



Meeting report of the 7th Heidelberg Myeloma Workshop: today and tomorrow

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Abstract

Purpose The 7th Heidelberg Myeloma Workshop was held on April 5th and 6th, 2019 at the University Hospital Heidelberg. **Methods and results** Main topics of the meeting were (1) diagnostics and prognostic factors, (2) role of immunotherapy in multiple myeloma (MM), (3) current therapy of MM, (4) biology and genomics of MM as well as (5) novel treatment concepts. A debate on the status of minimal residual disease (MRD) driven therapy was held. **Conclusion** Diagnostics and treatment of newly diagnosed and relapsed MM are continuously evolving. While advances in the field of (single cell) genetic analysis now allow for characterization of the disease at an unprecedented resolution, immunotherapeutic approaches and MRD testing are at the forefront of the current clinical trial landscape.

Keywords Multiple myeloma · Minimal residual disease · Immunotherapy · Single-cell sequencing

Keynote: The road to cure in multiple myeloma

In the first keynote lecture entitled “The road to cure in multiple myeloma”, Sagar Lonial from the Winship Cancer Institute of Emory University in Atlanta (USA) presented his concepts of what is needed to reach long-term disease control. To start with, Dr. Lonial put the definition of cure up for discussion. He argued that a state of ongoing disease suppression without significant impairment of quality and expectancy of life should be considered “functional” cure without necessitating total eradication of the disease. To achieve best possible outcome, he strengthened the notion that patients should be treated individually based on their risk profile. The goal of MM treatment should be to eradicate as much of the disease as possible to reach an MRD negative state and more importantly maintain the response. To maintain a good response, it might be necessary to change the

treatment to control or eradicate the remaining MM clones. Dr. Lonial pictured MM as a hybrid between plasma cell and cancer biology. Based on this concept he proposed a two-pronged approach of tumor-debulking with plasma cell biology-driven drugs (e.g. proteasome inhibitors, IMiDs) followed by targeting of MRD with agents against specific features of the remaining clones. Dr. Lonial summarized that exceptional progress has already been made in the past years improving outcomes of MM patients. Yet, individualized treatment concepts are urgently needed to eradicate all tumor clones.

Session I: Diagnostics and prognostic factors

Herve Avet-Loiseau from the University Cancer Center of Toulouse (France) started the first session by highlighting the importance of cytogenetic aberrations for the prognosis of MM patients. Dr. Avet-Loiseau presented a novel score that weighs the impact of six chromosomal aberrations [trisomy 5, deletion (del) 17p, del (1p32), gain (1q), t (4;14) and trisomy 21] on the 5 year survival rate (Perrot et al. 2019). Of note, the well-known high risk aberration t (4;14) is not necessarily associated with high risk disease. Deeper investigations on 200 patients with t (4;14) using whole genome sequencing and RNA sequencing are planned to find the determinants of a high risk t (4;14) pattern. In contrast to

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interphase FISH, many mutated genes (e.g. *KRAS*, *NRAS*, *FAM46C*) associated with MM revealed by exome sequencing have not been shown to have a prognostic impact to date.

Next, Martin Kortüm from the University Hospital Würzburg (Germany) talked about current and future concepts in positron emission tomography (PET)-imaging. ¹⁸F fluoro-deoxyglucose (FDG) PET has proven to be useful in staging and sensitive detection of disease in MM (Bailly et al. 2017). Moreover, PET imaging is powerful in improving the detection of minimal residual disease (MRD). The lack of standardization to interpret the data and a rate of PET false negative patients of 11% have been discussed as current problems of PET imaging. At the University Hospital Würzburg, further tracers such as ¹¹C methionine, ¹¹C choline and ⁶⁸ Ga Pentixafor are under investigation. Dr. Kortüm discussed the advantages of each tracer as well as the use of combining tracers to improve diagnostic sensitivity especially in detecting residual disease. The role of nuclear medical treatment in MM still needs to be evaluated.

Del (17p) as a hallmark of high risk MM was highlighted by Anjan Thakurta from Celgene, Summit (USA). He showed the prognostic value of the cancer clonal fraction (CCF) of this aberration. Incremental CCF change in newly diagnosed MM patients was associated with shorter survival with a robust CCF threshold separating poor prognosis patients established at 0.55 (Thakurta et al. 2019). Dr. Thakurta concluded that patients with either a biallelic inactivation of *TP53* or del (17p) in the majority of tumor cells (CCF > 0.55) have very poor prognosis and should be considered for risk adjusted therapy. Further studies are planned to clarify the underlying biological similarities and differences between biallelic inactivation of *TP53* and high CCF del (17p).

Keynote: How to define and when to treat smoldering myeloma

Shaji Kumar from the Mayo Clinic in Rochester (USA) gave his answers to the question of “How to define and when to treat smoldering myeloma” in a second keynote lecture. Several studies have identified patients with smoldering myeloma who have high-risk of progression to MM. These patients have been reclassified as having active disease requiring therapy (SLiM-CRAB criteria). Dr. Kumar emphasized that smoldering myeloma should not be seen as a biological entity but rather a mixture of monoclonal gammopathy of undetermined significance (MGUS) and early MM. The challenge is to distinguish these two groups of patients. A revised risk stratification based on bone marrow plasma cell count > 20%, M-protein > 2 g/dl and abnormal free light chain ratio (FLC) > 20 seems promising to redefine high risk smoldering myeloma patients in the era of

SLiM-CRAB criteria but further validation is needed (Lakshman et al. 2018). Currently, early intervention is a major concept to delay or prevent the progression to active MM. The GEM-CESAR trial (NCT02415413), the ASCENT trial (NCT03289299; Fig. 1) and the DETER-SMM trial (NCT03937635; Fig. 2) are addressing this concept. Whether some of these patients can even be cured remains to be answered. Finally, Dr. Kumar stressed the importance of combining screening programs, specific risk stratification systems and risk adapted treatment strategies to deal with smoldering myeloma.

Session II: Role of immunotherapy in multiple myeloma

Paola Neri from the Hematology Division at University of Calgary (Canada) started the second session by linking MM biology and the importance of the immune microenvironment. The mechanisms that promote immunosuppression and diminish immunorecognition in MM were extensively reviewed (Neri et al. 2016). Furthermore, immunotherapeutic strategies including immunomodulatory drugs, immune checkpoint inhibitors, monoclonal antibodies and cellular therapies were presented. Dr. Neri emphasized the importance of immunogenomics including single cell-profiling and neo-antigen discovery to identify patients who are most likely to benefit from immunotherapies. Moreover, strategies to re-establish sensitivity to immunotherapy are urgently needed. In this context, Dr. Neri presented an unpublished study that compared the T cell compartments of refractory MM patients treated with daratumumab using large scale single cell RNA sequencing. Preliminary results suggest an important role of effector memory T cells that might be necessary to respond to daratumumab treatment.

In the second talk, Niels van de Donk from the VU University Medical Center in Amsterdam (Netherlands) focused on the role of monoclonal antibodies in MM therapy. After summarizing the effects of anti-CD38 antibodies and SLAMF7-targeting agents, he showed how antibody-based combinations have improved response and survival of patients with relapsed MM. Current studies focus on the integration of antibody-based therapies in first line treatment also for transplant eligible patients. New management aspects concerning monoclonal antibodies like the impact on response evaluation, the clinical management of infusion reactions and blood transfusion typing were discussed (van de Donk et al. 2017).

Adam Cohen from the University Hospital Pennsylvania, Philadelphia (USA) closed the session by giving an extensive overview over the current development in antibody–drug conjugates, bispecific antibodies and CAR-T cells. He summarized several principles that could be learned from CAR-T

Fig. 1 Overview of the multi-center, phase II trials GEM-CESAR and ASCENT for early intensive treatment in patients with high risk smoldering myeloma. **a** The GEM-CESAR trial of the PETHEMA recruited 90 patients in Spain (<https://clinicaltrials.gov/ct2/show/NCT02415413>). The primary endpoint is immunophenotypic complete remission rate. **b** The ASCENT trial of the International Myeloma Foundation is currently recruiting patients (planned $n = 83$) in the USA (<https://clinicaltrials.gov/ct2/show/NCT03289299>). The primary endpoint is stringent complete response rate and secondary endpoints include MRD assessment. *HDM* high dose melphalan, *ASCT* autologous stem cell transplantation

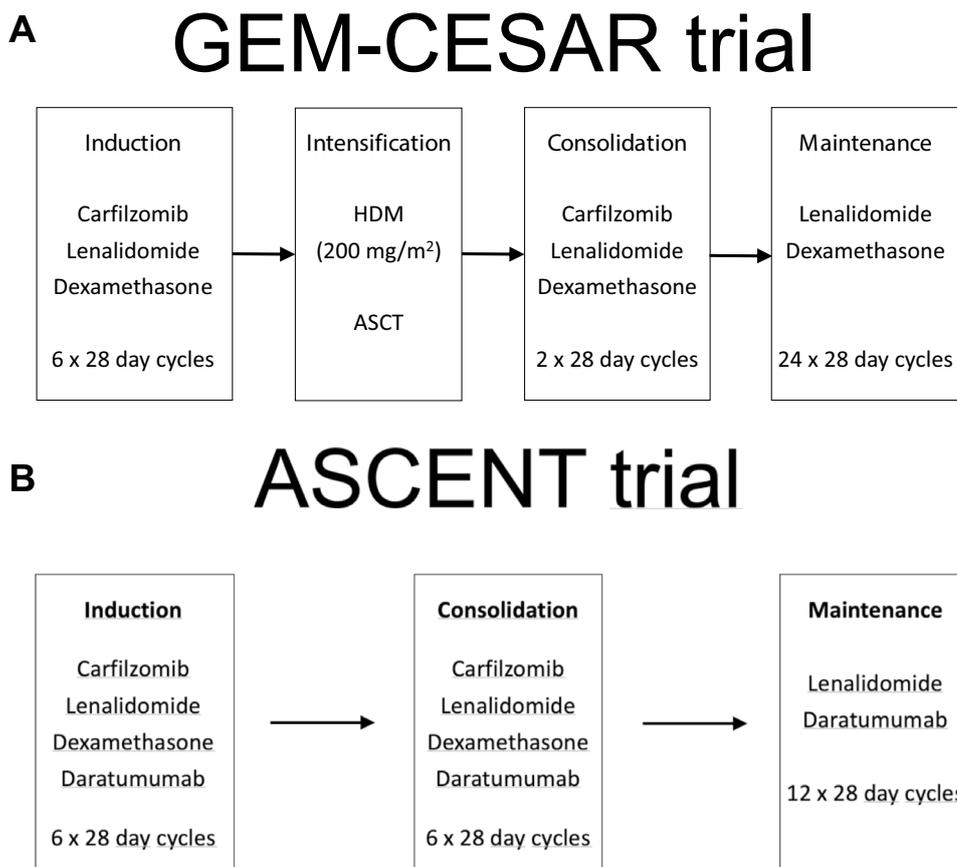
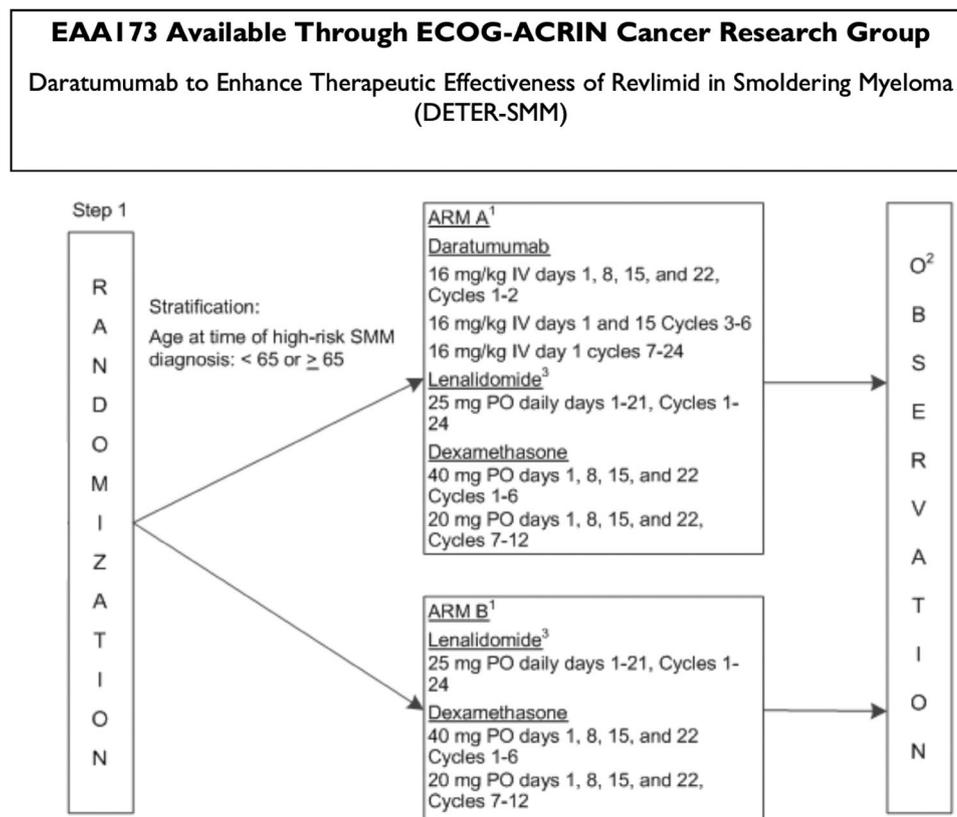


Fig. 2 Overview of the phase III, multicenter, randomized DETER-SMM (daratumumab to enhance therapeutic effectiveness of revlimid in smoldering myeloma) trial of the Eastern Cooperative Oncology Group (ECOG) currently recruiting patients (planned $n = 288$) with high-risk smoldering multiple myeloma for the evaluation of the addition of daratumumab to lenalidomide/dexamethasone in the USA. The primary endpoint is overall survival (<http://ecog-acrin.org/wp-content/uploads/2019/05/EAA173-physician-fact-sheet.pdf>; <https://clinicaltrials.gov/ct2/show/NCT03937635>)



cell studies (Susanibar Adaniya et al. 2019). First, the response to CAR-T cells targeting BCMA cannot be predicted by the level of BCMA expression on MM cells. Second, CAR-T cells showed promising efficacy but are not curative in refractory MM patients. And third, the quality of T cells at the time of harvesting by leukapheresis is highly relevant for the efficacy of the CAR-T cells at the time of reinfusion. Cohen predicted the first FDA approval of a CAR-T cell therapy in MM for early 2020. Future challenges are the management of costs, logistics, toxicity and durability of immunotherapeutic treatment as well as to elucidate the perfect timing and the perfect combination of these innovative immunotherapies.

Keynote: MRD-negativity for all patients

In the third keynote lecture of the meeting Brian Durie from Cedars-Sinai Medical Center in Los Angeles (USA) gave his views on MRD-negativity as a treatment goal in MM. He started his talk with a strong statement against seeking MRD negativity in all patients right away and cautioned the community against readily communicating MRD results to patients which may cause significant disturbance in the case of unachieved or lost negativity without clear clinical consequence as of 2019. Dr. Durie presented the efforts of the international I²TEAMM initiative seeking approval by the FDA/EMA of MRD as a surrogate endpoint based on excellent trial results (Munshi et al. 2017). With state of the art combination treatment the majority of patients can achieve MRD negativity (e.g. 58% with VRD-ASCT-VRD in a PETHEMA/GEM phase III trial) (Rosinol et al. 2017) which is associated with low relapse rates. Earlier intervention at the stage of high risk smoldering myeloma (e.g. ASCENT, CESAR trials; Fig. 1) is hoped to further improve on these results. However, early results indicate that even with this maximal intervention at least 30–40% of patients will still have resistant and recurrent disease. New therapies are, therefore, needed to target early biochemical relapse to achieve the best possible outcome including new MRD negativity. In this context, Dr. Durie cited the POLLUX trial (Dimopoulos et al. 2016) proofing that MRD negativity and prolonged remission can be achieved at relapse with daratumumab/Rd and anticipated a role for novel immune therapies such as CAR-T cells in the search for a “functional cure”.

Session III: Current therapy of multiple myeloma

Michele Cavo from the University of Bologna (Italy) opened the third session with his talk on the role of tandem autologous stem cell transplantation in the management of newly diagnosed MM. The European EMN02 trial (Cavo et al.

2017) found a benefit for tandem transplantation which was most pronounced in patients with cytogenetic high-risk disease, while the American STAMINA trial (Stadtmayer et al. 2019) did not find such a benefit. However, there were important differences in trial designs that limit comparability, especially more active (STAMINA 50% VRD vs. EMN02 100% VCD) and prolonged (STAMINA 2–12 vs. EMN02 2–3 cycles) induction treatment in the STAMINA trial which may have obviated the need for tandem transplantation. To further address the issue of tandem transplantation, Dr. Cavo performed a large retrospective meta-analysis ($n = 909$) of three phase III trials (GIMEMA/MMY3006, PETHEMA/GEM, HD4/HOVON-65) with bortezomib based induction (VTD or PAD) and a median follow-up of more than 10 years that was also presented at ASH 2018 (Cavo et al. 2018). This analysis again suggests a PFS and OS benefit from tandem transplantation, especially in high risk patients based on cytogenetics, ISS and failure to achieve CR.

Advances in frontline treatment for non-transplant-eligible patients were presented by Christof Scheid from the University Hospital of Cologne (Germany) and are centered on the incorporation of monoclonal antibodies in standard regimens with a shift from double to triple and quadruple combination regimens. Recent advances include EMA/FDA approval of Daratumumab-VMP which set a new benchmark in this patient population with 60% PFS at 30 months in the phase III ALCYONE trial (HR 0.43 compared to VMP) (Mateos et al. 2017). However, results of the phase III MAIA trial (Facon et al. 2018) with Daratumumab-Rd are even more promising with 71% PFS also at 30 months (HR 0.56 compared to Rd) and will likely define a new standard treatment for transplant-ineligible patients in the near future. Dr. Scheid concluded that the advent of these highly active regimens renders MRD negativity ($\sim 25\%$ at 10^{-5}) a realistic treatment goal and may more generally challenge the role of autologous stem cell transplantation in frontline treatment.

Marc Raab from the Heidelberg University Hospital (Germany) gave an overview of risk factors and adapted treatment approaches in MM. Multiple layers of risk include host-, disease-, and response-related factors. Especially in patients with high risk biology based on recurrent cytogenetic aberrations (e.g. del (17p), t (4;14), gain (1q21) > 3 copies) and the (revised) international staging system (ISS) (Palumbo et al. 2015) there continues to be a profound unmet clinical need. Strategies to adapt treatment in these high risk patients are aimed at inducing deep and lasting remissions. Current concepts include combination regimens, tandem autologous stem cell transplantation and bortezomib maintenance treatment (Sonneveld et al. 2016). The subgroup of high risk patients is increasingly being targeted in specialized clinical trials applying particularly intensive regimens such as Isatuximab-KRd in the CONCEPT trial

(NCT03104842; Fig. 3) of the German-speaking Myeloma Multicenter Group (GMMG).

Potentially curative allogeneic stem cell transplantation continues to be hampered by relevant—yet decreasing—treatment-related mortality (TRM; 8–30%) and high relapse rates (up to 60%), as reported by Nicolaus Kröger from University Medical Center Hamburg-Eppendorf (Germany). Randomized clinical trials have yielded conflicting results regarding survival compared to autologous stem cell transplantation and guidelines recommend allogeneic transplants to be applied only in clinical trials (Moreau et al. 2017). The large EBMT registry (Sobh et al. 2016) (> 7000 patients) documents current use of allogeneic transplantation in Europe primarily after relapse (> 60%), where it may be of benefit in patients with early relapse and high risk disease. Promising developments in the field include the implementation of post-transplant maintenance strategies using IMiDs and/or donor lymphocyte infusions.

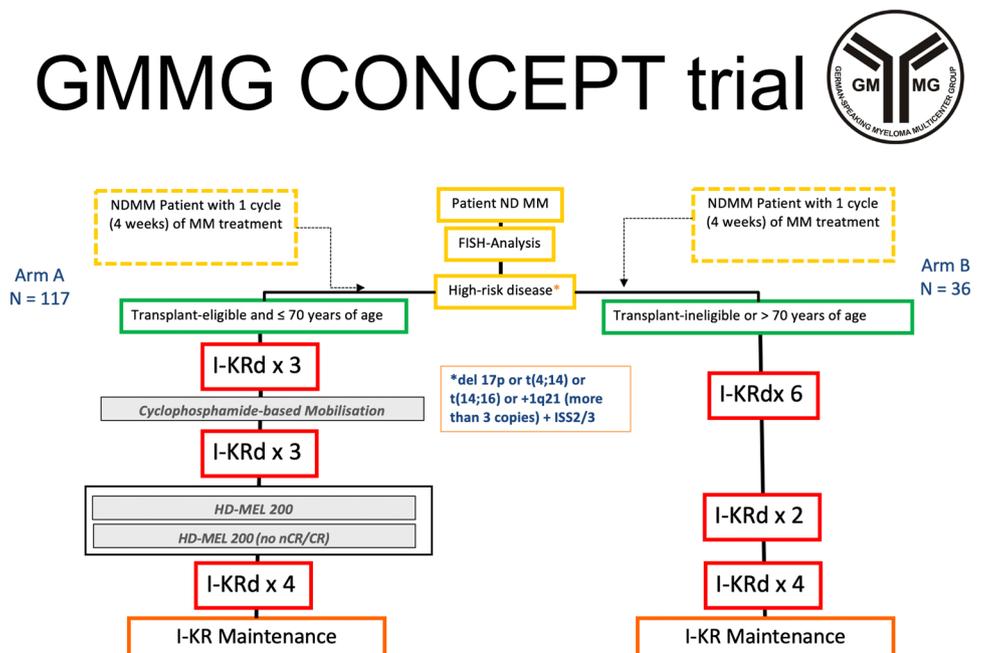
The session was completed by Katja Weisel, also from University Medical Center Hamburg-Eppendorf (Germany), who presented the treatment landscape for relapsed MM. A plethora of available regimens allows for treatment selection according to prior-treatment, disease characteristics and patient-related factors. In the absence of lenalidomide and bortezomib refractoriness patients have the choice between several highly active triplet regimens. Combinations of lenalidomide/dexamethasone (Rd) and/or bortezomib/dexamethasone (Vd) with monoclonal antibodies (elotuzumab, daratumumab), second generation proteasome inhibitors (carfilzomib, ixazomib) or the HDAC inhibitor panobinostat are FDA/EMA approved (Kumar et al. 2018).

The role of salvage autologous stem cell transplantation remains unclear. Due to extensive use of lenalidomide in early lines of treatment lenalidomide pretreatment/refractoriness is occurring increasingly earlier during the disease course. Randomized phase II or III trials showing superior efficacy of novel combination regimens in this setting based on pomalidomide/dexamethasone (POM/DEX) have recently been reported (OPTIMISM trial: bortezomib/POM/DEX [Richardson et al. 2019], ELOQUENT-3 trial: elotuzumab/POM/DEX [Dimopoulos et al. 2018]). Also addition of cyclophosphamide can induce remissions in patients not responding to POM/DEX alone as shown by Dr. Weisel in the GMMG PERSPECTIVE trial (Weisel et al. 2019). A more convenient once weekly dosing schedule of carfilzomib/dexamethasone has been shown to be superior to conventional biweekly dosing—albeit at a higher cumulative dose (70 vs. 54 mg/m²/week; ARROW trial) (Moreau et al. 2018). Once approved, these regimens will increase the flexibility of physicians to use or combine the available drugs more flexibly according to patient-individual factors in clinical practice.

Debate: MRD driven therapy—ready for primetime

Leading up to a debate on the use of MRD assessment Stefanie Huhn from Heidelberg University Hospital (Germany) recapitulated the technical aspects of MRD detection. Since 2016, MRD negativity is part of the International Myeloma Working Group (IMWG) consensus criteria for response

Fig. 3 Flow chart of the phase II, multicenter GMMG CONCEPT trial currently recruiting patients with newly diagnosed multiple myeloma (NDMM) with high-risk features (cytogenetic aberrations by iFISH, ISS) for intensive and prolonged treatment in Germany (<https://clinicaltrials.gov/ct2/show/NCT03104842>). The primary endpoint is minimal residual disease negativity after consolidation. *I-KRD* Isatuximab/Carfilzomib/Dexamethasone, *HD-MEL 200* high-dose melphalan 200 mg/m² followed by autologous stem cell transplantation



assessment (Kumar et al. 2016). Yet many important issues such as the technique, sensitivity, timing and frequency of MRD testing remain to be standardized. Based on the established prognostic significance of MRD for survival, regulatory authorities (FDA/EMA) are currently evaluating MRD as a surrogate endpoint for clinical trials to accelerate approval of effective new drugs in the face of long PFS/OS timeframes. For molecular MRD next generation flow cytometry (NGF) and sequencing (NGS) of bone marrow aspirates are the most widely applied techniques. Among them no gold standard exists and the technique may be chosen according to inherent strengths and weaknesses, e.g. the requirement for viable cells (NGF) or a baseline sample (NGS). Imaging-based MRD assessed by PET-CT can increase sensitivity due to the focal distribution and/or extramedullary disease in subgroups of MM patients.

Nikhil Munshi from Dana Farber Cancer Institute (Boston, USA) took a strong stance in favor of MRD assessment based on its proven prognostic value. In a large meta-analysis of 21 trials recently published in *JAMA Oncology* Dr. Munshi showed a consistent PFS/OS benefit associated with MRD negativity—even in patients in CR—despite a range of techniques, sensitivity thresholds and time points applied in the individual trials (Munshi et al. 2017). The prognostic impact of MRD negativity has recently been shown to be largely independent from the type of treatment received—e.g. stem cell transplantation vs. RVD in the IFM 2009 trial (Perrot et al. 2018) (newly diagnosed MM) or Dara/Rd vs. Rd in the POLLUX trial (Dimopoulos et al. 2018) (relapsed MM). Similar data have been reported from other trials including Myeloma IX (Rawstron et al. 2015), CASTOR (Spencer et al. 2018), and ALCYONE (Dimopoulos et al. 2018). Importantly, these trials also show that more effective regimens induce higher rates of MRD negativity. High risk status, e.g. according to cytogenetics and ISS is partially overcome by MRD negativity, but high risk patients have a lower probability of achieving MRD negativity. Dr. Munshi concluded that these results now suggest the need to adapt MRD-based treatment strategies in both patient management as well as future clinical trials.

Martin Kaiser from Royal Marsden Hospital (London, UK) also highlighted the prognostic significance of MRD negativity in trial populations and its value for regulatory purposes. However, he raised concerns regarding several issues that need to be resolved before MRD assessment may be used to guide clinical practice in the individual patient. As such the quality of the bone marrow sample for analysis may be compromised by hemodilution, MRD assessment in a random bone marrow aspirate cannot reliably pick up patchy or even extramedullary disease, NGF and NGS yield discordant results particularly in a number of patients with low level MRD due to measurement at the threshold of sensitivity, and different imaging techniques

have different sensitivities, e.g. false-negative PET/CT in patients with low hexokinase-2 expressing MM (Rasche et al. 2017). Most importantly, Dr. Kaiser emphasized the completely uncertain consequence of a positive or negative MRD result for patient management as MRD-adapted treatment approaches have not been tested in clinical trials yet.

Keynote: The future of multiple myeloma therapy in the next decade

In the last keynote lecture, Kenneth C. Anderson from Dana Farber Cancer Institute in Boston (USA) gave an outlook on potential future developments in characterization and treatment of MM and its precursor stages. With more accurate risk assessment the precursor stage of smoldering MM will likely dissolve in favor of a better distinction between early MM in need of treatment and actual MGUS (Lakshman et al. 2018). The latter may be amenable to immunologic targeting by immunostimulation-enhanced vaccination strategies aimed at early eradication of the abnormal clones. Current prognostication scores will be enhanced by targeted sequencing to simultaneously identify mutations, copy number alterations and translocations and may even include measures for microenvironment and immune function. Analysis of cell free DNA (Manier et al. 2018; Guo et al. 2018) and circulating tumor cells (Lohr et al. 2016) from peripheral blood will complement bone marrow sampling and allow for more comprehensive assessment of disease heterogeneity and treatment response. In the near future we will likely see the approval of a second CD38 monoclonal antibody (isatuximab) and maybe a BCL-2 inhibitor (venetoclax). Beyond these, several novel classes of agents are currently being developed preclinically including degronimids for the targeted degradation of cellular proteins, methylase/demethylase inhibitors targeting epigenetic features and off-the-shelf allo-CAR-T cells. Frontline regimens will most likely evolve from triple to quadruple combinations enhanced by a monoclonal antibody (Moreau et al. 2019) and autologous stem cell transplantation may be challenged by advanced immunotherapeutic approaches such as CAR-T cells. A novel form of clinical trials, so called umbrella trials, will aim at personalizing treatment by matching targeted treatments to recurrent genetic lesions in the individual patient (e.g. MyDRUG trial NCT02884102; Fig. 4). Dr. Anderson concluded that with these highly effective therapies MRD negativity and restoration of anti-MM host immunity will become a primary objective to ultimately allow for a potential cure of the disease.

Session IV: Biology and genomics of multiple myeloma

Leo Rasche from the University Hospital Würzburg (Germany) opened the fourth session with his talk about “radiogenomics”. This evolving field focuses on the relationship between imaging phenotypes and genomics. Dr. Rasche showed that the size of focal lesions is an important radiomic feature in newly diagnosed MM and smoldering myeloma. In this context, multiple large focal lesions (at least three lesions with a size of more than 5 cm²) constitute an independent high risk pattern (Rasche et al. 2018). In contrast, the amount of multiple small focal lesions is not correlated with prognosis. Moreover, the DW-MRI spleen signal was presented as a promising marker for tumor load (unpublished data). Correlation of genomic data with radiologic findings unveiled the role of low hexokinase expression in patients with false-negative PET-CT (Rasche et al. 2017). Rasche summarized that a radio-genomic approach linking molecular data with medical imaging could adjust for spatial heterogeneity and subsequently help to tailor therapy.

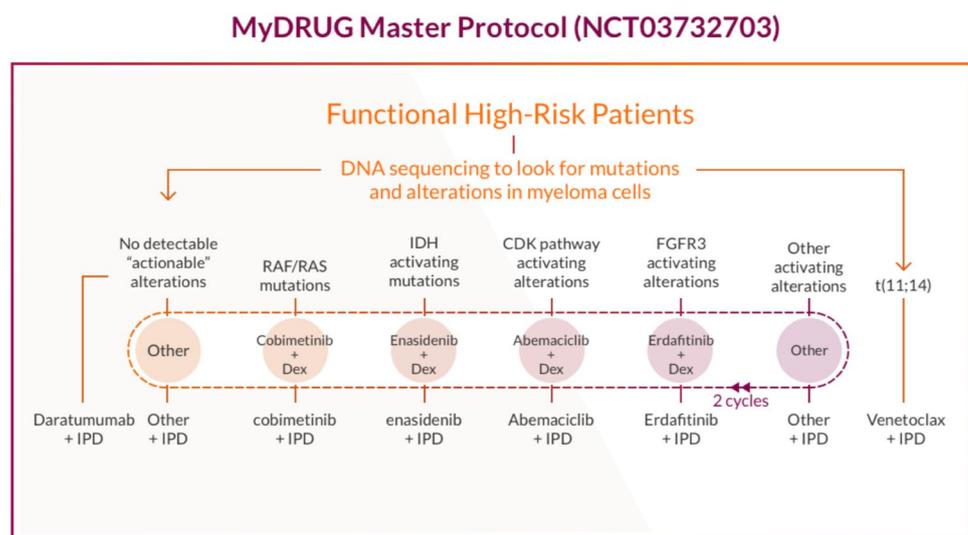
In the second talk, the importance of genetic heterogeneity and genomic evolution was discussed by Niels Weinhold from Heidelberg University Hospital (Germany). Recent studies have already shown intra-patient heterogeneity in MM and striking differences in the clonal architecture have been revealed by multi-region sequencing (Rasche et al. 2017). In this context, Dr. Weinhold presented a model for MM evolution with clonal sweeps in the early stage and regional evolution in the advanced phase. Evolutionary processes are currently investigated

by an unpublished longitudinal study of MM patients during treatment including functional imaging and multi-region sequencing. The results suggest that clonal selection occurs during therapy but more importantly clonal evolution is ongoing and leads to resistant subclones.

Bruno Paiva from the Clinica Universidad de Navarra and Centro de Investigaciones Medicas Aplicadas in Pamplona (Spain) continued the fourth session with his talk about non-invasive techniques for MM detection. Dr. Paiva underlined the high feasibility for liquid biopsy since circulating tumor cells (CTCs) could be detected in 60% of MGUS and 87% of MM patients by using next generation flow (Sanoja-Flores et al. 2018). High numbers of CTCs correlate with increased risk of progression. But further studies are needed to validate CTCs as a future marker to define high-risk smoldering myeloma. Moreover, the investigation of isolated CTCs was discussed as less invasive technique for cytogenetic characterization of MM cells. Genetic features of bone marrow clonal plasma cells could be determined with high accuracy by studying CTCs (Mishima et al. 2017). In the future, studying the transcriptome of CTCs might also reveal novel prognostic markers that are related to disease dissemination.

In recent years, single cell technologies have been evolving rapidly. Jens Lohr from Dana Farber Cancer Institute in Boston (USA) presented the application of single cell technologies in the field of MM. Based on a highly sensitive surface marker and morphology-based method individual circulating MM cells from peripheral blood and single MM cells from bone marrow can be isolated even when they are present at a frequency of less than one in 10⁶ cells (Lohr et al. 2016). Dr. Lohr showed how single cell RNA sequencing can be used to define subsets of disease, indicate the presence of chromosomal aberrations that result in

Fig. 4 Overview of the phase I/II, multicenter MyDRUG (myeloma-developing regimens using genomics) trial currently recruiting patients with relapsed and/or refractory multiple myeloma with 1–3 prior lines of therapy for targeted therapy in the USA. The primary endpoint is overall response rate (<https://themmrf.org/mydrug/>; <https://clinicaltrials.gov/ct2/show/NCT03732703>). IPD ixazomib/pomalidomide/dexamethasone, Dex dexamethasone



overexpression of oncogenes and establish lineage identity of these single cells. The analysis of the single MM cell revealed extensive heterogeneity beyond genetically defined clones. A major focus of his work lies on the determination of heterogeneity and evolution in MM with treatment over time (Guo et al. 2018). Clinical implications of the powerful approach of single cell sequencing need to be further addressed in the future.

The session was closed by Jens Hillengaß from Roswell Park Comprehensive Cancer Center in Buffalo (USA) focusing on novel imaging techniques in MM. Beyond low dose CT as gold standard for the assessment of bone disease in MM, the role of newer modalities such as MRI and FDG-PET/CT are still under investigation (Hillengass et al. 2019). To date, it remains unclear which technique should be implemented for imaging MRD. Larger head to head comparisons between the two modalities are still needed. In terms of future developments, Dr. Hillengaß mentioned imaging-based immune-profiling approaches using antibody-coupled tracers and machine-assisted image analysis as promising fields of research.

Session V: Novel therapeutic concepts

Effective novel concepts with acceptable toxicity profiles for patients (penta-)refractory to the current backbones of MM treatment, especially to IMiDs, proteasome inhibitors and CD38 antibodies are an urgent unmet clinical need. Roman Hajek from the University of Ostrava (Czech Republic) reviewed novel classes of drugs that are currently under clinical investigation. A prominent example with proven efficacy especially in combination with Vd is the BCL-2 inhibitor venetoclax (median PFS 22 vs. 12 months; BELLINI trial; NCT02755597). However, ongoing trials have recently been placed on partial hold by the FDA due to an excess of deaths in the venetoclax arm of the BELLINI trial (21% vs. 11%) which is not yet fully understood. Another first-in-class agent, the selective inhibitor of nuclear export (SINE) selinexor has shown modest activity in combination with dexamethasone (overall response rate (ORR) 26%; STORM phase II trial; NCT02336815) and relevant gastrointestinal toxicity (all grade nausea: 72%; diarrhea 44%). The FDA granted accelerated approval to selinexor/dexamethasone for extensively pretreated patients in July 2019. Very promising phase I data have been reported for BCMA-directed CAR-T cells (bb2121 (Raje et al. 2019), JNJ-68284528 (Zhao et al. 2018)) with unprecedented MRD negative responses in heavily pretreated patients and median PFS of 12–15 months at manageable toxicity. However, no plateau was seen in survival curves. Further immunotherapeutic agents with early evidence of efficacy include

a BCMA-targeted bispecific antibody (AMG 420) and a monomethyl auristatin-F-conjugated anti-BCMA antibody (GSK2857916).

The concept of personalized oncology for MM was discussed by Nicola Giesen from Heidelberg University Hospital (Germany). She briefly mentioned strategies to personalize treatment that are already being applied in clinical practice such as adaption according to fitness and frailty (Palumbo et al. 2014), renal function (Dimopoulos et al. 2016), and cytogenetic risk status (Sonneveld et al. 2016). Currently, there is a paucity of drugs and biomarkers that allow for targeted therapy of defined patient subgroups. One such combination is venetoclax and t(11;14) (Vaxman et al. 2018). The presence of the latter correlates with dependency on BCL2, the target of venetoclax. ORR for monotherapy in RMM is 40% and is much higher in combination with proteasome inhibitors. Another example is the sensitivity of patients with the BRAF V600E mutation to BRAF inhibition. Preliminary data from the ongoing GMMG BIRMA trial (NCT02834364) show that deep and durable remissions are achievable with encorafenib/binimetinib. A general problem of such targeted approaches is the unclear functional impact and subclonal nature of many mutations. This may be overcome by combination with more broadly acting backbone drugs (e.g. proteasome inhibitors, IMiDs). Due to the large interindividual heterogeneity in the mutational spectrum of MM, non-randomized platform trials matching patients with different potentially actionable mutations to targeted treatments may help to accelerate drug development. The first such trial for MM, which was also mentioned earlier during the meeting by Dr. Anderson, is the ongoing MyDRUG (myeloma—developing regimens using genomics; NCT02884102; Fig. 4) trial ($n = 228$) conducted by the Multiple Myeloma Research Foundation (MMRF) which uses ixazomib/pomalidomide/dexamethasone as a backbone for several targeted agents (abemaciclib, enasidenib, cobimetinib, erdafitinib, or venetoclax).

Nizar Bahlis from University of Calgary (Canada) introduced the mechanism and rationale for the development of protein targeting chimera (PROTAC). These protein adaptors can be designed to target virtually any cellular protein to a ubiquitin-ligase and subsequent degradation via the proteasome—in the same way IMiDs mediate degradation of IKZF1/3 via the ubiquitin E3 ligase cereblon. Degradation rather than inhibition of a target protein has several theoretical advantages. PROTAC may allow to target previously undruggable oncoproteins since binding is not limited to an active site within the target protein. Thus, PROTAC do not compete with a natural substrate and degradation of the target omits the need for the continuous presence of the drug. Targets for PROTAC currently under preclinical investigation that have potential implications for MM include BRD4, HDAC6 and MCL-1 (Papatzimas et al. 2019).

two GMMG trials (PERSPECTIVE [Weisel et al. 2019], ReLApSE) have recently been completed. The ReLApSE phase III trial was presented at ASH 2018. Salvage autologous stem cell transplantation compared to Rd failed to improve survival in the intention to treat population with a ~30% drop-out rate before transplantation (Goldschmidt et al. 2018); landmark analysis did show a survival benefit in patients that actually received the transplant (Baertsch et al. 2018). The phase II trials BIRMA (BRAF/MEK inhibition in BRAF V600E mutated MM; NCT02834364) and DANTE (Dara-Vd in severe renal insufficiency including hemodialysis; NCT02977494) are currently recruiting specific subgroups of patients with RMM. An overview of all active GMMG trials is available at <https://www.klinikum.uni-heidelberg.de/Studien.131764.0.html>.

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Compliance with ethical standards

Conflict of interest MAB: Takeda: Consultancy; Novartis: Consultancy, Research Funding; Celgene, Amgen, Janssen: Travel grants. RL: Janssen: Travel grants. MSR: Celgene: Consultancy, Honoraria; Novartis: Consultancy, Honoraria, Research Funding; BMS: Consultancy, Honoraria, Research Funding; Amgen: Consultancy, Honoraria, Research Funding. NW: No conflict. HG: Amgen: Consultancy, Research Funding; Novartis: Honoraria, Research Funding; ArtTempi: Honoraria; Janssen: Consultancy, Honoraria, Research Funding; Sanofi: Consultancy, Research Funding; Mundipharma: Research Funding; Takeda: Consultancy, Research Funding; Celgene: Consultancy, Honoraria, Research Funding; Bristol Myers Squibb: Consultancy, Honoraria, Research Funding; Adaptive Biotechnology: Consultancy; Chugai: Honoraria, Research Funding.

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