cycle 1 until the day of the last dose of study medication plus 28 days. Patients with stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) were considered as responders. Point estimates of overall response rate (ORR = sCR+CR+VGPR+PR) and disease control rate (DCR = sCR+CR+VGPR+PR+SD) as well as the associated 95% confidence intervals were provided.

Secondary endpoints are time to progression (TTP), time to partial response (TPR), overall survival (OS), progression-free survival (PFS), duration of response and quality of life as well as safety parameters.

Time to progression (TTP) is defined as the duration from the day of first administration of any study drug to the day of progression. Patients who were not known to have had an event by the time of the analysis were censored based on the last recorded date the patient was known to be event-free.
Time to partial response (TPR) is defined as the duration from the day of first administration of any study drug to the day first occurrence of partial response (PR) or better. Patients who were not known to have had an event by the time of the analysis were censored based on the last recorded date the patient was known to be event-free.
Overall survival (OS) is defined as the duration from the day of first administration of any study drug to the day of death of any cause. Patients who were not known to have had an event by the

time of the analysis were censored based on the last recorded date the patient was known to be event-free.

Progression-free survival (PFS) is defined as the duration from the day of first administration of any study drug to the day of first progression or death of any cause. Patients who were not known to have had an event by the time of the analysis were censored based on the last recorded date the patient was known to be event-free.

Duration of response is defined for the patients with response (sCR, CR, VGPR, PR) as the duration from the day of first response to the day of first progression or death of any cause. Patients who were not known to have had an event by the time of the analysis were censored based on the last recorded date the patient was known to be event-free.

Analysis of European Organization for Research and Treatment of Cancer Quality of Life questionnaire core 30 (EORTC QLQ-C30) was done according to statistical analysis plan.

4.2 Inclusion/Exclusion Criteria

Patients included in our study had to suffer from previously treated relapsed or refractory or progressive myeloma with measurable myeloma paraprotein in serum and/or urine, and meet all of the following criteria:

- At least 18 years old
- Able to adhere to the study visit schedule and other protocol requirements
- Diagnosed with multiple myeloma that is progressing or has relapsed with progressive disease after at least two different anti-myeloma treatments, from which one must have contained lenalidomide for phase II inclusion
- Patients that have progressive disease after complete remission during preceding treatment need to have serum monoclonal paraprotein (M-protein) $\geq$ 0.5 g/dl for IgG and IgA myeloma and $\geq$ 0.05 g/dl for IgD myeloma or urine M-protein $\geq$ 0.2 g excreted in a 24 hours collection sample
- Patients that have progressive disease without complete remission during preceding treatment need to have a > 25% increase of serum M-protein or urine M-protein in comparison to the preceding M-protein nadir in serum/urine M-protein in a 24 hours collection sample
- Previously treated with lenalidomide for phase II part; any first- and second line treatment is allowed for the phase I part

- Sufficient bone marrow function: neutrophils ≥ $1x10^9$ /l, hemoglobin ≥ 10 g/dl and platelets ≥ $100x10^9$ /l
- Eastern cooperative oncology group (ECOG) performance status of 0, 1 or 2
- Discontinuation of all anti-myeloma drug or non-drug therapy prior to the first dose of study drug for at least four weeks
- Liver function: total bilirubin < 1.5 times upper limit of local institution and SGPT and SGOT ≤ 2.5 times upper limit of local institution
- Renal function: serum creatinine ≤ 1.5 times upper limit of local institution
- Coagulation: international normalized ratio (INR) < 1.5 times upper limit of local institution
- Normal cardiac function
- Patients with prior thromboembolic events with adequate anticoagulation
- Life expectancy at least three months
- Written informed consent of the patient prior to screening procedure
- Patient must be available for treatment and follow up
- Any previous surgery must have taken place more than four weeks prior to inclusion
- Previous radiation therapy must have involved less than 25% of bone marrow, and must have been completed more than four weeks prior to inclusion
- Able to take aspirin 100mg daily as prophylactic anticoagulation. Patients intolerant to aspirin may use low molecular weight heparin. Patients at high risk for thromboembolic events should receive low molecular weight heparin. Patients with history of thromboembolic events should pursue their ongoing anticoagulants, e.g. phenproucoumon, warfarin, heparin, or receive another adequate prophylaxis, at least low molecular weight heparin.
- Female subjects with childbearing potential must:
  - Understand that the study medication has a teratogenic risk
  - Be capable of complying with effective contraceptive measures
  - Be informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
  - Understand the need to commence as soon as it is dispensed following a negative pregnancy test
  - Agree to use two reliable forms of contraception simultaneously or practice complete abstinence

- Agree to have two medically supervised pregnancy tests prior to starting lenalidomide
- Agree to have medically supervised pregnancy tests weekly for the first 28 days and then every 14 days while taking lenalidomide and at study discontinuation and at days 14 and 28 following the last dose of lenalidomide
- Agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide
- Immediately inform the investigator if she considers the need to change or stop a method of contraception
- Be counseled about pregnancy precautions and the potential risk of fetal exposure at least every 28 days
- Immediately discontinue lenalidomide if pregnancy or a positive pregnancy test does occur
- Perform pregnancy testing and counseling if she misses her period or if pregnancy test or her menstrual bleeding are abnormal. Lenalidomide must be discontinued during this evaluation.
- The investigator must ensure that a female of childbearing potential complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding and acknowledges the requirements mentioned before

- Females not of childbearing potential must acknowledge that they understand the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide
- Male subjects must
  - Practice complete abstinence or use a condom during sexual contact with a pregnant female or female of childbearing potential while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy
  - Immediately inform the investigator if pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide
  - Not donate semen or sperm while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
  - Be counseled about pregnancy precautions and the potential risks of fetal exposure at a minimum of every 28 days

- All subjects must
  - Agree to abstain from donating blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
  - Agree not to share lenalidomide with another person and to return all unused capsules to the investigator
  - Be aware that no more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide

If a patient is meeting one or more of the following criteria, he must not be included into the trial:

- Patients who require vitamin K antagonists except for low dose (INR $\leq$ 2.5)
- Known hypersensitivity to dexamethasone or prior history of uncontrollable side effects to dexamethasone therapy
- Active infection > grade 2 CTCAE version 3.0
- Known diagnosis of HIV, hepatitis B or hepatitis C infection
- Severe, unstable, or uncontrolled medical disease which would confound diagnoses or evaluations required by the protocol, including cardiac insufficiency (new York heart association NYHA I – IV), uncontrolled diabetes, chronic hepatic or renal disease, active uncontrolled infection, chronic inflammatory intestinal disease and autoimmune disease
- Prior radiation therapy > 25% of bone marrow
- Regular blood transfusions
- Treatment with other experimental substances within 30 days before study start
- Participation in another clinical trial within 30 days before study start or during the trial
- Unwilling or unable to comply with the protocol
- Pregnant or lactating females
- Patients with seizure disorders requiring medication, such as steroids or antiepileptics
- Known hypersensitivity to one of the medications
- Patients undergoing renal dialysis
- Major surgery within four weeks prior to start of study or incomplete wound healing
- Drug or alcohol abuse
- Psychological or social conditions that may interfere with the patients' participation in the study or evaluation of the study results

- Known (at time of entry) gastrointestinal disorder, including malabsorption or active gastric ulcer, present to the extent that it might interfere with oral intake and absorption of study medication
- Any previous or concurrent malignancy or any cancer unless curatively treated more than three years prior to study entry except cervical carcinoma in situ or adequately treated basal cell carcinoma
- Neuropathy > grade 2 CTCAE version 3.0
- Patients with bladder cancer or bladder cancer in their medical history
- Macrohematuria of unknown origin
- Patients with risk factors for bladder cancer, such as exposure to aromatic amines or heavy tobacco smokers

4.3 Treatment, Dose Modifications and Study Discontinuation

In phase I, we determined the dose for phase II part based on dose limiting toxicities occurring in the first four weeks of treatment. Dose limiting toxicity is defined as any toxicity with CTCAE grade ≥ 3 for which a causal relationship to the administration of lenalidomide, treosulfan, pioglitazone and dexamethasone is assumed. According to the study protocol, 3 patients were treated with 10 mg p.o. daily of lenalidomide, 60 mg p.o. daily of pioglitazone, initially 40mg dexamethasone daily day 1-4 and day 15-18, then 20 mg day 1 and 15, while dexamethasone 1 mg p.o. daily was given continuously within the intervals of pulsed dexamethasone therapy, and 250 mg treosulfan p.o. twice daily. Three more patients were treated with the same regime, except for a dosing of 15 mg p.o. daily of lenalidomide. Dose limiting toxicities were monitored to determine the dosing of lenalidomide for phase II.

Drug supply

Lenalidomide capsules (Revlimid®) were supplied by Celgene corporation, Treosulfan capsules (Ovastat®) by Medac and pioglitazone tablets (Actos®) by Takeda for the duration of the trial. Dexamethasone was prescribed as usual.

Duration of treatment

All patients, phase I and phase II, received study medication as long as they showed no signs of progression and as long as no withdrawal criteria were met. The treatment regimens were

performed as explained in chapter 4.1. If any toxicity occurred, dose delays and modifications were performed as listed in the chapters below.

4.3.1 Visit schedule

A treatment cycle consists of 28 days. In cycles 1-4, patients need to be physically examined on day 1 and 15 of the cycle. In the following cycles, an examination is only needed on day one. Laboratory diagnostics for the evaluation of efficiency and safety of the study medication during the study included immunofixation electrophoresis, measuring of serum ß2 microglobulin, serum albumin, immunoglobulin concentration, free light chain concentration, serum calcium, coagulation including fibrinogen, partial thromboplastin time (PTT) and prothrombin time (PT), differential blood count, urine analysis and thyroid function tests. We also examined the ECOG performance status, vital signs, neurology, contraception warranty, quality of life, adverse events and performed a physical examination.

At the screening visit, among others we performed an electrocardiogram, bone marrow examination, skeletal survey, physical examination and assessment of soft tissue myeloma. At the end of each cycle, the response to therapy was evaluated. 28 days after the last intake of study medication, we performed a final examination.

Follow up visits were performed three and six months after end of treatment. We collected information about survival, initiation of new antimyeloma therapies and occurrence of secondary or primary malignancies. Thereafter, we collected this information every six months for at least three years, if the patient was available for follow up.

The assessments and examinations were performed as listed in the visit schedule which is attached at the end of this dissertation.

4.3.2 Dose Modifications and Discontinuations

Treatment Schedule in Phase II

Drug	Dosing
Lenalidomide	15 mg p.o. daily
Pioglitazone	60 mg p.o. daily
Dexamethasone	Initially 40 mg p.o. daily day 1-4 Then 20 mg p.o. daily day 1 and 15 1 mg p.o. daily within the intervals of pulsed therapy
Treosulfan	250 mg p.o. twice daily

Table 5: Treatment schedule für phase II for Lenalidomide, Pioglitazone, Dexamethasone and Treosulfan

Dose Modifications and Discontinuations due to Lenalidomide Toxicity:

Lenalidomide toxicities were graded according to NCI-CTCAE v3.0 and treated as listed in Table 6. Dose reduction steps for lenalidomide are listed in Table 7**.**

NCI Toxicity	Action
Therapy-associated Neutropenia ≥ grade 3	• Hold dose • Follow hematology weekly • Restart at one dose level lower when neutropenia has resolved to ≤ grade 2 • Notify medical monitor if neutropenia does not resolve to ≤ grade 2 within four weeks
Therapy-associated Thrombopenia (platelet count < 50.000/mm^3)	• Hold dose • Follow hematology weekly • Restart at next lower dose level when platelet count has increased to ≥ 50.000/mm3 without evidence of hemostatic failure (for example bleeding or petechiae) • Notify medical monitor if platelet count does not increase within four weeks
Non-blistering rash	

- Grade 3 **- Grade 4**	• Hold/interrupt dose, follow weekly • If the toxicity resolves to ≤ grade 1, restart at next lower level • Discontinue Lenalidomide
Desquamating or blistering rash any grade	• Discontinue Lenalidomide
Allergic reaction or hypersensitivity **- Grade 2** **- ≥ Grade 3**	• Hold dose, follow at least weekly • When toxicity resolves to < grade 1, restart at next lower dose level • Discontinue Lenalidomide
Venous thrombosis/thromboembolism > grade 3	• Hold dose and start therapeutic anticoagulation • Restart at investigators discretion (maintain dose level)
Hyperthyroidism or hypothyroidism > grade 2	• Hold dose, evaluate etiology • Initiate appropriate therapy • Restart when stable
Neuropathy **- Grade 2 (preexisting)** **- Grade 2 (new occurrence)** **- ≥ Grade 3**	• No dose reduction • Follow at least weekly • When toxicity resolves to < grade 1, restart at next lower dose level • Discontinue Lenalidomide
Other non-hematological ≥ grade 3 toxicity deemed likely to be related to Lenalidomide	• Hold dose • When toxicity has resolved to ≤ grade 2, restart at next lower dose level • Notify medical monitor if toxicity does not resolve to ≤ grade 2 within four weeks

Sinus bradycardia or other cardiac arrhythmia **- Grade 2** **- ≥ Grade 3**	• Hold dose, follow at least weekly • When toxicity resolves to < grade 1, restart at next lower dose level • Discontinue Lenalidomide
Creatinine clearance **- 30-50 ml/min** **- < 30 ml/min but serum creatinine < 2.5 mg/dl** **- < 30 ml/min and serum creatinine > 2.5 mg/dl**	• 10 mg Lenalidomide daily • 15mg of Lenalidomide every second day • Discontinue Lenalidomide
Hepatotoxicity ≥ grade 3	• Hold dose • Monitor liver toxicity at least weekly with liver ultrasound, liver enzymes, bilirubin and alcalic phosphatase (AP) if patient is asymptomatic. Monitor daily, if patient is symptomatic • In case of grade 4 toxicity, Lenalidomide and pioglitazone shall not be resumed • When toxicity has resolved from grade 3 to < grade 2, restart at next lower dose level of lenalidomide and of pioglitazone • Notify medical monitor if toxicity does not resolve to < grade 2 within 4 weeks. Then lenalidomide and pioglitazone shall not be resumed

Table 6: Lenalidomide Dose Modifications

Lenalidomide Dose Level	Action
Starting Dose	15 mg once daily
Dose Level -1 (neutropenia only)	The initial dose of 15 mg every day plus G-CSF
Dose Level -2	10 mg every day
Dose Level -3	Interruption of Lenalidomide until resolution of toxicity < grade 1, resumed one dose level lower

Table 7: Lenalidomide Dose Reduction Steps (Phase II)

Dose Modifications and Discontinuations due to Dexamethasone Toxicity:

Dexamethasone toxicities were graded according to NCI-CTCAE v3.0 and treated as listed in Table 8. Dose reduction steps for lenalidomide are listed in Table 9**.**

NCI Toxicity	Action
Dyspepsia, gastric or duodenal ulcer or gastritis **- Grade 1 or 2**	• Treat with H2-Blockers, sucralfate or omeprazole • If symptoms persist, decrease dose by one dose level as needed
- ≥ Grade 3	• Hold until symptoms controlled • Restart by decreasing dose by one dose level and add H2-blockers, sucralfate or omeprazole
Edema ≥ Grade 3	• Decrease dose by one level • Use diuretics as needed
Confusion or mood alterations ≥ Grade 2	• Hold until symptoms resolved • Restart dosing by decreasing dose by one dose level
Muscle weakness ≥ Grade 2	• Decrease dose by one dose level

	• If symptoms persist, then decrease dose by one dose level as needed
Hyperglycemia ≥ Grade 3	• Decrease dose by one dose level • Treat with insulin or oral hypoglycemics as needed
Acute pancreatitis ≥ Grade 3	• Discontinue subject from dexamethasone

Table 8: Dexamethasone Dose Modifications

Dexamethasone Dose Level	**Action**
Pulsed Therapy: Starting Dose Dexamethasone 40 mg p.o. Daily Days 1-4 and 15-18	
Dose Level -1	Dexamethasone 40 mg daily day 1-4
Dose Level -2	Dexamethasone 20 mg daily day 1-4
14 Days Interval Therapy: Starting Dose Dexamethasone 20 mg daily day 1 and 15	
Dose Level -1	Dexamethasone 20 mg daily day 1
Dose Level -2	Dexamethasone 10 mg daily day 1
Continuous Therapy: Starting Dose Dexamethasone 1 mg daily days 5-14 and 19-28	
Dose Level -1	Dexamethasone 0,5 mg daily
Dose Level -2	Dexamethasone 0,5 mg every second day

Table 9: Dexamethasone Dose Reduction Steps

Dose Modifications and Discontinuations due to Pioglitazone Toxicity:

Pioglitazone toxicities were graded according to NCI-CTCAE v3.0 and treated as listed in Table 10. Dose reduction steps for lenalidomide are listed in Table 11**.**

NCI Toxicity	**Action**
Weight gain due to adipositas ≥ grade 3	• Decrease dose by one dose level until weight keeps stable
Headache ≥ grade 1	• Decrease dose by one dose level • Treat symptomatic

Edema or fluid retention ≥ grade 3	• Decrease dose by one dose level until edema are ≤ grade 1 • Use diuretics as needed • Keep dose with diuretics if possible
Muscle weakness or pain ≥ grade 2	• Decrease dose by one dose level • If symptoms persist, decrease dose by one dose level as needed
Clinically manifest congestive heart failure ≥ NYHA Class I	• Hold until symptoms resolved • Restart dosing by decreasing dose down one dose level
Hepatotoxicity ≥ grade 3	• Hold dose • Monitor liver toxicity at least weekly with liver ultrasound, liver enzymes, bilirubin and AP if patient is asymptomatic. Monitor daily, if patient is symptomatic • In case of grade 4 toxicity, Lenalidomide and pioglitazone shall not be resumed • When toxicity has resolved from grade 3 to < grade 2, restart at next lower dose level of lenalidomide and of pioglitazone • Notify medical monitor if toxicity does not resolve to < grade 2 within 4 weeks. Then lenalidomide and pioglitazone shall not be resumed

Table 10: Pioglitazone Dose Modifications

Pioglitazone Dose Level	**Action**
Starting Dose	60 mg once daily
Dose Level -1	45 mg once daily
Dose Level -2	30 mg once daily
Dose Level -3	15 mg once daily

Table 11: Pioglitazone Dose Reduction Steps

Dose Modifications and Discontinuations due to Treosulfan Toxicity:

Treosulfan toxicities were graded according to NCI-CTCAE v3.0 and treated as listed in Table 12. Dose reduction steps for lenalidomide are listed in Table 13**.**

NCI Toxicity	Action
Therapy-associated neutropenia ≥ grade 3	• Hold dose • Follow hematology weekly • Restart at one dose level lower when neutropenia has resolved to ≤ grade 2 • Notify medical monitor if neutropenia does not resolve to ≤ grade 2 within four weeks
Therapy-associated Thrombocytopenia (Platelet count < 50.000/mm^3)	• Hold dose • Follow hematology weekly • Restart at one dose level lower when platelet count has increased to ≥ 50.000/mm^3 without evidence of hemostatic failure (for example bleeding or petechiae) • Notify medical monitor if platelet count does not increase within four weeks

Table 12: Treosulfan Dose Modifications

Treosulfan Dose Level	Action
Starting Dose	• 250 mg twice daily
Dose Level -1 (neutropenia only)	• 250 mg once daily
Dose Level -2	• 250 mg once daily plus G-CSF
Dose Level -3	• Interruption of treosulfan treatment for four weeks, restarted on Level -2 every four weeks

Table 13: Treosulfan Dose Reduction Steps

4.3.3 Study Discontinuation

There are several reasons for removing a patient from study. Reasons for removal can be:

- If a treating physician determines that a study patients' medical condition requires the use of an additional anticancer therapy or other angiogenetic therapy
- At their own request or at the request of their legal representative
- If, in the investigators' opinion, continuation in the study would be detrimental to the patients' well-being
- The specific request of the sponsor
- Substantial non-compliance with the requirements of the study
- Pregnancy
- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy
- The development of a second malignancy including any bladder cancer
- Patient who is lost to follow-up
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing results
- Simultaneous interruption of treosulfan and pioglitazone administration for greater than 28 days
- Disease progression. In cases where radiographic imaging is not possible, clinical progression may be used
- Complete remission. In case of complete remission, treatment will be interrupted

4.3.4 Concomitant Therapy

Prior and concomitant therapy were recorded in the case report form.

All patients were recommended to receive aspirin 100mg daily for preventing deep vein thrombosis. Patients unable to tolerate aspirin or patients with history of thromboembolic events received low molecular weight heparin. Patients with other high-risk factors for thromboembolic events continued ongoing anticoagulation like phenprocoumon, warfarin or heparin or received low molecular weight heparin.

Bisphosphonates were given according to the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines or the UK Myeloma Forum and the Nordic Myeloma Study Group (209)(210).

All subjects were recommended to receive a prophylactic anti-infectious therapy like levofloxacin, ciprofloxacin, or other broad-spectrum antibiotics due to the predisposition to infections caused by high dose dexamethasone therapy. They were also recommended to receive appropriate antibacterial, antifungal or antiviral therapy if infections occurred.

4.4 Assessment Tools

4.4.1 NCI-CTCAE

We used the Common Toxicity Criteria for Adverse Events v3.0 published by National Cancer Institute to classify clinical adverse events occurring during our study. The NCI-CTCAE provides terms and gradings for AEs, which can be used to report AEs in the Case Report Form (CRF). It is linked in source (211).

4.4.2 ECOG Performance Status

In 1982, the Eastern Cooperative Oncology Group (ECOG) presented the ECOG performance status (212) (213) as a tool to evaluate the fitness and the ability to master everyday life. In our study, the attending physician was asked to evaluate the ECOG performance status at each visit. The ECOG criteria for estimating the performance status of patients are listed in Table 14 (214).

Grade	Scale
0	Fully active, able to carry out all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out work activities. Active about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

Table 14: ECOG Criteria for Estimation of Performance Status (214)

4.4.3 EORTC QLQ-30

European Organization for Research and Treatment of Cancer developed the Core Quality of Life Questionnaire to determine life quality of cancer patients. We used the EORTC-QLQ-30 and handed it to our patients at every study visit. A copy of this questionnaire is attached to this document in “attachments”.

4.4.4 IMWG Response Criteria

To determine the efficiency of our treatment, we used the International Myeloma Working Group Response Criteria for multiple myeloma, which distinguish between stringent complete response, complete response, very good partial response, partial response, minimal response, stable disease, progressive disease, clinical relapse, relapse from complete response and relapse from MRD-negative response (215). In our study protocol, we used the response categories listed in Table 15 (215).

Response	Criteria
Stringent Complete Response sCR	Complete response as defined below plus normal free light chain (FLC) ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)
Complete Response CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very Good Partial Response VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h

Partial Response PR	• ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30% • In addition to these criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease SD	Not meeting criteria for complete response, very good partial response, partial response or progressive disease

Progressive Disease PD	Any one or more of the following criteria:
	• Increase of 25% from lowest confirmed response value in one or more of the following criteria:
	  • Serum M-protein (absolute increase must be ≥0.5 g/dl)
	  • Serum M-protein increase ≥1 g/dl, if the lowest M component was ≥5 g/dl
	  • Urine M-protein (absolute increase must be ≥200 mg/24 h)
	• In patients without measurable serum and urine M-protein levels, the difference

	between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl) • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in diameter of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis • ≥50% increase in circulating plasma cells (minimum of 200 cells per µl) if this is the only measure of disease

Table 15: IMWG Response Criteria for Multiple Myeloma (215)

4.5 Safety analysis

4.5.1 Study population

The following populations were evaluated:

Safety set (Safety analysis): All patients who have received at least one dose of any study medication (lenalidomide, pioglitazone, dexamethasone and/or treosulfan) and had at least one post-baseline safety assessment (cycle 1 or later) were included in the safety set (SAF). The statement that a patient had no adverse events (on the Adverse Event CRF) constitutes as safety assessment. Patients who have received at least one dose of the study drug but have no post-baseline safety data of any kind were excluded from the safety population.

The safety set I (SAF-I) includes all patients from the safety set who were registered in the phase I part of the study and the safety set II (SAF-II) includes the patients from the safety set who were registered in the phase II part of the study.

Full analysis set (intent-to-treat analysis): The full analysis set (FAS) includes all treated patients who received at least one dose of any study drug (lenalidomide, pioglitazone, dexamethasone and/or treosulfan). The full analysis set contains the safety set.
The full analysis set I (FAS-I) includes all patients from the full analysis set who were registered in the phase I part of the study and the full analysis set II (FAS-II) includes the patients from the full analysis set who were registered in the phase II part of the study.

Per-protocol set (per-protocol analysis): The per-protocol set (PP) includes all patients from the full analysis set who showed no major protocol violations. Protocol violations that may have an impact on the study outcome are considered as major protocol violations.
The per-protocol set I (PP-I) includes all patients from the per-protocol set who were registered in the phase I part of the study and the per-protocol set II (PP-II) includes the patients from the per-protocol set who were registered in the phase II part of the study.

Dose-limiting toxicity set (analysis): The dose-limiting toxicity set (DS) contains all patients of the phase I part who have received at least 80% of the dose of lenalidomide, dexamethasone, pioglitazone and treosulfan or experienced a DLT.

4.5.2 Adverse events

The severity of adverse events is graded by the investigators according to NCI-CTCAE version 3.0 whenever possible. Recorded adverse events were coded by preferred term and system organ class using medical dictionary for regulatory activities (MedDRA) version 16.1; per system organ class and preferred term each patient is counted only once, irrespective of the number of episodes of the event. Adverse events were documented per cycle with highest NCI-CTCAE grade. An AE is seen as related to study treatment if it is related to at least one substance (including missing and unknown causality). Analysis of treatment-emergent adverse events (TEAE) (i.e. events starting in the period from first administration of study medication (Day 1 of Cycle 1) to 30 days after the last administration of study medication) were done for the safety set.

5 Results

5.1 Demographic Data and Patient Characteristics

15 women (31.9%) and 32 men (68.1%) were treated; the median age was 63.0 years with an overall range from 47.0 to 77.0 years. The baseline ECOG performance status was 0 for 19 patients (40.4%) and 1 for 24 patients (51.1%), only 4 patients (8.5%) had an ECOG of 2.
Patient characteristics are summarised in Table 16.

Age	
Median (range)	63 (47 to 77)
18 to <65, n (%)	29 (61.7)
65 to <85, n (%)	18 (38.3)
Sex, n(%)	
Women	15 (31.9)
Men	32 (68.1)
Ethnic origin, n (%)	
Caucasian	46 (98)
African	1 (2)
Eastern Cooperative Oncology Group Score, n (%)	
0	19 (40.4)
1	24 (51.1)
2	4 (8.5)
International Staging System Stage, n (%)	
I	13 (27.7)
II	21 (44.7)
III	11 (23.4)
Type of Myeloma at Diagnosis, n (%)	
Immunoglobulin A	8 (17.1)
Immunoglobulin G	27 (57.4)
Immunoglobulin D	1 (2)
Light Chain κ and λ	11 (23.4)
Cytogenetic profile, n (%)**	
Unfavorable:	

t(4/14), del (17/17p), 1q21ampl	5 (11)
Standard risk :	
Del 13q	23 (52)
Others	9 (20)
Normal :	8 (17)
Extramedullary myeloma ≥ 1 Site ; n (%)	4 (8.5)
Time since initial diagnosis (years); median (range)	4.2 (0.7 to 21.8)
More than 3 previous therapies	
Number of patients, n (%)	40 (85)
Number of therapies, median (range)	4 (2 to 10)
Previous proteasome inhibitor, n (%)	
Bortezomib	37 (79)
Carfilzomib	2 (4)
Previous IMiD, n (%)	
Lenalidomide	41 (87)
Pomalidomide	1 (2)
Thalidomide	5 (11)
Previous dexamethasone, n (%)	47 (100)
Previous HD-CT plus ASCT	
Number of patients, n (%)	33 (70)
Number of HD-CTs	48
Previous conventional chemotherapy*, n (%)	**47 (100)**
Others, n (%)	
Clarithromycin	1 (2)
Everolimus	1 (2)
Refractoriness based on most recent medication, n (%)	
IMiD	16 (34)
Proteasome inhibitor	10 (21)
IMiD plus proteasome inhibitor	1 (2)
HD-CT plus ASCT	6 (13)

Conventional chemotherapy	12 (26)
Peg-Interferon	2 (4)
LGH 447 (PIM kinase inhibitor)	1 (2)

Table 16: Patients characteristics

*Mobilizaton therapy not considered; HD-CT plus ASCT = High-dose chemotherapy and autologous blood stem cell transplantation; ** cytogenetic abnormalities were studied by fluorescence in-situ hybridization or karyotyping or both at baseline. Cytogenetic profile was available for 44 out of 47 patients (93.6%)

Duration of disease at time of registration was 63.7 months (median, range from 33.1 to 132.8 months) in the phase I part and 50.2 months (median, range from 8.0 to 261.9 months) in the phase II part. 91.5% of the patients had a progressive multiple myeloma and 8.5% a relapsed multiple myeloma. Stage of multiple myeloma according to ISS at study entry was I for 27.7%, II for 44.7% and III for 23.4% of the patients.

The most frequent subtype of multiple myeloma was IgG (54.7%), Light Chain κ and λ (23.4%) and IgA (17.1%). 5 Patients (11%) had a high risk cytogenetic profile (t(4/14), del(17/17p) or 1q21 amplification). 40 Patients (89%) had a standard risk (either del 13q, normal or others) as shown in Table 16. Four Patients (8.5%) had extramedullary myeloma.

The median time since initial diagnosis was 4.2 years (range 0.7 to 21.8 years). All patients had at least two previous therapies (median 4; range 2 to 10). All patients (100%) received dexamethasone in previous treatments and all patients (100%) were previously treated with conventional chemotherapy. 39 Patients (83%) received proteasome inhibitors (Bortezomib; 79% or Carfilzomib; 2%). All Patients (100%) had a previous treatment with IMiD (lenalidomide 87%, pomalidomide 2%, thalidomide 11%). 33 Patients (70%) have had prior high-dose chemotherapy plus allogenic stem cell transplantation.

5.2 Treatment with Study Medication

The mean treatment duration was 11.6 months in the phase I part and 8.1 months in the phase II part with an overall range from 0.9 to 24.0 months and 0.2 to 57.1 months in the SAF, respectively. More than half of the patients had ≤ 6 cycles study medication. The most frequent reason reported for termination of study therapy was relapse/progression (50.0% in the phase I part and 35.9% in the phase II part. The following Table 17 summarizes the treatment data:

SAF	Phase I (N=8)	Phase II (N=39)	Overall (N=47)
	N (%) / mean ± standard deviation (median)		
Treatment duration (months)	11.6 ± 8.4 (11.2)	8.1 ± 11.6 (3.9)	8.7 ± 11.1 (4.7)
Number of cycles: 1	1 (12.5)	4 (10.3)	5 (10.6)
Number of cycles: 2	1 (12.5)	1 (2.6)	2 (4.3)
Number of cycles: 3	-	9 (23.1)	9 (19.1)
Number of cycles: 4	-	4 (10.3)	4 (8.5)
Number of cycles: 5	-	3 (7.7)	3 (6.4)
Number of cycles: 6	-	3 (7.7)	3 (6.4)
Number of cycles: > 6	6 (75.5)	15 (38.5)	21 (44.7)

Table 17: Number of cycles

5.3 Dose Reduction

The scheduled dose reduction scheme allowed adequate dose reduction and the quadruple therapy could be maintained as quadruple therapy to study end. The median dose of the potentially myelotoxic drugs, lenalidomide and treosulfan had to be reduced in median by 50% of the starting dose (Table 18). 40 patients (85%) received more than two 4-week cycles.

	Phase I				**Phase II**	
	Lenalidomide 10 mg/d	Lenalidomide 15 mg/d	Lenalidomide 10 mg/d	Lenalidomide 15 mg/d	Lenalidomide 15 mg/d	
Study drug	Number of patients / overall dose reduction*		Number of patients / overall dose intensity (%)**, % median (range)		Number of patients / overall dose reduction*	Number of patients / overall dose intensity (5)**, median (range)
Dexamethasone	1*** /12.5 4 / 50	3 / 37.5	5 / 96.2 (39 – 100)	3 / 68.8 (56 – 90.3)	5*** / 12.8 34 / 87.2	39 / 91.0 (35 – 100)
Treosulfan	1*** / 12.5 4/50	3 / 37.5	5 / 64.3 (52 – 100)	3 / 38.7 (37 – 51)	2*** / 5.1 37 / 94.9	39 / 49.2 (16 – 100)
Pioglitazone	2*** / 25 3 /37.5	3 / 37.5	5 / 82.3 (52 – 100)	3 78.6 (54 – 88.5)	2*** / 5.1 37 / 94.9	39 / 80.0 (17 – 100)

Lenalidomide	1*** / 12.5 4 / 50	3 / 37.5	5 / 82.3 (53 – 100)	3 / 47.9 (37 – 61)	2*** / 5.1 37 / 94.9	39 / 50.0 (17 – 100)

Table 18: Dose reduction and dose intensity per protocol.

* A cycle with dose reduction is defined as a cycle with dose intensity lower 90%. Overall dose reduction is defined as at least one cycle with dose reduction. Percent based on number of patients in the respective phase (8 patients in phase I and 39 patients in phase II). Percent based on number of patients in each cycle. **Dose intensity is calculated as given dose divided by planned dose for each cycle. For overall dose intensity of the total dose per patient is used. *** No dose reduction

5.4 Primary Endpoints

In phase I, we investigated dosing of lenalidomide based on the occurring dose limiting toxicities. Results for the primary endpoint of the phase I part of the study (occurrence of DLTs) are presented for DS. As no dose limiting toxicities occurred, the higher dosing of lenalidomide with 15 mg p.o. daily was chosen. For details about the study design of phase I see chapter 4.1.

Primary endpoint of the phase II part of the study was the response rate to treatment. One patient of the phase II part of the study experienced CR. 7 patients (17.9%) experienced VGPR, 13 patients (33.3%) PR and 15 patients (38.5%) SD. Thus, 20 patients out of the 39 patients of the phase II part of the study achieved a response. The objective response rate is 51.3%. The p-value of the one-sided binomial hypothesis is 0.0043. The null hypothesis H0: $p \leq p0$ ($p0 = 0.30$) is rejected at the target significance level $\alpha = 0.10$. The overall disease control rate was 91.5%. Results of the analyses of objective response rate and disease control rate are shown in Table 19 and Table 20.

FAS	Response (sCR-PR) achieved	p-value (binomial hypothesis test)
	N (%) [95%-CI]	
Phase I (N=8)	7 (87.5) [47.3, 99.7]	-
Phase II (N=39)	20 (51.3) [34.8, 67.6]	0.0043
Overall (N=47)	27 (57.4) [42.2, 71.7]	-

Table 19: Objective response rate

FAS	Disease control (sCR-SD)
	N (%) [95%-CI]
Phase I (N=8)	8 (100.0) [63.1, 100.0]
Phase II (N=39)	35 (89.7) [75.8, 97.1]
Overall (N=47)	43 (91.5) [79.6, 97.6]

Table 20: Disease control rate

Response rates differed between IMiD-exposed and IMiD-refractory patients (see Figure 1). Notably, VGPR rate in IMiD-refractory patients was higher than in IMiD-exposed patients (31.3% vs. 8.0% respectively). Overall response rate in IMiD-refractory patients was 62.5% vs. 52% in IMiD-exposed, but not refractory patients. This effect could not be shown for proteasome inhibitors (Figure 2). Here, response rates were much higher in proteasome inhibitor-exposed, but not in refractory patients, but no PI-refractory patient hat progressive disease. Also of interest, patients with more than 3 prior therapies (Figure 3) showed higher rates of partial response than patients with 2 or 3 prior therapies (41% vs 26.7% respectively).

From 33 patients in total with prior high dose chemotherapy and autologous stem cell therapy, one patient achieved complete remission, 7 patients hat VGPR, and 10 patients had PR (Figure 4), so the overall response rate for these patients is 54.5%.

We enrolled 5 patients with a high cytogenetic risk, from which no one had progressive disease (Figure 5). One of these patients even had VGPR, 2 patients had PR, and 2 patients had SD, so the overall response rate for these patients was 60%.

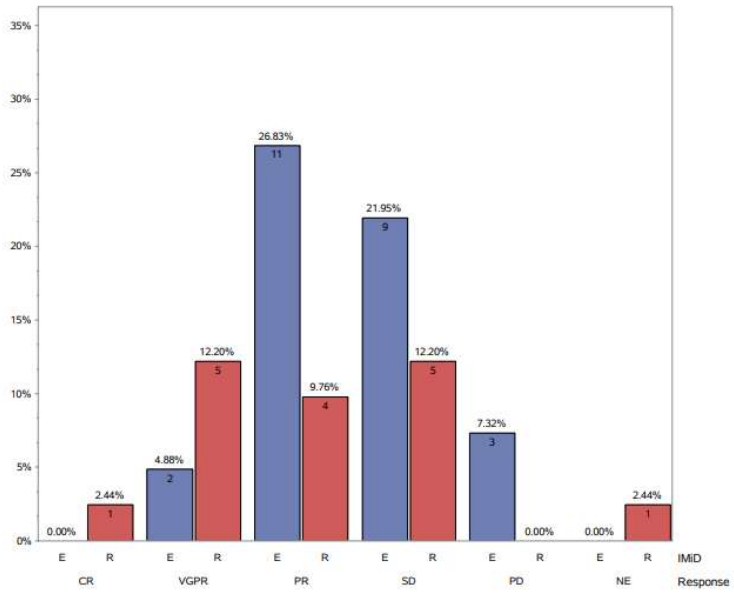

Figure 1: Response rates in IMiD exposed (E) and refractory patients (R).

IMiD = immunomodulatory drugs; E = IMiD exposed; R = IMiD refractory; CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated

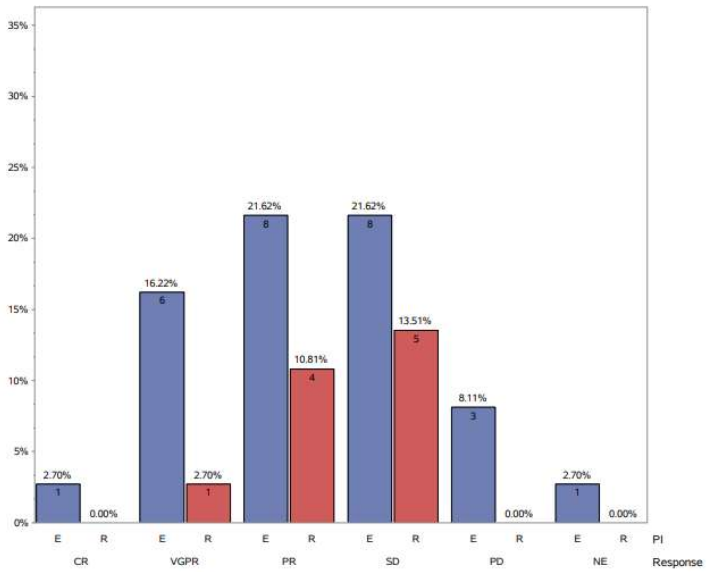

Figure 2: Response rates in proteasome inhibitor exposed (E) and refractory patients (R)

PI = proteasome inhibitor; E = PI exposed; R = PI refractory; CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated

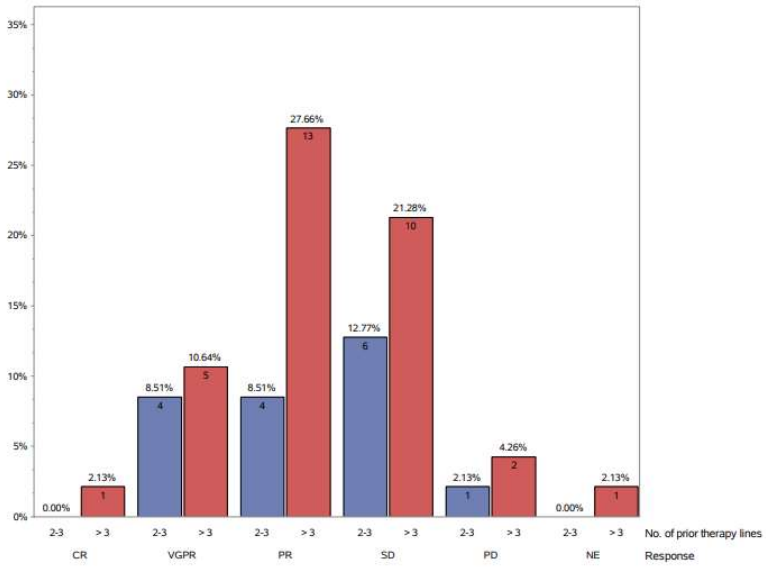

Figure 3: Best overall response rates depending on number of previous therapies
CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated

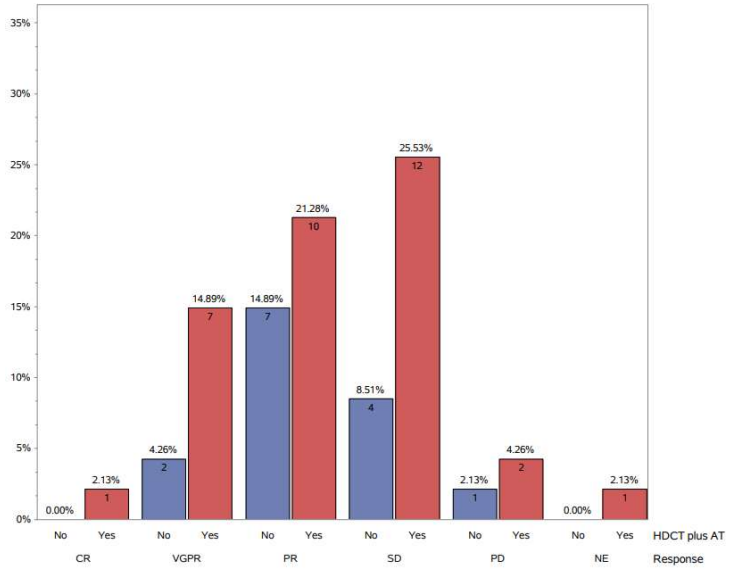

Figure 4: Best overall response rates depending on previous high-dose chemotherapy plus autologous transplantation
HDCT plus AT = high dose chemotherapy plus autologous transplantation; CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated

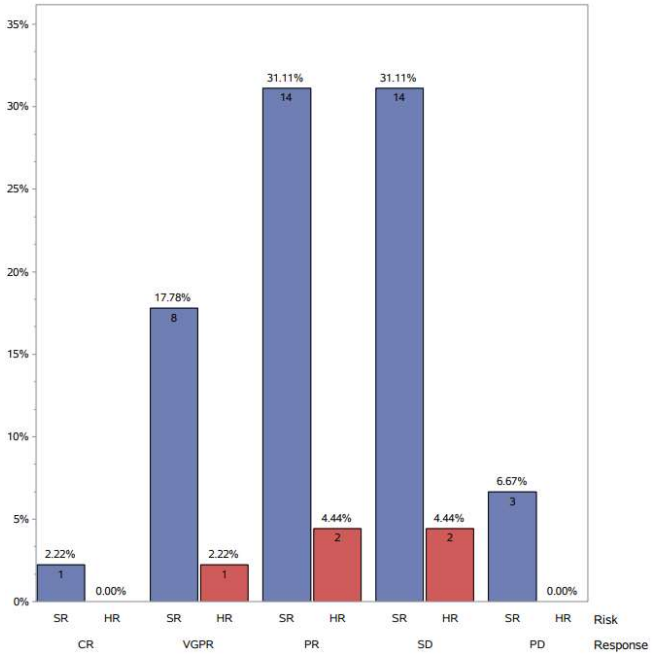

Figure 5: Best overall response rates depending on cytogenetic risk

SR = standard risk (blue); HR = high risk (red); CR = complete response; VGPR = very good partial response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated

5.5 Secondary Endpoints

Secondary endpoints are time to progression (TTP), time to partial response (TPR), overall survival (OS), progression-free survival (PFS), duration of response, quality of life and tolerability and safety.

In a Kaplan-Meier analysis, the median TTP was 18.5 month in the phase I part and 6.0 months in the phase II part (Figure 6). The longest TTP was about 80 months. The median TPR was 1.0 month in the phase I part and 3.7 months in the phase II part with an overall median TPR of 2.8 months (Figure 7). Additionally, the analysis was performed only for patients with sCR-PR. The median TPR was 1.0 month in the phase I part and 1.0 months in the phase II part.

The median OS was 39.2 months (Figure 8). The median PFS was 18.5 month in the phase I part and 6.0 months in the phase II part and 8.3 months in total (Figure 9). The median duration of response was 13.8 months in total (Figure 10).

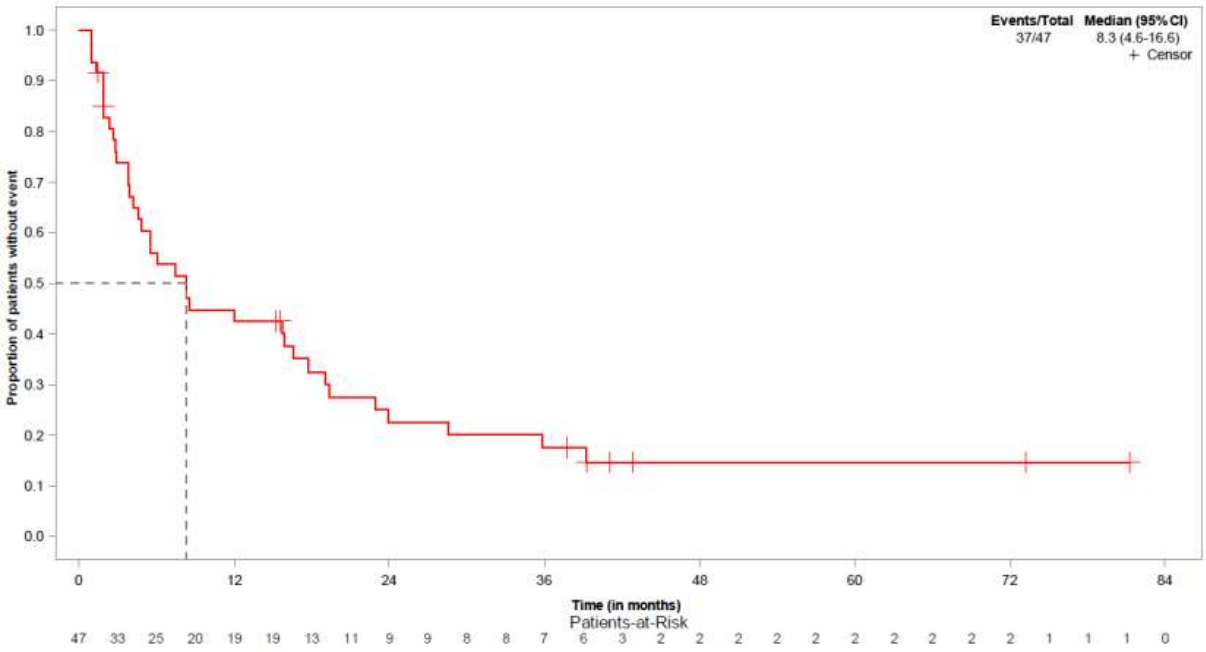

Figure 6: Time to progression

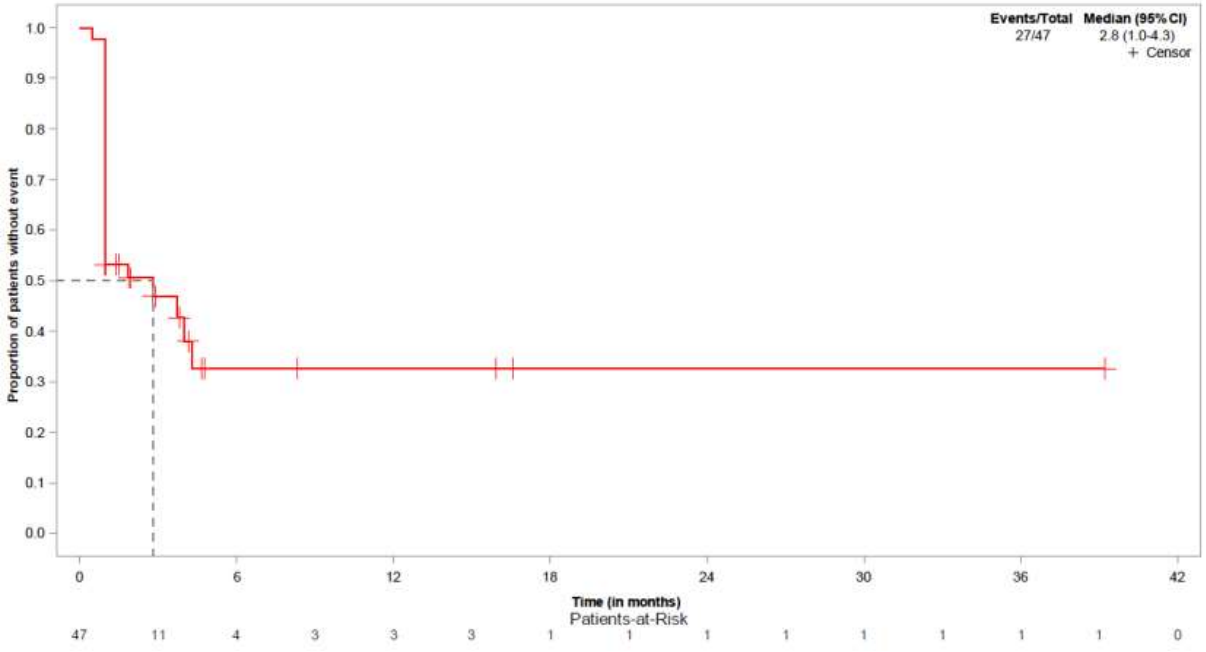

Figure 7: Time to partial response

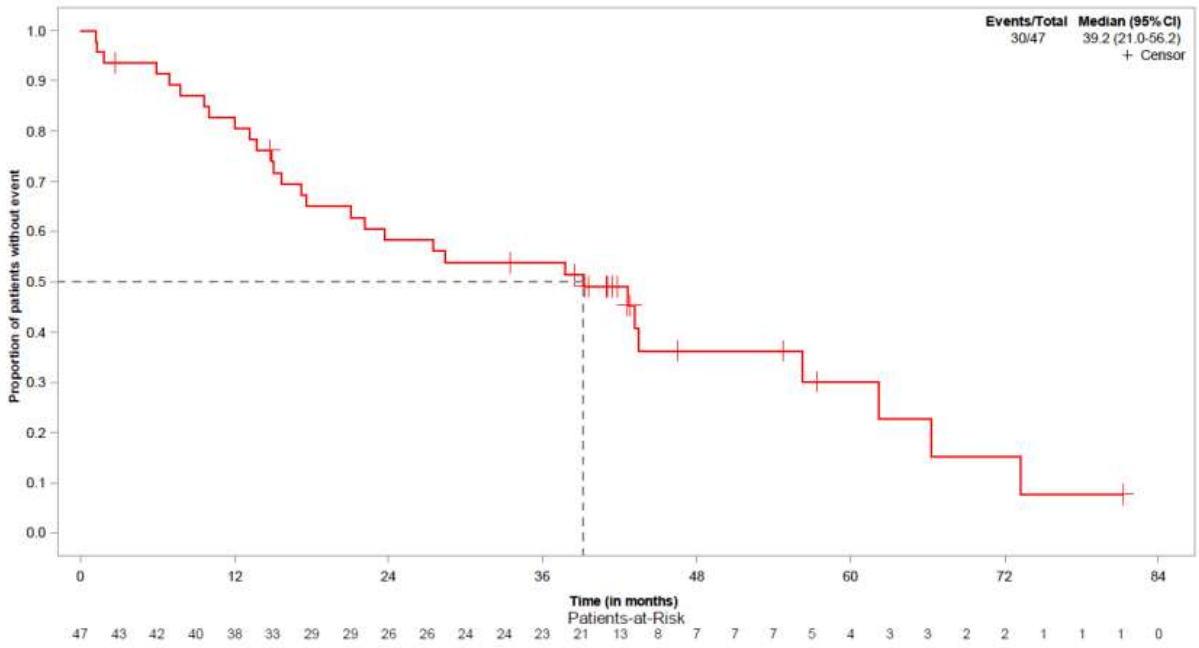

Figure 8: Overall survival

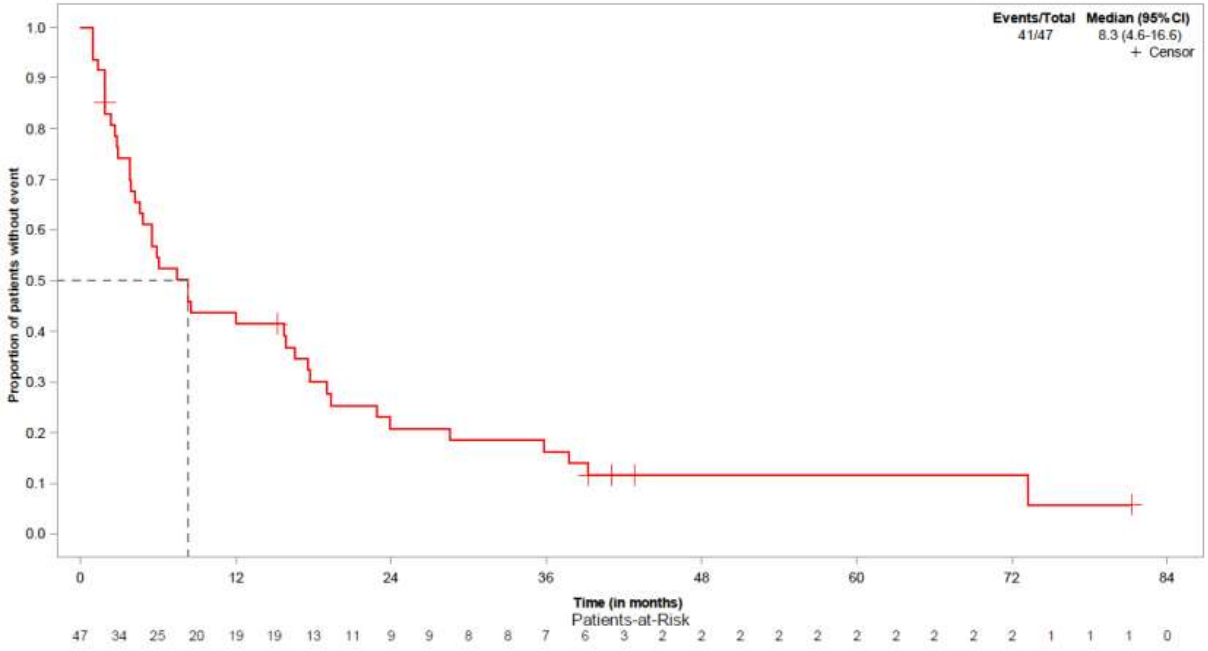

Figure 9: Progression free survival

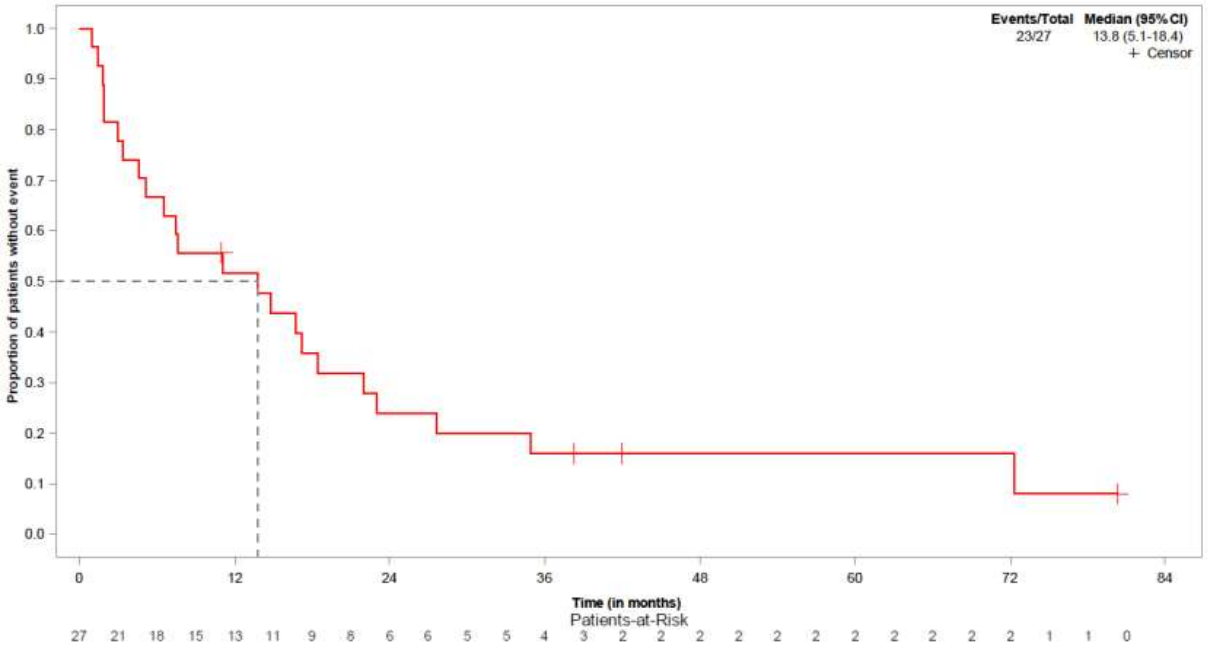

Figure 10: Duration of response

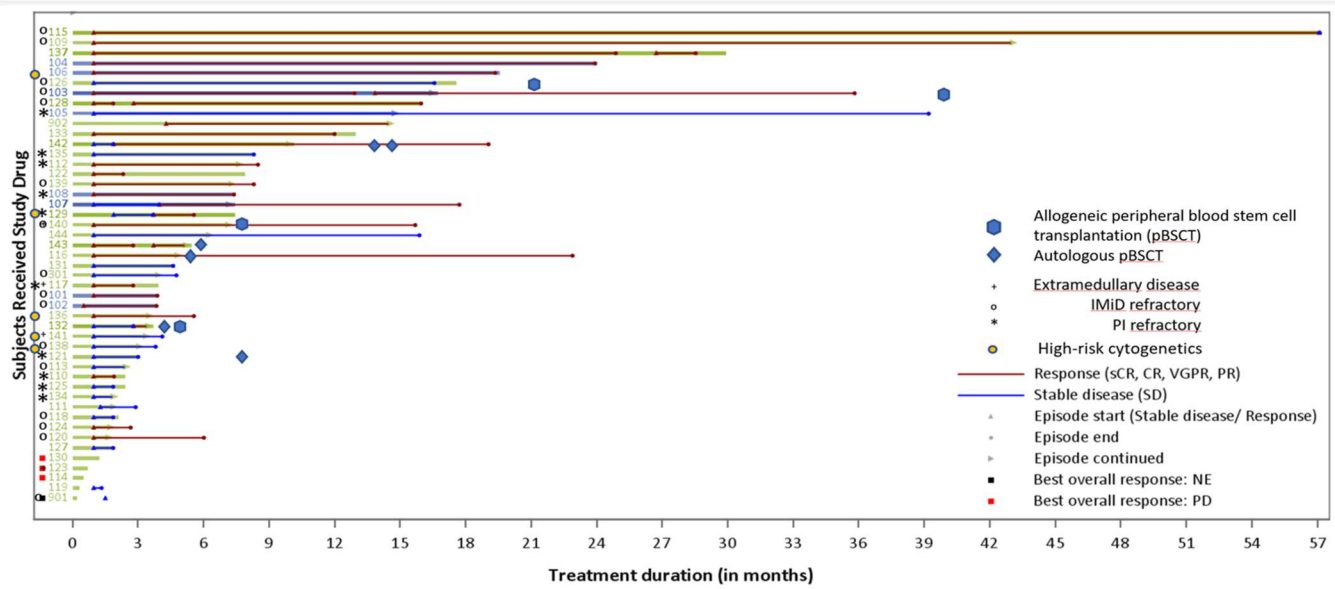

Figure 11: Swimmer plot of all patients. Each bar represents one subject in the study. Right arrow cap indicates continued stable disease or continued response respectively.

Figure 11 shows a swimmer plot of all patients. The longest treatment duration was 57 months with a sustained response. 8 patients were transplant-eligible after treatment, of which 3 patients received allogenic peripheral blood stem cell transplantation (pBSCT), 4 patients received autologous pBSCT and one patient had allogenic and autologous pBSCT. 16 patients were treated for one year or more, from which 2 had stable disease and 14 responded (PR, VGPR, CR or sCR).

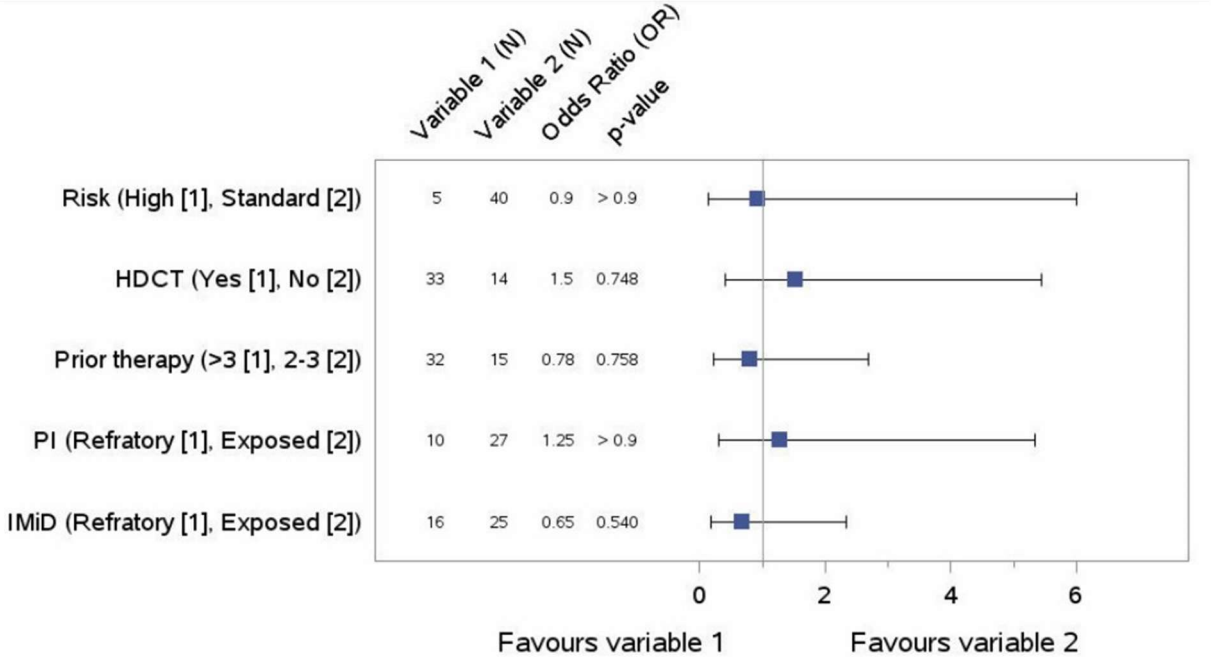

Figure 12: Objective response rates depending on cytogenetic risk, prior high dose chemotherapy (HDCT), number of prior therapies, prior proteasome inhibitor (PI)-exposure and prior IMiD-exposure

The graphic show odds ratio (OR) and 90%-confidence interval (CI) and is based on the full analysis set (FAS).

A dichotomous explorative analysis (Figure 12) shows cytogenetic risk, resistance to lenalidomide (n=16), bortezomib or HD-CT have no significant impact on disease control rate (DCR), ORR, and OS. Cytogenetic high-risk patients achieved either an objective response or stable disease. Previous lenalidomide resistance did not influence short- or long-term outcome parameters. Of 16 patients with IMiD refractory disease one achieved CR (6%), 5 VGPR (31%), 4 PR (25%) and 5 SD (31%), in one patient response was not evaluable (6%). The respective disease control rate was 94%. A single patient achieving CR with IMiD refractory MM was heavily pre-treated, including autologous HSCT, and had a treatment duration of 26 months before study inclusion.

Duration of response (DoR) on MM03-therapy was longest in 17 patients (36%) when compared previous treatment lines. We would like to highlight one patient, who was repeatedly treated with schedules containing IMiDs before being enrolled to our trial. For this patient metronomic quadruple therapy which again contained an IMiD, lenalidomide, significantly achieved the longest myeloma response as compared to prior therapy regimens (Figure 13), indicating the striking effect of low dose metronomic chemotherapy plus pioglitazone.

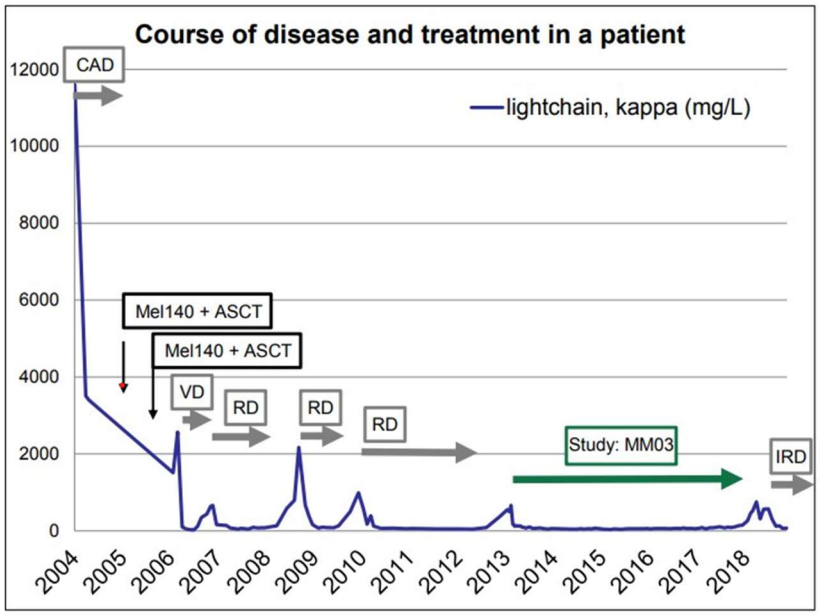

Figure 13: Example of a patient's course of disease

CAD = cyclophosphamide/Adriamycin/dexamethasone; VD = bortezomibe/dexamethasone; RD = lenalidomide/dexamethasone; IRD = ixazomibe/lenalidomide/dexamethasone

5.5.1 ECOG Performance Status and Quality of Life

For 34 patients (72.3%), there was no change of the ECOG performance status at baseline to the minimum ECOG during study therapy. 6 patients (12.8%) had a lower ECOG performance status during the study therapy than at baseline. For 22 patients (46.8%) there was no change of the ECOG performance status at baseline to the maximum ECOG during study therapy. 21 patients (44.7%) had a higher ECOG performance status during the study therapy than at baseline.

Patients were categorized according to their best therapy response over their whole treatment regime in stable disease (n = 16) and therapy responder (n = 27, including complete response, very good partial response, and partial response). Patients with progressive disease (n =3) and where the best response was not evaluable (n =1) were excluded from QoL analyses.

Of 47 included patients, three patients had no QoL assessment and for three patients no baseline QoL assessment was available. The follow-up QoL assessments ranged from once up to 64 times. Mean changes in overall quality of life, fatigue, and pain from baseline to each treatment cycle are presented in Figure 14.

Overall quality of life declined from baseline to best response for therapy responder ($p = 0.025$) and for patients with stable disease ($p = 0.086$). However, these declines did not reach the minimal clinical cut-off of 10 points. Both patient groups did not differ in overall quality of life at baseline and time of best response (p values > 0.05).

Fatigue increased from baseline to best response for therapy responder ($p = 0.148$) and for patients with stable disease ($p = 0.054$). In patients with stable disease, the increase exceeded the minimal clinical cut-off of 10 points. Both patient groups did not differ in fatigue at baseline and time of best response (p values > 0.05).

Pain increased from baseline to best response for therapy responder ($p = 0.713$) and decreased for patients with stable disease ($p = 0.750$). However, these changes did not reach the minimal clinical cut-off of 10 points. Patients with stable disease reported higher pain scores ($\geq$ 10 points) at baseline ($p = 0.041$) and at time of best response ($p = 0.121$) than therapy responder.

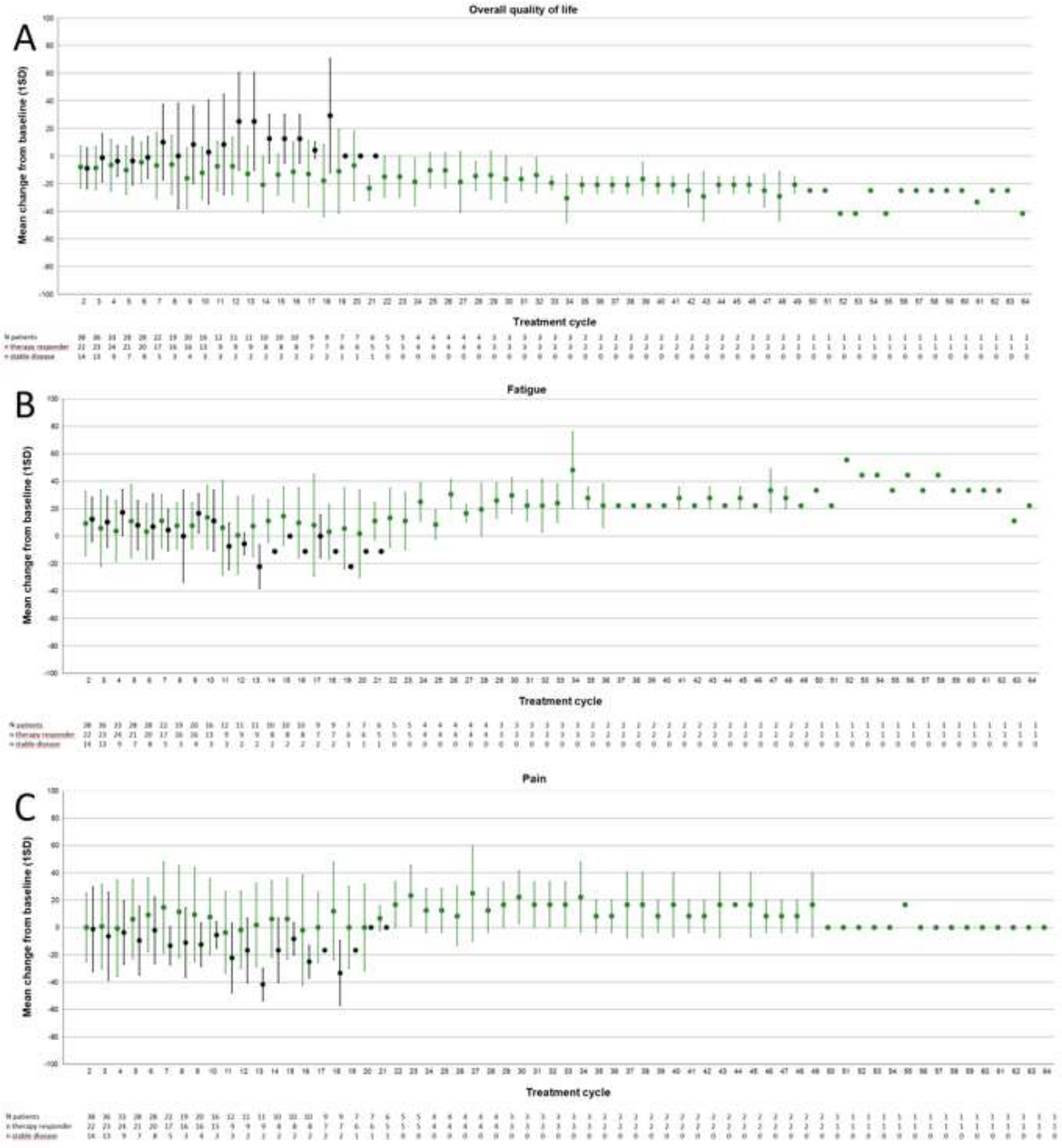

Figure 14: Mean changes in overall quality of life, fatigue, and pain from baseline to each treatment cycle. Green = responders; black = stable disease

5.6 Safety parameters

In total, 47 patients were registered , 8 in the phase I part and 39 in the phase II part of the study. All patients started treatment. For the definition of safety set (SAF), full analysis set (FAS), per-protocol (PP) set and dose limiting toxicity set (DS) see chapter 4.5.1.

6 patients were included in the dose-limiting toxicity set of phase I, although 2 of these patients did not receive 80% of dexamethasone or experienced a DLT.

47 patients were included in the safety set: 8 in phase I (SAF-I) and 39 in phase II (SAF-II). All patients received study medication; no patient was excluded. Also, 47 patients are included in the full analysis set: 8 in phase I (FAS-I) and 39 in phase II (FAS-II), so SAF und FAS are identical. A systematic search for protocol violations was done for the determination of the per protocol set. A Data Review Meeting was not performed. A list of the detected protocol violations was sent to the representative of the sponsor who determined the major protocol violations. 3 patients were excluded from the per-protocol population due to major protocol violation. 44 patients were included in the per-protocol set: 6 in phase I (PP-I) and 38 in phase II (PP-II).
47 patients of the FAS were treated in 3 study sites, of which site 1 (Reichle) treated the most patients (44 patients: 8 patients in phase I part and 36 patients in phase II part). The registration period was from October 14, 2009, until December 13, 2016. An overview of study population is shown in Table 21.

Population	**Phase I part**		**Phase II part**	
	N	**%**	**N**	**%**
Registered patients	8	100.0	39	100.0
Safety set (SAF)	8	100.0	39	100.0
Full analysis set (FAS)	8	100.0	39	100.0
Per-protocol set (PP)	6	75.0	38	97.4
Dose-limiting toxicity set (DS)	6	75.0	-	-

Table 21: Study population

5.6.1 Adverse events (AE)

As expected, a majority of adverse events were hematological side effects. Anemia of any grade occurred in 72% of all patients, leukopenia in 70% and thrombocytopenia in 55%. The most frequent adverse event with grade 3 or 4 was also leukopenia, which occurred in 25% of phase I patients and 69% of phase II patients. Infections with grade 3 or 4 were detected in 50% of phase I and 38% of phase II patients. Notably, despite the continuously administration of dexamethasone, there were only few patients reporting insomnia (19% of all patients, no grade 3

or higher). Rates for grade 3 or more fatigue, diarrhea, nausea, dyspnea, epistaxis, hyperhidrosis, polyneuropathy, dysgeusia and decreased appetite are comparatively low, so this findings are consistent with the therapy's low impact on quality of life described in chapter 5.5.1. The adverse events sorted by categories are listed in Table 22.

	Phase I		**Phase II**		**Phase I/II**
Adverse events	Grade 3-4 n (%)	**Any grade n (%)**	Grade 3-4 n (%)	**Any grade n (%)**	**Any grade n (%)**
Total TEAEs	5 (63)	**8 (100)**	36 (92)	**39 (100)**	**47 (100)**
Anemia	1 (13)	**4 (50)**	18 (46)	**30 (77)**	**34 (72)**
Leukopenia	2 (25)	**3 (38)**	27 (69)	**30 (77)**	**33 (70)**
Any kind of infection	4 (50)	**6 (75)**	15 (38)	**25 (64)**	**31 (66)**
Thrombocytopenia	1 (13)	**1 (13)**	22 (56)	**25 (64)**	**26 (55)**
Fatigue	-	**3 (38)**	1 (3)	**20 (51)**	**23 (49)**
Muscle spasm	-	**5 (63)**	-	**14 (36)**	**19 (40)**
Diarrhea	-	**2 (25)**	3 (8)	**16 (41)**	**18 (38)**
Nausea	-	**2 (25)**	-	**8 (21)**	**10 (21)**
Cough	1 (13)	**6 (75)**	-	**10 (26)**	**16 (34)**
Edema	2 (25)	**5 (63)**	1 (3)	**11 (28)**	**16 (34)**
Influenza-like illness	-	**2 (25)**	2 (5)	**12 (31)**	**14 (30)**
Dyspnea	-	**2 (25)**	-	**10 (26)**	**12 (26)**
Epistaxis	-	**1 (13)**	1 (3)	**11 (28)**	**12 (26)**
Hyperhidrosis	-	**2 (25)**	-	**9 (23)**	**11 (23)**
Hematoma/hemorrhage	-	**1 (13)**	-	**9 (23)**	**10 (21)**
Constipation	1 (13)	**1 (13)**	-	**9 (23)**	**10 (21)**
Polyneuropathy	-	**1 (13)**	-	**9 (23)**	**10 (21)**
Insomnia	-	**-**	-	**9 (23)**	**9 (19)**
Dysgeusia	-	**1 (13)**	-	**6 (15)**	**7 (15)**
Visual impairment	-	**-**	-	**5 (13)**	**5 (11)**
Decreased appetite	-	**-**	1 (3)	**5 (13)**	**5 (11)**

Table 22: Treatment-related adverse events; TEAE = treatment-emerged adverse event

5.6.2 Serious adverse events (SAE)

61.7% of the patients had at least one treatment-emerged serious adverse event (TESAE) (Table 23). 24 patients (51.1%) had at least one SAE related to study medication.

Total number of patients with TESAE of any grade:	Phase I (N=8)	Phase II (N=39)	Overall (N=47)
	N (%)		
Infections and infestations	5 (62.5)	16 (41.0)	21 (44.7)
General disorders and administration site conditions	1 (12.5)	5 (12.8)	6 (12.8)
Gastrointestinal disorders	2 (25.0)	3 (7.7)	5 (10.6)

Table 23: Total number of patients with TESAE of any grade; TESAE = treatment-emerged serious adverse event

5.6.3 Laboratory Values

Based on the laboratory values documented in the CRF events with at least NCI-CTCAE grade 3 were calculated. Table 24 summarizes the results:

SAF	Phase I (N=8)	Phase II (N=39)	Overall (N=47)
	N (%)		
Haemoglobin [g/dL]	2 (25.0)	12 (30.8)	14 (29.8)
Leucocytes [/nL]	5 (62.5)	27 (69.2)	32 (68.1)
Platelets [/nL]	3 (37.5)	19 (48.7)	22 (46.8)
Neutrophils [/nL]	5 (62.5)	29 (74.4)	34 (72.3)
Alanine Aminotransferase ALT [U/L]	-	1 (2.6)	1 (2.1)
Total bilirubin [mg/dL]	1 (12.5)	-	1 (2.1)

Table 24: Laboratory values - absolute and relative frequencies of NCI-CTCAE grade ≥ 3, SAF = safety set

5.6.4 Deaths

30 (63.8%) patients deceased during study, of which 3 (6.4%) during the treatment period (death no longer than 30 days after last treatment) and 27 (57.4%) during follow-up period (more than 30 days after last treatment). The most common reason of death was relapse/progression with 11 patients (23.4%).

6 Discussion

To determine the efficiency and safety of biomodulatory therapy in patients with relapsed or refractory or progressive multiple myeloma, we performed a prospective phase I/II, one-arm, one-stage multicenter open label study of lenalidomide in combination with pioglitazone, dexamethasone, and metronomic low-dose chemotherapy with treosulfan as third-line therapy.

The median progression-free survival time was 8.3 months (95%-CI: [4.6, 16.6]), which is comparable to standard therapies for relapsed or refractory myeloma such as Pomalidomide/Bortezomib/Dexamethasone or Pomalidomide/Elotuzumab/Dexamethasone and even superior to Bortezomib/ Panobinostat/Dexamethasone.

Myeloma tissue editing including lenalidomide in combination with pioglitazone, dexamethasone, and metronomic low-dose treosulfan for >= 3rd-line treatment demonstrates an objective response rate of 51.3%, including CR and a favorable toxicity profile in heavily pretreated patients with refractory or relapsed multiple myeloma. Median progression-free survival of 8.3 months (95%-CI: [4.6, 16.6]) compares to standard therapies for relapsed or refractory myeloma, such as Pomalidomide/Bortezomib/Dexamethasone or Pomalidomide/Elotuzumab/Dexamethasone or novel targeted experimental approaches with teclistamab, a B-cell maturation antigen (BCMA) × CD3 directed bispecific antibody, and is superior to Bortezomib/Panobinostat/Dexamethasone (216–218). Bone marrow toxicity is comparable with established combination therapies including mAbs (see Table 4). The combination IMiD/GC/Isatuximab was tested in a similar, heavily pretreated patient population with two or more previous therapies. IMiD/GC/Isatuximab achieved an inferior median overall survival of 24.6 mo vs. 33.6 mo in the present trial (127).

Even in IMiD-exposed and -refractory patients, the present biomodulatory therapy achieved response rates of 50% and 35%, respectively. This means myeloma tissue editing with a biomodulatory therapy approach may overcome IMiD resistance (Figure 1).

Despite the recent treatment advances, patients with MM often progress through standard drug classes including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 mAbs (219). Continuous complete remission in RRMM is still a rare event, despite of the rapidly growing repertoire of MM therapeutics including mAbs and cellular immunotherapies. Development of genetic heterogeneity, resistance in multiple myeloma cells, metastatic spread and repopulation of myeloma cells (M-CRAC) following pulsed MM therapies remains a major obstacle for cure also in the era of novel immunotherapies (5).

The lack of pre-clinical and clinical therapeutic models addressing M-CRAC hampers major advances of therapeutic discoveries to cure RRMM (205, 220, 221). Current study protocols do

not systematically address M-CRAC control in RRMM and cover the problem by combining two therapeutic elements, targeted immunotherapies, applied with maximum tolerable doses, and consecutive maintenance therapies, basically combinations of one or two drugs, for achieving and maintaining deep remissions (222, 219, 223, 224).

With tissue editing techniques, prevention, or resolution of M-CRAC move to the forefront of myeloma therapy to advancing cure (5). In r/r multisystem Langerhans cell histiocytosis, r/r Hodgkin's lymphoma and non-promyelocytic leukemia, CR or cCR could be frequently induced with on-topic designed tumor tissue editing techniques for inflammation control, enhancing immunosurveillance or differentiation induction (5).

M-CRAC attenuation or resolution affords novel therapy techniques unlocking MM tissue plasticity. With editing techniques, tumor plasticity is now a therapeutically addressable hallmark of cancer (5, 225). Biomodulatory active drugs for myeloma editing therapy are well established, such as dexamethasone, IMiDs, proteasome inhibitors, and elotuzumab. However, the therapeutic repertoire may be expanded inclusively those biomodulatory drugs with no or poor monoactivity, like pioglitazone, and integrated in MM editing schedules, for finally unlocking myeloma tissues' phenotypic plasticity as a prerequisite for attenuating or resolving M-CRAC (5, 201, 157).

In contrast to the available targeted immunotherapies, such as CAR-T cells, monoclonal antibodies, and other drugs, e.g. BRAF inhibitors or bcl-2 inhibitors, tissue editing approaches do not directly target myeloma cells for inducing cell death (226). Instead, by inducing anakoinosis, cellular myeloma promoters and communication lines are reprogrammed. For inducing anakoinosis, we used triple transcriptional modulation plus low dose metronomic chemotherapy.

The novelty of the present treatment schedule is the synergistic profile as indicated by the poor or no monoactivity of the applied drugs but the feasibility to induce objective response with a favorable safety profile. In our study, Anemia (72.3%), leukopenia (70.2%), neutropenia (66.0%) and thrombopenia (55.3%) were comparable with established therapies such as Lenalidomide/ Daratumumab/ Dexamethasone or Pomalidomide/ Daratumumab/ Dexamethasone and superior to Pomalidomide/ Isatuximab/ Dexamethasone (see Table 4). The latter regimen was tested in heavily pretreated patients (127), so this might seem an adequate comparison for our study, which also included patients with two or more previous therapies.

The schedule can re-establish immune surveillance, inhibits angiogenesis, alters myeloma metabolism, reduces inflammation, promotes epigenetic modeling and control of cell cycle (227, 228, 168, 229, 163, 230, 231, 170, 232). On-topic unlocking of phenotypic plasticity in hematologic malignancies has been successfully introduced and is also the aim of biomodulatory

drug combinations for RRMM, as exemplarily shown with the present trial (5, 201, 157). The successful change from classic myeloma cell targeted therapy for rescuing RRMM to a novel biomodulatory therapy approach targeting communicative networks in RRMM tissue highlights that also schedules with pro-anakoinotic activity facilitate long-term response in RRMM up to CR without supplementation of classic myeloma cell-directed drugs, such as monoclonal antibodies.
Tissue editing, that simultaneously targets MM cells and the neighboring 'ecosystem', is efficacious in RRMM with resistance to IMiDs, proteasome inhibitors or both and may facilitate long-term MM control despite of the suggested genetic myeloma heterogeneity in the advanced and relapsed stage (233).
Moreover, biomodulatory therapy may edit myeloma tissue to overcome IMiD resistance and establishes long-term control of myeloma cell regrowth, even beyond study discontinuation (Figure 11). This tissue-driven cell communication remodeling was also observed in castration-resistant prostate cancer, namely durable response beyond discontinuation of therapy (234). Therefore, the quadruple metronomic biomodulatory therapy may presumably promote in many cases a less aggressive biologic behavior of multiple myeloma similar to the biologic behavior of smoldering myelomas (235).
Modulating MM stress response with low dose metronomic chemotherapy instead of proteasome inhibitors, and simultaneous triple transcriptional modulation with dexamethasone and pioglitazone may edit myeloma tissue to re-establish IMiD mediated myeloma response, and control of M-CRAC (5, 236, 237, 139, 238).
These editing results in myeloma tissues are in line with those observed in r/r Hodgkin's lymphoma. Here, edited non-oncogene addiction to mTOR could be observed, even combined with the induction of cCR (5).
Worldwide, immunomodulatory IMiD-based regimens are frequently used in first to third-line (121, 106). The special myeloma tissue-related impact of lenalidomide is underlined by a randomized trial with watch and wait versus IMiD maintenance after autologous pBSCT. Lenalidomide significantly improved PFS in patients with preceding IMiD maintenance (239, 239). Thus, response to consecutive therapies may be improved in comparison to non-IMiD exposed myeloma tissues.
The present study now demonstrates that the biomodulatory extension of the MM tissue editing approach even re-established IMiD sensitivity and facilitated equivalent response compared to targeted therapies in the r/r stage of MM (Figure 1).

IMiD resistance may be multi-leveled (3). Overcoming resistance to IMiDs remains a therapeutic challenge in the management of MM. Our understanding of IMiD resistance is growing but there are still many unanswered questions due to multifold underlying resistance mechanisms (176). Although, myeloma therapeutics are rapidly diversifying, particularly immunotherapies, IMiDs could have an on-going important impact when integrated at low doses in myeloma editing therapy approaches.

A completely novel therapy element for transcriptional modulation is pioglitazone, a PPARα/γ agonist and the synergistic triple transcriptional modulation with dexamethasone (201, 240, 241). PPAR expression is upregulated in patients newly diagnosed with MM and correlates with poor clinical outcome (242).

Glitazones can reprogram T-lymphocytes and adipocytes involved in myeloma progression, can suppress osteoblastogenesis and enhance osteoclastogenesis (243, 244, 166). Considering tissue communication, glitazones modulate communication lines which are essential for myeloma growth, such as Wnt signaling, MAPK, PI3K/Akt pathway, NF-κB and STAT3 signaling as well as exosomes, extracellular matrix and metabolites involved in tissue communication, thereby enhancing apoptosis, suppressing myeloma growth, reducing cell adhesion of myeloma cells, controlling inflammation as negative regulator of STAT3 and angiogenesis in myeloma (245, 231, 246, 247, 163, 248, 169).

Wnt/β-catenin/CD44 signaling is epigenetically dysregulated in multiple myeloma and is linked to progression. The overexpression of CD44 was found to be a Wnt transcriptional target in lenalidomide resistance models (172). Classical targeted therapies aim at blocking Wnt/β-catenin/CD44 signaling, but instead, pioglitazone attenuates Wnt/β-catenin signaling with its reprogramming profile, so CD44 is downregulated and the Wnt-driven cereblon (CRBN), a required IMiD target, is regulated (173–175, 172). Aberrant CRBN DNA methylation was uncovered as a mechanism of IMiD resistance in multiple myeloma recently and predicts IMiD response (176).

Activated Wnt signaling promotes protein synthesis, such as PDK and MCT-1, and therefore involves target genes of beta-catenin and angiogenesis (174). PPARγ agonists can downregulate MCT-1 (177). Thus, further evaluation of pioglitazone and its mechanism of action are necessary to explain the exact mechanisms how it contributes to overcoming IMiD resistance.

The clinical results of our editing approach are contrary to those derived from pre-clinical studies on the PPARα agonist fenofibrate and the clinically not approved PPARγ agonist troglitazone, describing PPAR agonist-related reduced CRBN activity as resistance mechanism for IMiDs

(242, 249). These opposing results highlight that activities of combined transcriptional modulation must be context-dependently interpreted as shown by differential clinically important tumor editing results in many histologically different neoplasias, dependent on the transcriptional modulator administered in addition to pioglitazone. Importantly, pioglitazone is a dual PPARα/γ agonist (201, 5). Also, in non-oncologic disease PPARα and γ agonistic component makes a huge difference and led to the withdrawal of rosiglitazone, a PPARγ agonist (201).

Treosulfan is a well-known alkylating agent for conditioning myeloma patients before autologous or allogeneic peripheral blood stem cell transplantation (250, 251). Oral low dose treosulfan has been used for the first time for myeloma tissue editing in analogy to low dose melphalan (252). Most patients received scheduled dose reduction to once daily treosulfan 250 mg without any loss of editing capacity. A randomized trial could demonstrate the clinical benefit of metronomic chemotherapy in addition to pomalidomide plus GC in lenalidomide refractory multiple myeloma (138).

Biomodulatory approaches focus on reprogramming communication patterns in tumor cells and their environment for reducing tumor growth and achieving control of cell cycle (8). E.g., combinations including elotuzumab, IMiD, proteasome inhibitor, pioglitazone and GC as proanakoinotic drugs support the immunomodulatory track, valproic acid the epigenetic (253, 107, 254).

Tissue editing in RRMM shows modest toxicity and efficacy in the r/r stage. The editing approach does not substantially compromise normal tissue, besides modest bone marrow toxicity. That means modifying MM stress response to low dose metronomic chemotherapy by additionally including triple transcriptional modulation has a well tolerable therapeutic ratio. MM editing is still efficacious under the conditions of frequently performed scheduled dose reductions of each biomodulatory drug. Dose reductions without loss of efficacy, underline the synergistic pro-anakoinotic activity profile of the drug combination (Table 18, Table 20). The poor monoactivity of each biomodulatorily active drug contrasts with commonly used therapeutically necessary maximum tolerable doses for inducing myeloma cell death. Particularly, further dose reductions of alkylating agents in metronomic low dose chemotherapy and IMiD doses seem to be important (5). An IMiD-associated increased risk of TP53-mutated myeloid neoplasms has been reported (255).

In RRMM, clinical access to clinical surrogates indicating reprogramming of myeloma-promoting cancer hallmarks is limited. But reprogramming effects of the tested schedule, as indicated by

inflammation control, immunomodulation, altering the metabolic status or by differentiation induction could be clinically objectivated in histologically quite different neoplasias (5).

Long-term disease stabilization indicates that disease proliferation may be stopped, irrespectively of the lesional genetic heterogeneity (205). Myeloma-associated inflammation might be attenuated, immunosurveillance enhanced and myeloma metabolism reprogrammed (5). Tissue editing addresses genetic or molecular genetic heterogeneity as indicated by PR and one CR induction in this study.

A strong immunomodulatory activity profile of low dose metronomic chemotherapy in RRMM may be suggested by the synergism of metronomic chemotherapy with immune checkpoint inhibitors and induction of tumor-specific T-cell response in cancer (227, 256). Enhanced immune checkpoint inhibitor expression may play a crucial role in RRMM (33).

In future, tissue editing and classic targeted therapy may combine 'the best of two worlds' (257). Edited RRMM may attenuate or resolve M-CRAC and re-establish IMiD sensitivity. The addition of classic targeted immunotherapies for MM may enhance the remission quality and overall survival. For example, classic targeted therapy with daratumumab, in addition to a combination therapy with dexamethasone and lenalidomide that follows a biomodulatory approach, improved overall survival compared to lenalidomide/dexamethasone (258). These results underline the possible future direction, to combine classic targeted therapy with diversified tissue editing approaches for M-CRAC control. Classic combined biomodulatory consolidation and/or maintenance therapies are already well established in MM (259, 106).

However, as shown, the biomodulatory part may be extended, specified and on-topic diversified (5). Novel combinations of transcriptional modulators have been already tested in vitro in MM, namely dexamethasone combined with mineralocorticoid and may address differential patterns of myeloma hallmarks (157).

7 Conclusion

The present trial represents more than a proof of principle. Myeloma tissue editing is efficacious even without commonly used targeted immunotherapies and efficacy compares to standard third-line therapies including targeted therapies. Therefore, myeloma editing lends itself for the combination with currently available targeted immunotherapies in RRMM. Further, myeloma tissue editing may address a major obstacle of pulsed myeloma therapies in the r/r stage, namely M-CRAC, the metastatic process, myeloma cell repopulation, the development of drug resistance and genetic/molecular-genetic myeloma heterogeneity (5).

Besides the promising therapeutic effect, the uncomplicated administration and the applicability in elderly or frail patients and patients with underlying health conditions such as diabetes or inflammatory diseases are clear advantages of this concept. Due to the all-oral administration, it fits well with the patients' daily routines. In person medical appointments can be reduced, and doses can be adjusted easily, for example in case of side effects. Biomodulatory therapy uses preexisting drugs, so therapy costs are lower than for newly developed, patented substances.
Further exploration of myeloma tissue editing might be a missing link to myeloma cure with or without the addition of targeted therapies.

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloic leucemia
AP	alcalic phosphatase
ASCO	American society of clinical oncology
ATP	adenosine triphosphate
ATRA	all trans retinoic acid
BMI	body mass index
BCL3	B cell lymphoma 3
BCL6	B cell lymphoma 6
CAM	cell adhesion molecule
CAR	chimeric antigen receptor
CI	confidence interval
COX2	cyclooxygenase 2
CR	complete remission
CR	complete response
CRBN	cereblon
CRF	case report form
CTCAE	common toxicity criteria for adverse events
DCR	disease control rate
DKK1	dickkopf-related protein 1
DLT	dose limiting toxicity
DNA	desoxyribonuclein acid
DS	dose limiting toxicity set
ECOG	Eastern cooperative oncology group
EGF-R	epidermal growth factor receptor
EORTC-QLQ30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30
FAS	full analysis set
FAS-I	full analysis set I
FAS-II	full analysis set II
FDG	fluordesoxyglucose

FGF	fibroblast growth factor
FLC	free light chain
GC	Glucocorticoid
GFR	glomerular filtration rate
GLUT-1	glucose transporter 1
HR	high risk
IDH	isocitrate dehydrogenase
IFNß	interferon ß
IgA	immuneglobuline A
IgD	immuneglobuline D
IgE	immuneglobuline E
IGF	insulin like growth factor
IgG	immuneglobuline G
IgM	immuneglobuline M
IL-1ß	interleukin-1ß
IL-3	interleukin-3
IL-6	interleukin-6
IMiDs	immunomodulatory drugs
IMWG	international myeloma working group
INR	international normalized ratio
ISS	international staging system
IκB	inhibitor of kappa B
JAK	januskinase
mAbs	monoclonal antibodies
Mcl-1	myeloid leukemia cell differentiation protein 1
M-CRAC	metastatic spread, cancer repopulation and acquired tumor cell resistance
MDSCs	myeloid-derived suppressor cells
MedDRA	medical dictionary of regulatory activities
MGUS	monoclonal gammopathy of undetermined significance
MHC	major histocompatibility complex
MM	multiple myeloma
M-protein	monoclonal paraprotein
mTOR	mechanistic target of rapamycin
N-CAM	nerve cell adhesion molecule
NF-κB	nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
NK-cells	natural killer cells
NYHA	New York Heart Association
OPG	osteprotegerin
OR	overall response
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDGF	platelet-derived growth factor
PET	positrone emission tomography
PFS	progression free survival

PP	per protocol set
PPAR	peroxisome proliferator activated receptor
PPARγ	peroxisome proliferator activated receptor γ
PP-I	per protocol set I
PP-II	per protocol set II
PR	partial response
pRb	retinoblastoma protein
PSA	prostate specific antigen
PT	prothrombin time
PTEN	phosphatase and tensin homolog
PTT	partial thromboplastin time
RANK-L	receptor activator of NF-κB
rrMM	refractory or relapsed multiple myeloma
SAF	safety set
SAF-I	safety set I
SAF-II	safety set II
SCAMF7	surface antigen CD139
sCR	stringent complete response
SCT	stem cell transplantation
SD	stable disease
SR	standard risk
STAT	Signal transducer and activation of transcriptation
TEAE	treatment-emerged adverse event
TESAE	treatment-emerged serious adverse event
TGFß	transforming growth factor ß
TGFα	transforming growth factor α
TNFα	tumor necrosis factor α
TPR	time to partial response
TTP	time to progression
VEGF	vascular endothelial growth factor
VGPR	very good partial response
VRd	Bortezomib, lenalidomide, dexamethason
WHO	world health organization
Wnt	wingless

Register of Illustrations

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Attachments

Visit schedule
EORTC-QLQ 30

Table 6-1: Visit evaluation schedule

Procedure	Screening/ Baseline (-28 Days of Cycle 1 Day 1)	Cycles 1-4 Day 15[1]	Every Cycle Day 1 (Starting with Cycle 2)	Treatment Phase Discontinuation[2]	Follow up
Entry Assessments					
Informed consent	X				
Inclusion/exclusion criteria	X				
Cancer History	X				
Physical examination	X	X	X	X	
Performance status (ECOG)	X	X	X	X	
Immunofixation electrophoresis	X	X	X	X	
Serum β2 microglobulin	X	X	X	X	
Serum albumin	X	X	X	X	
Coagulation[12]	X			X	
Urinanalysis[13]	X				
Serological testing for hepatitis A, B, C	X				
Efficacy Assessments					
Protein electrophoresis [11] (serum or 24 hour urine)	X	X	X	X	
Immunglobulin concentration	X	X	X	X	
Serum calcium	X	X	X	X	
Free light chain concentration	X	X	X	X	
Skeletal survey [3]	X				
Assessment of soft-tissue plasmocytomas[3]	X				
Bone marrow aspiration/-biopsy[3]	X[3]				
Response rate/disease progression assessment	X	X	X	X	
Safety Assessments					
Adverse event query including second primary malignancies		X	X	X	
Vital Signs	X	X	X	X	
Neurological assessment (NCI CTCAE)	X	X	X	X	
Hematology [1]	X[1]	X[1]	X[1]	X	
Serum Chemistries [8]	X		X [8]	X	
Thyroid function tests[4]	X		X[4]	X	
ECG[5]	X				
Contraception assessment	X		X		
Pregnancy testing for FCBP [6], counselling[7]	X[6]	X[6]	X[6]	X[6]	
Quality of life (EORTC)	X[9]		X[9]	X	
Study Drug					
Dispense and account study drug	X[10]		X		
Documentation of survival and new antimyeloma therapy					X
Record second primary malignancies					X

Footnotes

1 Full blood counts must be checked weekly for the first 8 weeks and at least monthly thereafter. Haematology studies are to be performed within 14 days of Cycle 1 Day 1 to obtain accurate baseline measurements, weekly during Cycles 1 and 2, every two weeks during Cycle 3 and 4. After Cycle 4, haematology studies are to be performed every four weeks, or as directed in Section 5.6 (Dose Modification or Interruption), and as clinically indicated.

2 All subjects are to have the designated tests performed upon discontinuation of study drug.

3 Skeletal survey (whole body CT or MRT, conv. X-ray), an assessment for soft-tissue plamocytomas (whole body CT- or MRT-scan), and a bone marrow biopsy is to be performed within one month before baseline and at any time if clinically indicated. A bone marrow aspiration/-biopsie is also to be performed to confirm CR or sCR.

4 fT3, T4 and serum TSH (thyroid stimulating hormone) levels at baseline and every three month thereafter starting at cycle 4.

5 ECG at baseline and as clinically indicated thereafter.

6. A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).wo pregnancy tests must occur before enrollment (the first pregnancy test within 10 to 14 days and the second pregnancy test within 24 hours prior to initiation of lenalidomide) once the subject has been on effective contraception for at least 4 weeks, weekly for the first 28 days of study participation and then every 28 days while on therapy, at study discontinuation, and at day 28 following study drug discontinuation. Women with irregular menstruation must have a pregnancy test every 14 days while on therapy, at study discontinuation, and at days 14 and 28 following study drug discontinuation. Pregnancy testing and counselling must be performed if a subject missed her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. Study drug treatment must be discontinued during this evaluation.

7 All male and FCBP patients must be counselled monthly about pregnancy precautions and risks of fetal exposure. At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.

8 Before each cycle the creatinine clearance (CrCL) needs to be obtained by using the MDRD formula http://nephron.com/mdrd/default.html. Na, K, Ca, SGOT, SGPT, alkaline phosphatase, albumin, bilirubin, creatinine, CRP, LDH and glucose (glucose only in case of known diabetes mellitus) at baseline and from cycle 1 day 1 onwards every four weeks..

9 EORTC questionnaire every 4 weeks

10 Study drug has to be dispensed following enrolment. No more than a 28 days supply of capsules may be dispensed at a time.

11 Has to be performed at screening, during treatment period only if clinical indicated

12 At screening, at visit cycle 2 day 15 afterwards at any time when clinically indicated and at the treatment discontinuation visit. .

13 Urinanalysis at screening and at any time as clinically indicated

Post-Text Supplement 3 – EORTC QLQ-30 (Version 3.0, Core-Fragebogen)

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Wir sind an einigen Angaben interessiert, die Sie und Ihre Gesundheit betreffen. Bitte beantworten Sie die folgenden Fragen selbst, indem Sie die Zahl ankreuzen, die am besten auf Sie zutrifft. Es gibt keine "richtigen" oder "falschen" Antworten. Ihre Angaben werden streng vertraulich behandelt.

Patienten-Nr.

Das heutige Datum (Tag, Monat, Jahr):

	Überhaupt nicht	Wenig	Mäßig	Sehr
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen?)	1	2	3	4
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	1	2	3	4
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke außer Haus zu gehen?	1	2	3	4
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4

Während der letzten Woche:

	Überhaupt nicht	Wenig	Mäßig	Sehr
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8. Waren Sie kurzatmig?	1	2	3	4
9. Hatten Sie Schmerzen?	1	2	3	4
10. Mussten Sie sich ausruhen?	1	2	3	4
11. Hatten Sie Schlafstörungen?	1	2	3	4
12. Fühlten Sie sich schwach?	1	2	3	4
13. Hatten Sie Appetitmangel?	1	2	3	4
14. War Ihnen übel?	1	2	3	4
15. Haben Sie erbrochen?	1	2	3	4

Während der letzten Woche:

	Überhaupt nicht	Wenig	Mäßig	Sehr
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet