haematologica
Journal of the Ferrata Storti Foundation

5th EUROPEAN MYELOMA NETWORK MEETING

Turin, Italy, April 18-20, 2024

ABSTRACT BOOK

ISSN 0390-6078
Volume 109
APRIL
2024 - S2

www.haematologica.org

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MAIN PROGRAM

MGCS: DIAGNOSIS AND TREATMENT

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Monoclonal gammopathies of clinical significance (MGCSs) describes a heterogeneous group of conditions (syndromes or single organ/tissue damage) associated with the presence of a usually small and non-malignant B- or plasma cell clone. Mechanisms of tissue damage in MGCS roughly include those associated with the physicochemical or the immune properties of monoclonal immunoglobulins (MIg) and "paraneoplasmatic" related to cytokine secretion. MGCSs have varying clinical presentations even among the same "condition" and the diagnostic approach is challenging. Immunoglobulin light chain (AL) amyloidosis is the most common among the MGCS; is a well-recognized entity with defined diagnostic approach, treatment and follow-up strategies unlike most of other MGCSs. The kidneys are common target-organ of MIg either directly or indirectly. Different renal histologies have been associated with the presence of an indolent clone coined the term Monoclonal Gammopathies of Renal Significance (MGRS). Renal biopsy is the key diagnostic tool to diagnose MGRS. Peripheral nerve is common target of MIg, through different mechanisms, either directly, as in IgM anti-MAG polyneuropathy, or indirectly, as in POEMS syndrome. Skin may be involved and certain conditions have been strongly associated with an underlying monoclonal gammopathy (scleromyxedema, necrobiotic xanthogranuloma, Schnitzler syndrome etc); muscles may also be a target (as in nemaline myopathy). Monoclonal gammopathy of ocular significance refers to eye involvement by immunoglobulins. Systemic syndromes may be related to specific properties of the MIg (cryoglobulinemia, cold agglutin activity, autoantibody activity) or to cytokine activity. In some conditions the exact mechanism is unknown and new entities (such as the TEMPI syndrome) carry new challenges to diagnosis. Registry studies indicate increased incidence of complications such as thrombosis or osteoporosis among subjects with MGUS but further investigation is required to provide causative relationships. The real incidence of MGCS is unknown, the definitions and classifications are evolving while associations may be problematic given the high incidence of MGUS in the general population. Providing convincing evidence of a causative relationship with an underlying B-cell or plasma cell clone is critical to treat appropriately. For many conditions there is a clear benefit from the use of anticlonal therapies; in others benefits may not be as prominent while in some MGCS, other therapies, not targeting the clone, may be indicated.

SMOLDERING MULTIPLE MYELOMA (SMM): RISK STRATIFICATION AND MANAGEMENT

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Asymptomatic (smoldering) multiple myeloma (SMM) is a heterogeneous precursor condition, associated with a risk of progression to symptomatic MM that differs substantially among patients ranging from one similar of MGUS to more than 60% probability at two years from diagnosis. Defining high-risk SMM has been critical to individual risk assessment and the design clinical trials that would attempt to clarify the optimal management strategy. Several criteria have been used, each of which has demonstrated utility but are clinically distinct. The 20/2/20 risk stratification model, provided a new definition of high-risk SMM but a caveat of such models is that patients with rapidly evolving M spike or serum free light chains or progressive fall in hemoglobin are not included. Dynamic models that consider biomarker evolution over time may provide more accurate predictions but factors such as circulating tumor cells and genomic aberrations have yet to be adopted. Currently there is no approved therapy for patients with SMM, even for those defined as "high risk". Two randomized studies showed that fixed duration therapy with lenalidomide/dexamethasone or continuous lenalidomide alone are associated with significant prolongation of time to disease progression and perhaps with overall survival benefit. These studies were conducted several years ago, in different patient populations, and since, risk stratification criteria, follow-up modalities and treatments have evolved. More than 70 studies which evaluate different strategies and regimens in patients with SMM, including randomized phase 3 studies, continue or have completed recruitment. Two major strategies can be deciphered: a "mild" approach aiming to delay or abort the disease evolution and a more aggressive one, targeting to eliminate the plasma cell clone; given the precursor nature of SMM, the safety and tolerability of the therapeutic interventions is critical. Due to the clinical, prognostic, and demographic heterogeneity of SMM patients it is likely that both strategies will be relevant. Unfortunately, high variability in clinical trial inclusion criteria or assessments of outcomes makes it difficult to perform meta-analyses, use data from past trials or perform cross-trial comparisons. Clinical trial end-points is a matter of debate but patient-reported outcomes or patient preference assessments are critical components of any evaluation. Given the rapid evolution of treatments and their combinations, the critical limitation to develop therapies for SMM remains the identification of those patients in which the benefit-risk ratio is most favorable.

IMAGING *VERSUS* BM MRD: WHEN AND HOW?

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According to International Myeloma Working Group (IMWG) recommendations, minimal residual disease (MRD) after therapy should be evaluated within the bone marrow (BM), either with flow cytometry or with next generation sequencing (NGS) and outside the BM, with imaging. The reasons for this need rely on the patchy infiltration of bone marrow plasma cells (BMPCs), the presence of extramedullary disease (EMD), with different incidence in different disease' phases (increased in the relapsed/refractory population and after T cell redirecting therapies) and, last but not least, in possible spatial heterogeneity of the disease, with possible coexistence of different disease clones in the BM and focal lesions (FLs), displaying different genomic profiles. EM sites of clonal proliferating PCs, in a context of BM MRD negativity, are more frequent in patients with EMD at diagnosis (5-10%) or with para-medullary plasmacytomas or in very advanced stages of the disease. Positron emission tomography with computed tomography (PET/CT) is currently the recommended imaging technique by the IMWG to assess residual disease after therapy, thanks to its capability to provide a comprehensive overview of the tumor burden beyond osteolytic lesions, distinguishing active from inactive/fibrotic tissue. Several studies have demonstrated an unfavorable prognostic role for PET positive lesions after completion of therapy, also in the subset of patients achieving complete remission (CR) and, less frequently, BM MRD negativity. PET/CT is currently standardized. More recently, diffusion weighted (DWI) whole body MRI has been used to stage the disease, showing higher sensitivity, and to evaluate response after therapy, in a standardized fashion; prospective studies are currently on-going. The complementarity between imaging (either FDG-PET/CT or WB-DWI-MRI) and BM techniques in defining the prognosis of patients was demonstrated by several prospective studies, using flow cytometry or NGS with a sensitivity of 10^{-4} and 10^{-5}; data with higher BM sensitivity are currently not available. Re-definition of imaging response in patients carrying soft or para-skeletal plasmacytomas as well as receiving immunotherapies is currently on-going. Newer techniques for MRD evaluation in peripheral blood, such as mass spectrometry and flow cytometry, are currently under development and investigation and will for sure integrate in the future the algorithm for MRD evaluation. While waiting for correct positioning of all these techniques, PET/CT remains the most widely available and reliable imaging technique for the assessment of residual disease in areas outside of the BM and should be evaluated at baseline and prior to maintenance in transplant-eligible patients and after 1 year of therapy in non-transplant eligible.

THE FUTURE OF MRD TESTING IN MULTIPLE MYELOMA

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Remarkable improvements in the therapy for newly diagnosed or relapsed multiple myeloma over the last decade have led to deeper responses that are beyond the limit of detection by historical immunohistochemistry and conventional flow cytometry in bone marrow samples. In parallel, more sensitive techniques for assessing minimal residual disease (MRD) through next - generation flow cytometry and sequencing have been developed and are now routinely available. Deep responses when measured by these assays clearly correspond with improved outcomes and survival. These tests prognosticate survival and duration of response and should be incorporated as part of clinical trials. The role of these test results to inform treatment decisions concerning therapy discontinuation or change largely remains to be determined. We will discuss the data supporting MRD testing as well as its limitations and how it may best fit in with current and future clinical trials and care.

TREATMENT ALGORITHM IN TRANSPLANT-INELIGIBLE PATIENTS

S. Manier

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In the past two decades, several tools have been developed to assess frailty in different populations, including older adults in general, patients with cancer, and more recently specifically patients with myeloma. The initial work in the field of MM frailty assessment was generated less than 10 years by the International Myeloma Working Group Frailty Score. It demonstrated that frail patients have shorter survival but also more frequent non-hematological side effect or treatment discontinuation. Treatment intensity is often questioned in elderly patients. A commonly expressed opinion is that for older or frail patients, two-drug regimens, may be preferable over three-drug regimens. However, this perspective requires careful evaluation and discussion with patients as anti-CD38 antibody-based therapies have demonstrated significant efficacy benefits, including improvements in of quality of life, with greater and faster improvement in bone pain, while maintaining an acceptable tolerability profile for each patient. Another important observation from the MAIA study is that only a small number of patients achieve very deep responses with negative minimal residual disease (MRD) status (only 15% with 1-year sustained MRD negativity). However, these patients have significantly prolonged median progression-free survival (PFS). This suggests that maintaining a continuous low-intensity treatment helps control residual clones and improves patient outcomes. The use of short term dexamethasone should however be considered in regards to the important toxicity of long term dexamethasone. The GIMEMA group has led a dexamethasone sparing regimen in elderly patients, who were randomly allocated to either lenalidomide and low-dose dexamethasone continuously or lenalidomide and 9 cycles of low-dose dexamethasone followed by lenalidomide alone. Both treatment approaches were equally effective, but discontinuing dexamethasone was associated with a better safety profile [12]. Furthermore, the ongoing IFM2017-03 trial is evaluating the possibility of earlier discontinuation after only 2 cycles, in the context of daratumumab and lenalidomide combination. With the advent of new effective agents, it is expected that the use of dexamethasone will be significantly reduced in the future for older patients. Ongoing trials are evaluating the value of adding bortezomib initially to improve the rates of MRD negativity (IMROZ, CEPHEUS and BENEFIT) in elderly and fit patients.

TAILORING TREATMENT IN FRAIL PATIENTS: CURRENT KNOWLEDGE AND FUTURE DIRECTIONS

S. Bringhen

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Multiple myeloma (MM) mostly affects older patients, who represent a highly heterogeneous population. In the last few years, the introduction of novel agents led to a significant improvement in the outcome of MM patients. Nonetheless, this positive trend is less likely to occur in all elderly patients due to frailty, that is, a state of increased vulnerability to stressors due to a critical decline in physiologic reserves. The optimal treatment of frail patients is not easily derived from available clinical trials because this type of patients are usually excluded or underrepresented in most registrational trials. Even when trials have tried to include frail patients, inclusion and exclusion criteria permit enrolment of only patients with relatively good performance status, and most frail and very frail MM patients who need therapy are excluded. In this context, physicians have called for greater caution in extrapolating data from clinical trials to real-world patients, because many frail patients seen in daily and routine practice are not be the type of patients eligible for clinical trials. The goal of treatment in frail patients is reducing therapy-related toxicities and preserving the best levels of quality of life and independence as long as possible. A careful balance between efficacy and safety is essential in frail patients. Dose reduction and a dexamethasone-sparing approach can be considered if toxicity limits treatment tolerability, since there is emerging evidence of similarly effective dose-reduced regimens. The prevention and treatment of infections and the optimization of supportive care improve patients' tolerability, reduce toxic deaths, and have consequently become mainstays in the treatment of frail MM patients. The identification of frail patients is essential not only to guide treatment decisions, but also to tailor available treatments and design studies dedicated to frail patients. The implementation of subanalyses on quality of life and studies on patient-reported outcomes could complete the picture, helping to optimize patient management. Anti-CD38 monoclonal antibodies and upcoming immunotherapeutic drugs have been revolutionizing the treatment of MM. In the near future, we need to define and investigate the role and feasibility of these new immunotherapies in frail patients and clinical trials should assess the risk/benefit ratio in frail patients.

NEW TARGETS AND NOVEL COMBINATIONS TO TREAT RRMM: BEYOND IMMUNOTHERAPY

N. Rakesh Popat

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Whilst the treatment for newly diagnosed myeloma has significantly improved with the use of CD38 Mab combinations, patients are continuing to progress through to relapse and require effective treatments. Much of this is dominated by T cell mediated immunotherapy such as bispecifics and CAR-T; however non immune approaches are required for those that remain unsuitable for them or those that have become refractory to them. Targeting cereblon has been found to be an effective strategy in myeloma as evidenced by the earlier IMiDs, thalidomide, lenalidomide and pomalidomide. However CELMoDs represent agents specifically designed to specifically and potently inhibit cereblon. This talk will cover data on Iberdomide, Mezigdomide and combinations with standard of care both in the multiple relapsed setting but also at earlier lines. These agents can also be combined with T cell immunotherapies.Inobrodib represents a novel inhibitor of the bromodomains of p300 and CBP which is being evaluated for relapsed myeloma and may represent a novel approach. Preliminary safety and efficacy data will be discussed

MOVING IMMUNOTHERAPY IN EARLY LINES

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Novel immunotherapies are currently transforming the landscape of multiple myeloma treatment through all lines of therapy. In addition to the established monoclonal antibodies against CD38 (daratumumab, isatuximab) and SLAM-F7 (elotuzumab), the most recent immunotherapies against multiple myeloma include bispecific antibodies and CAR T- cells directed against BCMA, GPRC5D, and FcRH5. Though some of these therapies are already approved for multiple myeloma, their potential compels the investigation in earlier lines of therapy and even precursor conditions. This talk will summarise trial concepts and results from current clinical trials including bispecific antibodies and CAR T-cells. This will include studies in early relapsed multiple myeloma, newly diagnosed multiple myeloma, and smouldering multiple myeloma.

CLINICAL STUDIES FOR RRMM PATIENTS

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Novel and improved agents for treatment of relapsed/refractory multiple myeloma (RRMM) are currently introduced and approved for clinical use at high frequency. The most advanced developments are novel immunomodulatory drugs (CELMoD's), T cell-engaging antibodies (TEC) and CAR T-cells that are used as monotherapy or in drug combinations. The incorporation of such agents in our standard treatment algorithms is a rolling development. Changing clinical practice ultimately requires to demonstrate superiority of such developments over the established clinical practice standard of care in a randomized phase III trial with a clinically meaningful, definitive endpoint. In RRMM, the established clinical standard based on such phase III comparisons is the use of conventional triplet combinations (DRd, KRd, D/IsaPd, D/IsaRd, Kd, PVd, EloPd) in patients with RRMM and at least one prior therapy line, while the use of CAR T cells has currently shown superiority over such triplet-based therapy in phase III in patients with at least two prior lines. To date, phase III data in RRMM involving TEC or CELMoD are not published. This presentation identifies and puts into perspective currently active or completed, but as yet unpublished phase III trials in RRMM that challenge the current clinical standard regimens in phase III randomized trials and that may therefore have the potential to change clinical practice in RRMM.

OPPORTUNITIES IN THE UTILIZATION OF SYNTHETIC DATA IN MULTIPLE MYELOMA RESEARCH

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Synthetic data (SD) are data that are artificially generated by using real data as a template. SD generation uses AI techniques to train a model to reproduce the characteristics of original data. An important application of SD is enhancing privacy and, hence, overcome the GDPR imposed limits. There is no one-to-one mapping between the SD and the original patient-specific data. Therefore, SD can preserve the privacy of individuals whose personal data should not be disclosed, while still allowing the sharing of important characteristics of a given dataset. SD can also be used to generate control arms in RCTs. RCTs often suffer from challenges with patient recruitment and retention, which can severely impact the timelines of placebo-controlled trials. A synthetic control data set could instead be used as the comparator arm, allowing for medicines to reach the market patients sooner. A recent case study was done in multiple myeloma, assessing whether synthetic control arms could replicate the findings from RCTs. The synthetic control arms showed comparable balance in baseline characteristics and replicated the conclusions from the target RCT. SD can be used for data augmentation, imputation, and for enhance data quality to improve machine learning performances. In many illnesses there is a lack of available data to train reliable models, however data augmentation can provide more information to these models and allow for a more reliable output. SD are also being used in survival analysis, medical imaging, and histopathological imaging analysis. SD can mitigate bias within medical research by using "fair synthetic datasets" to train AI models. Fair synthetic datasets are datasets that have been altered to have a better representation of the world as it would be without, for instance, gender-based or racial discrimination and age classes. Sex and age are important covariates in HMs and often they are under-represented. Within the HARMONY project, classical and advanced methods are used for generating SD, starting from tabular data (e.g., genomic, cytogenetic mutations and clinical data).

SD are validated by direct comparison with the original data for the specific AI or statistical tasks. Given that SD are generated from original data using a model that is trained to reproduce their characteristics, SD and original data should give the same results when undergoing a statistical analysis.

AI-ENABLED PROGNOSTIC & PREDICTIVE MODELS AND MULTIDIMENSIONAL DATA INTEGRATION FOR MULTIPLE MYELOMA

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The integration of Artificial Intelligence (AI) within the medical sciences heralds a transformative epoch, particularly within the domain of hematology. This discourse aims to shortly elucidate the multifaceted implications of AI adoption in the study and treatment of Multiple Myeloma (MM). Commencing with an introductory exposition on AI, the presentation intends to acquaint the uninitiated with the fundamental paradigms and computational methodologies that underpin AI. Special attention will be accorded to the regulatory landscapes governing AI's integration into pharmaceutical arenas, highlighting the imperative of navigating these frameworks to ensure both the innovative potential and ethical integrity of AI applications in drug development and market introduction. Afterwards, the narrative will articulate the capacity of AI to enhance prognostic and predictive models within MM research. AI's prowess in amalgamating and analyzing data from disparate sources — encompassing clinical metrics, genomic data, and radiological imaging — will be detailed, illustrating the potential for a holistic, data-driven approach to MM patient management. Such an approach not only promises to elucidate the pathophysiological intricacies of MM but also to tailor therapeutic interventions to the individualized molecular and genetic profiles of patients, thereby advancing the precision medicine paradigm. The discourse will culminate in an examination of AI applications within the context of the Harmony consortium. By showcasing exemplary implementations of AI in MM research, particularly in analyzing Harmony consortium data, this presentation will underscore the impact of AI in decoding the complexity of MM, thereby fostering a deeper understanding of disease dynamics and enhancing the efficacy of therapeutic strategies. In summation, this presentation endeavors to traverse the spectrum of AI's application in MM, from its theoretical underpinnings to its practical implications, with a specific focus on prognostic improvement and the synergistic potential of collaborative frameworks such as the Harmony consortium. Through this exploration, the discourse aspires to illuminate the prospective avenues through which AI may redefine the paradigms of research and clinical practice in MM, heralding a new frontier in the pursuit of precision oncology in hematology.

ACADEMIC IN-HOUSE MODEL FOR CAR-T CELLS DEVELOPMENT IN MULTIPLE MYELOMA

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The introduction of B-cell maturation antigen (BCMA) directed chimeric antigen receptor T-cell (CART) therapy to the treatment of relapsed/refractory (R/R) multiple myeloma (MM) is undoubtedly revolutionary, with the achievement of high response rates and median survivals that overcome those achieved previously. Consequently, the demand for this therapy overcomes availability and, in some countries and health systems, the costs of this therapy are unaffordable. These unmet needs may be improved by academic CARTs. Our institution developed ARI0002h, a second generation 4-1BB-based CAR, with a humanized scFv directed against BCMA. A pivotal, single-arm, open label clinical trial (CARTBCMA-HCB-01; EudraCT 2019-001472-11 and ClinicalTrials.gov NCT04309981) for the treatment of R/R MM patients was performed in 7 Spanish centers across the country, with two CAR-T cell production centers in Pamplona and Barcelona. Patients aged 18-75 years old with RRMM were eligible if they had measurable disease, received ≥2 prior regimens, including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody, and were refractory to the last line of treatment. A booster dose of up to $3x10^6$ CAR+cells/kg was planned at least 3 months after the first dose in patients with any kind of response and no limiting side effects. Results of the first cohort of 30 patients showed an overall response rate (ORR) of 100%, with 67% achieving complete responses (CR). In a more recent update, with 60 patients treated and a median follow-up of 23.1 months, overall response rate in the first 3 months was 95%; cytokine release syndrome (CRS) was observed in 90% of patients (5% grades≥3) and grade 1 immune effector cell-associated neurotoxicity syndrome was reported only in 2 patients (3%). Median progression-free survival was 15.8 months. Despite promising results, patients continue to relapse after ARI0002h, so strategies to overcome relapses are of clear interest. Correlative studies performed on patient samples highlight different mechanisms that may be responsible for ARI0002h relapses. In summary, ARI0002h administered

in a fractioned manner with a booster dose can provide deep and sustained responses in patients with R/R MM, with a relatively low-grade toxicity, especially neurologic events, and the possibility of a point-of-care approach.

DIAGNOSIS OF AL AMYLOIDOSIS

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The first step in the diagnosis of amyloidosis is considering the diagnosis. There is ongoing work to enhance the awareness of the condition and its red flags through education, machine learning and natural language processing techniques. Delays in diagnosis result in more advanced disease and poorer outcomes. AL amyloidoses is multisystemic and can affect any or all of the following systems: heart (diastolic dysfunction, heart failure with preserved ejection fraction, arrhythmia), kidney (nephrotic syndrome, more often with preserved eGFR), nervous system (most often distal symmetric small fiber neuropathy characterized by numbness and dysesthesia; and the autonomic nervous system, resulting in orthostasis, changes in digestive tract), soft tissue (periorbital purpura, purpura at the webbing of the neck, waxy infiltration of the skin, deposition at joints and ligaments, infiltration of the tongue, infiltration of the lymph nodes), the digestive tract (bleeding and malabsorption), the liver (hepatomegaly and signs of cholestasis), and the spleen (functional asplenia). Once the diagnosis is considered, the next step for an AL amyloidosis diagnosis is a tissue biopsy. Becase AL amyloidosis is typically a systemic disease, surrogate biopsies are often used. The most common surrogates are fat, bone marrow, gut, and lip. An underutilized practice is the use of existing biopsies, which when subjected to Congo Red staining may lead to a diagnosis. If surrogate biopsy does not provide an answer, then biopsy of the suspected organ is appropriate. Once there is biopsy evidence of amyloidosis, the 3rd step of the diagnosis process begins. The amyloid tissue must be typed. AL amyloidosis is not the only form of systemic amyloidosis. Transthyretin (ATTR) amyloidosis is in the differential, both wild-type and mutated (or variant), as well as others types not limited to fibrinogen, LECT2, APOAI, etc. Our preferred method of amyloid typing is by laser capture tandem mass spectrometry, but other alternatives in experienced hands include immunohistochemistry, immunoelectron microscopy, and immunofluorescence. Finally, once the diagnosis of amyloidosis is made, full elaboration of organs involved and extent of organ involvement is required before contemplating therapy.

THERAPEUTIC APPROACH IN AL AMYLOIDOSIS

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In the last decade, significant progress has been made in plasma cell clone-directed therapy for immunoglobulin light chain (AL) amyloidosis. Despite these advancements, early mortality due to advanced cardiac involvement remains a significant challenge, even with the introduction of bortezomib, a proteasome inhibitor. Recently, the combination of the anti-CD38 monoclonal antibody daratumumab (Dara) with CyBorD (cyclophosphamide-bortezomib-dexamethasone) has become the standard frontline regimen for AL amyloidosis following the ANDROMEDA-AL trial, which showed a threefold increase in hematologic complete responses with Dara-CyBorD compared to CyBorD alone. Although the overall survival data from this trial is still limited, the proportion of deaths was notably lower in the Dara-CyBorD arm than in the CyBorD arm (17% vs. 24%) after a median follow-up of 26 months. Therapeutic options for relapsed refractory AL amyloidosis patients are limited. However, several smaller studies have shown that venetoclax, a BCL-2 inhibitor is effective in t(11;14) positive AL amyloidosis alone or in combination with other established plasma-cell-directed agents, leading to profound and rapid overall response rates with more than 80% of patients achieving VGPR. This is critical in Dara-refractoriness, where therapeutic options are minimal. Several multicenter randomized clinical trials are ongoing to evaluate venetoclax's role in relapsed-refractory AL amyloidosis. Bispecific antibodies targeting B-cell maturation antigen (BCMA) have transformed the landscape of relapsed/refractory multiple myeloma, with single-agent response rates of 60–70% in patients who have undergone extensive prior treatments. However, only limited data are available for AL amyloidosis. Chakraborty et al. reported efficacy data of 7 patients achieving 100% hematologic VGPR or better. At the 1-month landmark from treatment initiation, 6/7 patients had achieved a stringent dFLC response (defined by dFLC<1 mg/dl). Morbidity and mortality remain high in AL amyloidosis due to organ involvement despite hematologic remission. Two anti-amyloid fibril therapies targeting amyloid, Anselamimab, and Birtamimab, have promising data in advanced stage 4 AL amyloidosis. Both antibodies are currently being tested in randomized clinical trials. In summary, although the treatment options for AL Amyloidosis are limited, the use of anti-CD38 antibodies, BCMA bispecific T-cell engagers, BCL-1 inhibitors, and anti-amyloid antibodies has significantly improved the outcome of this devastating disease.

CAR-T OR BISPECIFICS OR ADCS

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Modern immunotherapy approaches are revolutionizing the treatment scenario of relapsed/refractory (RR) multiple myeloma (MM) patients, providing an opportunity to reach deep level of responses and extend survival outcomes also in advanced stages of the disease.

Antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs) and chimeric antigen receptor (CAR) T cells therapy have demonstrated substantial activity in heavily pretreated, triple-class exposed (TCE) MM patients, and represent a new standard of care after third line of therapy. Some agents have already received regulatory approval, while newer constructs, novel combinations, and application in earlier lines of therapy are currently being explored. All these three immunotherapies carry advantages and disadvantages, with different accessibility and new toxicities that require appropriate management and guidelines. Also, patient-, disease- and treatment-related factors should be considered to select the most suitable therapeutic approach. Among the 3 strategies, CAR-T, and in particular ciltacel, have shown the highest depth of response and the longest PFS, close to 3 years, while Belantamab Mafodotin has shown lower efficacy, with approximately one third of responsive patients and a median PFS of about 3 months but extended up to 14 months in patients achieving at least VGPR . On the other hand, ADCs are potentially suitable for frail patients, provided there is close monitoring for ophthalmological side effects, and have the logistic advantage of a 3-weeks interval administration not requiring hospitalization. Differently, BsAbs and CAR-T cell therapy may be limited by life-threatening AEs (CRS and ICANS from one side and serious infections from the other), thereby requiring a multidisciplinary teamwork approach. Incidence of infection after BsAbs may probably be improved with a reduced dose intensity schedule or a fixed duration treatment. The risk of infection seems to be lower with anti-GPRC5D than anti-BCMA agents, likely due to the different expression of the

targets on B-lymphocyte and normal PCs, albeit anti-GPRC5D-targeting treatments correlate with on target off-tumor toxicities including skin, mucosal, hair and nail AEs. Recommended measures to prevent and manage AEs during T-cell redirecting therapies are now available. Moreover, CAR-T cell therapies are hampered by the complexity of multistep processes ultimately affecting the percentage of patients who have actual access to the final product, mainly for progression disease and loss of eligibility criteria, therefore currently excluding patients with highly proliferative disease. By contrast, off-the-shelf treatment based on ADCs and BsAbs can be quickly provided to the patients. The availability of different new immunotherapies, sometimes directed against the same target, raises the issue of sequencing, with few data available and mechanisms of resistance still to be unraveled.

NEW GUIDELINES FOR NEWLY DIAGNOSED MULTIPLE MYELOMA IN 2024

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Patients who are eligible for Autologous Stem Cell Transplantation (ASCT): For patients <70 years without comorbidities, induction therapy followed by high-dose melphalan (HDM) and ASCT remains the recommended treatment [I,A]. The addition of subcutaneous daratumumab to bortezomib, lenalidomide and dexamethasone (VRd) induction and consolidation therapy and to lenalidomide maintenance therapy conferred a significant benefit with respect to progression-free survival (PFS), based on the recently published PERSEUS study; thus Dara-VRD is a new standard of care for induction before ASCT [I,A]. The four-drug combination Dara-VTD (T: thalidomide) is more efficacious than VTD [I, A] and is also considered a standard of care for induction in these patients, as there is no direct comparison between Dara-VRD and Dara-VTD. The recently presented ISKIA study (ASH 2023) showed that the addition of isatuximab to carfilzomib, lenalidomide and dexamethasone (KRd) induction and consolidation significantly increased minimal residual disease (MRD) negativity rates in every treatment phase as compared to KRd; however, as KRD is not approved in this setting, Isa-KRD may not be approved as a new induction treatment. Regarding number of induction cycles, 4-6 cycles are the recommended approach. High-dose melphalan (200 mg/m^2) is the standard conditioning regimen before ASCT [I, A]. Consolidation therapy post-ASCT has not been established to date as standard therapy; however, based on the PERSEUS study, Dara-VRD consolidation may be considered as a new standard soon. Tandem ASCT is recommended for patients with genetically defined high-risk disease [II, B] or in all patients who received VCD induction [II, B]. Allo-SCT following ASCT does not offer OS benefit even in high-risk disease compared to tandem ASCT. Maintenance with lenalidomide is considered the standard of care for all MM patients post-ASCT [I, A]; bortezomib may be considered for patients with high-risk disease [II, B]. Ixazomib maintenance offers PFS benefit over placebo [I, A], but has not been approved by EMA or FDA. Based on the PERSEUS study, addition of daratumumab to lenalidomide may be a new standard of care soon. For patients who are not eligible for ASCT: In this setting we have three standards of care: Dara-Rd, Dara-VMP, and VRD [I, A]. When Dara-Rd or Dara-VMP are not available, VRd is the preferred option in fit patients. Recently (Dec 2023), Sanofi announced that isatuximab added to VRd significantly reduced the risk of disease progression or death compared with VRd alone. If these results are published, Isa-VRD may be a new standard of care in this setting.

THE MYELOMA AND AL AMYLOIDOSIS CLINICAL TRIAL NAVIGATOR, A CLINICAL TRIAL SEARCH TOOL BY MYELOMA PATIENTS EUROPE

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The Myeloma and AL Amyloidosis Clinical Trial Navigator is an online clinical trial search tool providing information on ongoing academic and industry trials for MGUS, smouldering myeloma, myeloma and AL amyloidosis patients in Europe. Existing clinical trial search tools are not very patient-friendly and important information, which would help a patient to make an informed choice about potential participation in a trial, as well as understand possible risks or benefits, is not always clear or available. The patient community needs a patient-friendly, easy to use, and disease specific tool, where users can freely search and find clinical trial information from multiple countries in their own language. The Navigator will improve patient understanding about clinical research, clinical trials, enrolment and eligibility, and cross-border healthcare, as well as support informed discussions between patients and their healthcare provider around the selection of and participation in clinical trials. In addition, the tool will be used to drive research to advocate for increased access to clinical trials and improved health equity across Europe. Finally, the Navigator will improve clinical trial engagement and enrolment, ultimately promoting scientific progress and developments in myeloma and AL amyloidosis treatments, diagnostics, quality of life, and care.

INFECTIONS AND VACCINATION

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Infection remains the leading cause of death in patients with multiple myeloma (MM). Several factors account for this infectious risk: the net state of immunosuppression from MM and its treatment, age and comorbidities such as renal failure and frailty. The periods of highest infectious risk are during the first three months after diagnosis and when treating relapsed/refractory MM (RRMM). Most infections in patients with MM are caused by viruses and bacteria. During periods of increased infectious risk, *i.e.* during first three months of therapy, antibacterial prophylaxis with levofloxacin may be considered. Acyclovir prophylaxis is used for patients who are seropositive for herpes simplex virus and varicella zoster virus (VZV), if tested. Acyclovir prophylaxis is also recommended for patients treated with proteasome inhibitors (PIs) or MM-targeted monoclonal antibodies (mAbs), specifically CD38 directed mAbs. We reserve trimethoprim-sulfamethoxazole for patients at risk of *pneumocystis jiroveccii* pneumonia (RRMM or receipt of high doses of dexamethasone such as ≥ 40 mgs/day for 4 days/wk). Vaccination recommendations include immunization with yearly inactivated influenza vaccine (preferably with a two-dose series of high-dose influenza vaccine, regardless of age) and inactivated *S. pneumoniae* vaccines (Pneumococcal 13 - valent conjugate (PCV13, Prevnar) followed by Pneumococcal 23-Valent polysaccharide (PPSV23, Pneumovax) every 5 years. Only inactivated vaccines are recommended. Yearly immunization against SARS-CoV-2 with new mRNA vaccines is also suggested. The ability to develop a protective response after immunization depends on the patient's net state of immunosuppression (disease burden and remission status, cumulative immunosuppression from antineoplastic therapies), and the timing of vaccination. Vaccination just before or during treatment with bispecific antibodies (BsAbs) or CAR-T cells provides limited or no benefit because the chances of a protective immune response are low. Vaccination should be considered 3-6 months after completion of therapy in patients who respond to treatment. After ASCT, patients with MM may lose their immunity to the pathogens against which they were vaccinated. These patients should be re-vaccinated 6-24 months after ASCT. Recent data suggest that immunization with recombinant zoster vaccine [RZV; Shingrix] is safe and effective post-ASCT. Thus, RZV vaccination post-ASCT is recommended; however, continuous use of VZV prophylaxis where indicated is mandatory despite vaccination.

Prophylactic administration of high-dose (400mg/kg) immunoglobulin at short intervals of 1-4 weeks is recommended in patients with low IgG levels (<400mg/dl), especially in those who receive BsAbs or CAR-Ts. In a recent study in patients treated with anti-BCMA-BsAbs, immunoglobulin replacement resulted in an 80% reduction in grade ≥3 infections compared to patients without this support. This efficacy rate appears to be higher than usually observed but supports the recommendation of IVIg as primary prophylaxis or treatment. Treatment with immunoglobulins may also be considered in patients with higher IgG levels and recurrent bacterial infections.

BEST ABSTRACTS

B01

ABSTRACT NOT PUBLISHABLE

B02

HIGH BODY MASS INDEX AND LOW AMOUNT OF IGM ARE ASSOCIATED TO MGUS PROGRESSION: A RETROSPECTIVE SINGLE-CENTER STUDY

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Background. MGUS is a clinically asymptomatic, clonal plasma cell disorder and is an obligatory precursor for several lymphoplasmacytic disorders (LPD), including multiple myeloma (MM), WM, and AL, defined by the presence of serum or urine M protein, <10% clonal plasma cells in the bone marrow, and the absence of a diagnosis of MM or related LPDs. Recent studies have shown that obesity may promote the transition from MGUS to MM. Since obesity accelerates age-associated defects in B cell function and antibody production leading to decreased secretion of protective antibodies and increased autoimmunity in this study we evaluated the correlation between B-cell function and obesity, defined as body mass index (BMI) >25.

Methods. Enumeration of total CD19-positive (CD19+) cells and their subpopulations together was done in a training cohort in peripheral blood (PB) of newly diagnosed MGUS (N=15), MM (N=34) and control subjects (N=32). Unstimulated PBMCs were membrane stained with Live/Dead detection kit and anti-CD45/CD19/CD27/IgD antibodies, to identify B-cell subsets in peripheral blood by flow cytometry. Findings were compared among groups and relationships between subset percentage and BMI, cytogenetic/biochemical findings were analyzed. In a retrospective series of 674 MGUS diagnosed in our Center between 2006 and 2016 we investigated if B-cell dysfunction and obesity could identify patients with increased risk to MM or related LPDs progression. Patients were eligible for inclusion if aged 18 years or older, diagnosed with non-IgM MGUS by the IMWG criteria. We retrieved patient information for total protein, IgA IgM, IgG, via nephelometry, κ-free light chain (FLC) λ-FLC, FLC ratio (involved and uninvolved), calcium, creatinine, albumin, hemoglobin, lactate dehydrogenase, C-reactive protein, β2-microglobulin, M-protein, heigh and bodyweight (to calculate BMI) from medical records within two months from the first access to our center. Time to progression (TTP) was defined as the time from MGUS diagnosis per IMWG criteria to MM per SLiM-CRAB criteria.

Results. We found a redistribution of B cell subsets with reduced pool of IgM+ CD27- naïve B cells, increased frequencies of IgM+ memory B cells (p<0.001), known for their association to to chronic inflammation, aging and senescence. 606/674 non-IgM patients were evaluable for the study, after exclusion of patients diagnosed with overt multiple myeloma at diagnosis, high-risk MGUS according to IMWG criteria and those in whom all clinical variables were not available. Median follow-up was 9.6 years (range: 0-10.6), while 118 patients died and 71 progressed and developed MM (N=65), AL amyloidosis (N=3), lymphoma (N=1), or Waldenstrom-macroglobulinemia (N=2). According to IMWG criteria, 547 (90 %) patients were classified as low- and 59 (10%) as intermediate- risk MGUS. In univariate analyses, BMI ≥ 25 (HR=4.1, CI: 2.4-6.9, p<0.0001), and a suppressed uninvolved immunoglobulin, quantified as IgM ≤40 mg/dL (HR = 3.3, CI: 1.9-5.6, p<0.0001) were associated with increased risk of MGUS progression, and were independently associated in a multivariable model (c-statistic = 0.7, CI:0.6-0.8).

Conclusions. Our findings show that two additional parameters (IgM<40 and BMI>25) should be investigated also in the low-risk MGUS patients to improve clinician's ability to make therapeutic decisions for individual patients.

B03

ALTERATIONS IN EXPRESSION OF GENES CONTROLLING CELL SURFACE SIALYLATION IMPACT PROGNOSIS OF PATIENTS TREATED WITH CURRENT ANTI-MYELOMA THERAPIES

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Introduction. Alterations in glycosylation are a hallmark of cancer. Glycosylation is aberrantly regulated in MM along with increased expression of sialic acid sugars (hypersialylation), which is associated with abnormal cellular trafficking, drug resistance, immune evasion and poor survival. Siglec ligands are highly expressed by MM cells and we identified PSGL-1 and CD43 as the main glycoconjugates for Siglec-7 ligands. These ligands facilitate immune evasion by inhibition of NK cells and possibly macrophages and T cells. The sialyltransferase enyzme ST3GAL1 is implicated in Siglec-7 ligand synthesis and can inhibit complement dependent cytotoxicity via sialylation of CD55, increased expression of which is associated with Daratumumab (Dara) resistance. We previously reported that increased ST3GAL1 was associated with poor prognosis in the UK MRC Myeloma IX study. Elevated levels of ST3GAL1 were associated with inferior PFS (p=0.0147) with a trend for poor OS (p=0.0695) and this was independent of ISS. Given this background we wished to see whether altered expression of genes involved in hypersialylation, such as ST3GAL1, influenced the prognosis of patients treated with current treatment approaches, including VTD Dara, established by the CASSIOPEIA study as a new standard of care for transplant eligible patients with newly diagnosed MM (NDMM).

Methods. The CoMMpass dataset (IA16 release) was used to access RNA-seq, clinical outcomes and genomic features of NDMM patients. RNA-seq data for 628 patients enrolled in the CASSIOPEIA trial (ClinicalTrials.gov identifier NCT02541383) were generated from sorted CD138+ bone marrow cells.

Results. In CoMMpass, elevated ST3GAL1 and ST3GAL4 expression were associated with inferior PFS (p=0.0123, p<0001, respectively) and OS (p=0.0039, p<0.0001, respectively). In CASSIOPEIA, increased expression of ST3GAL1 was also associated with inferior PFS (p=0.0006). High expression of the sialyltransferase

ST6GAL1 and the sialidase NEU3 were associated with improved PFS (p=0.0051, p=0.0041, respectively). In Dara treated patients, the estimated 36-month PFS for patients with low levels of expression (< median) of ST3GAL1 was 83.9% (95%CI: [78.1;90.2]) versus 72.9% (95%CI: [65.9;80.6]) for patients with high levels of expression (> median). ST3GAL1 expression was associated with genetically-defined high-risk features. In CoMMPass there was a significant association with t(4;14) (p=0.0066) and 1q+/amp (1qamp v WT: 6.05E-05). Moreover, expression of the glyconjugates for Siglec-7 ligands, PSGL-1 and CD43 was also significantly increased in proportion to 1q copy number (1q amp .v. WT: 7.66E-09 and 5.44E-10, respectively). In CASSIOPEIA, ST3GAL1 expression was significantly associated with t(4;14). On multivariable analysis the negative effect of ST3GAL1 on PFS was independent of both del17p and FGFR3 but there was a trend with t(4;14) and WHSC1 expression. There was a significant link between ST3GAL1 expression and del17p (p=0.0044). Of note, in isogenic myeloma cells with or without expression of p53, we found that ST3GAL1 was negatively regulated upon stress exposure in a p53-dependent manner.

Conclusions. These data suggest that hypersialylation, leading to increased expression of Siglec-ligands, may be associated with inferior prognosis in patients receiving current therapies for NDMM, potentially contributing to the poor outcome observed in patients with genetically defined high risk features, such as 1q amp, t(4;14) and del17p.

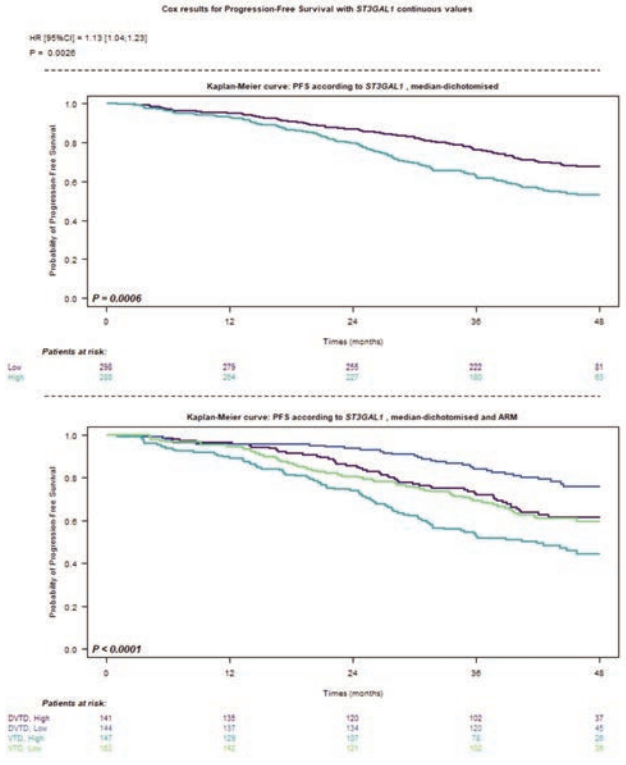

Figure 1. Cox results for PFS with ST3GAL1 continuous values.

B04

PROSPECTIVE FUNCTIONAL BONE DISEASE EVALUATION OF NEWLY DIAGNOSED MULTIPLE MYELOMA WITH COMBINED USE OF 18F-FDG PET/CT AND WHOLE-BODY DIFFUSION WEIGHTED MAGNETIC RESONANCE

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Background. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is the most widely used imaging technique to detect and evaluate bone and extramedullary disease (EMD) in multiple myeloma (MM) and is recommended by the International Myeloma Working Group to assess response to treatment. Despite high sensitivity (85-90%), the presence of skeletal disease and/or EMD cannot be detected in approximately 10-15% of patients (pts). In clinical practice, PET/CT is usually associated to spine and pelvis magnetic resonance imaging (MRI). Its sensitivity is considered similar to PET/CT in detecting focal lesions (FLs), greater in defining bone marrow (BM) infiltration, but lower in detecting EMD and evaluating response. The recently introduced whole-body MRI (WB-MRI), including traditional and diffusion weighted imaging (DWI) sequences, has further increased sensitivity (about 95%) with no need for contrast agents; it allows to study all bones and possible EMD and may be useful in response assessment, as lately proposed by MY-RADS guidelines.

Results. We herein present a monocentric prospective study aimed at comparing diagnostic performance of PET/CT and WB-MRI in early phases of the disease (smoldering MM, SMM), in staging of newly diagnosed MM (NDMM) and in defining response to therapies in transplant-eligible (TE) and ineligible (TIE) pts. Both imaging techniques were planned at staging, prior to maintenance therapy (TE) or after 1 year of treatment (TIE). Secondary aims are comparison and validation of imaging criteria (Deauville Score for PET/CT and MY-RADS for WB-MRI) and definition of prognostic role of PET/CT and WB-MRI in relation to hematologic response, minimal residual disease and patients' outcome. Between October 2022 and December 2023, 61 pts underwent baseline PET/CT and WB-MRI: 20 (33%) were classified as SMM and 41 (67%) as NDMM. Among SMM pts, 4 (20%) had diffuse BM infiltration (2 in WB-MRI, 2 in both) and 2 (10%) a single FL in WB-MRI, negative in PET/CT. Among MM patients, 9 (22%) were negative for FLs with both techniques (4 having diffuse BM infiltration: 2 in PET/CT, 1 in WB-MRI, 1 in both), whereas in 32 (78%) bone disease emerged: 24 (58.5%) had FLs detected by both techniques (2 pts had a single FL in WB-MRI but multiple FLs in PET/CT); 8 (19.5%) had positive WB-MRI with FLs but negative PET/CT (3 had diffuse BM uptake without FLs); 7 pts (17%) had paramedullary disease (PMD): 5 (12%) by both techniques, 2 (5%) in WB-MRI only; no pts had EMD. To December 2023, only 4 pts have reached the maintenance phase or 1 year of treatment and have received imaging evaluation.

Conclusions. Our preliminary data support combined use of PET/CT and WB-MRI for baseline staging of MM pts. In NDMM pts, these techniques were concordant in 80.5% of cases and WB-MRI was more sensitive than PET/CT in 19.5% of cases for bone disease and in 7% of cases for PMD. In SMM pts, WB-MRI was more sensitive in identifying BM diffuse infiltration in 10% of cases and showed a single FL in 10% of cases. Further expansion of the study population and a

larger number of pts who have reached the post-treatment time-point are needed to properly define the role of WB-MRI *vs* PET/CT for detection of bone disease and assessment of response to therapy. Updated data will be presented at the meeting.

B05

PROLONGED DOSING SCHEDULE OF BELANTAMAB MAFODOTIN PLUS LENALIDOMIDE AND DEXAMETHASONE SIGNIFICANTLY REDUCED OCULAR ADVERSE EVENTS WITHOUT COMPROMISING CLINICAL ACTIVITY IN TRANSPLANT INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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Belantamab mafodotin (belamaf) has demonstrated efficacy and tolerability in the treatment of multiple myeloma. Ocular adverse events (OAEs) are common with belamaf and the main reason for dose modifications. In the ongoing phase 1/2 BelaRd study we evaluate a novel, extended dosing schedule for belamaf, in combination with lenalidomide and dexamethasone (Rd), in transplant-ineligible (TI) patients (pts) with newly diagnosed multiple myeloma (NDMM). BelaRd (NCT04808037) aims to enroll 66 TI NDMM pts. Part 1 of the study evaluates 3 belamaf doses (2.5/1.9/1.4 mg/kg) plus Rd and establishes the recommended phase 2 dose. Belamaf is initially given Q8W, which is extended to Q12W in the presence of grade (Gr)≥ 2 OAEs (best corrected visual acuity [BCVA] change from baseline and keratopathy). Ocular assessments include Snellen BCVA and slit lamp corneal evaluation. OAEs are graded by the Ker-

Table. Patient/disease baseline characteristics, treatment characteristics, and safety/efficacy outcomes.

	All patients (N=36)	Cohort 2.5 mg/kg (n=12)	Cohort 1.9 mg/kg (n=12)	Cohort 1.4 mg/kg (n=12)
Demographics and disease characteristics				
Age in years, median (range)	72.5 (64.0-86.0)	75.0 (66.0-86.0)	74.5 (68.0-82.0)	69.0 (64.0-79.0)
Male	19 (52.8)	8 (66.7)	5 (41.7)	6 (50.0)
R-ISS staging				
I	6 (16.7)	1 (8.3)	2 (16.7)	3 (25.0)
II	27 (75.0)	9 (75.0)	10 (83.3)	8 (66.7)
III	3 (8.3)	2 (16.7)	0 (0.0)	1 (8.3)
Presence of high-risk cytogenetics*	3 (8.3)	1 (8.3)	2 (16.7)	0 (0.0)
Belamaf dosing				
Total planned belamaf doses	452	157	162	133
Number of doses skipped due to any reason§	164 (36.2)	69 (43.9)	56 (34.6)	39 (29.3)
Number of doses skipped due to OAE§	163 (36.1)	68 (43.3)	56 (34.6)	39 (29.3)
Intended dose intensity, mg/kg/Q4W	-	1.25	0.95	0.70
Dose intensity, mg/kg/Q4W, median (range)	0.6 (0.4-1.7)	0.8 (0.5-1.7)	0.6 (0.5-1.0)	0.5 (0.4-0.6)
Safety - OAEs, Assessments with OAEs/ Total number of ophthalmological assessments				
OAEs				
Total number of assessments	804	268	295	241
Grade 0-1	387 (48.1)	103 (38.4)	155 (52.6)	129 (53.5)
Grade 2	293 (36.4)	108 (40.3)	100 (33.9)	85 (35.3)
Grade 3	109 (13.6)	44 (16.4)	39 (13.2)	26 (10.8)
Grade 4	15 (1.9)	13 (4.9)	1 (0.3)	1 (0.4)
BCVA change from baseline				
Total number of assessments	804	268	295	241
Grade 0-1	408 (50.8)	107 (39.9)	167 (56.6)	134 (55.6)
Grade 2	283 (35.2)	113 (42.2)	89 (30.2)	81 (33.6)
Grade 3	113 (14.1)	48 (17.9)	39 (13.2)	26 (10.8)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Keratopathy				
Total number of assessments	804	268	295	241
Grade 0-1	692 (86.1)	222 (82.8)	257 (87.1)	213 (88.4)
Grade 2	97 (12.1)	33 (12.3)	37 (12.5)	27 (11.2)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	15 (1.9)	13 (4.9)	1 (0.3)	1 (0.4)
Assessments with BCVA decline worse than 20/50^ and ≥3 lines drop in the better seeing eye/Total ophthalmological assessments	84/798 (10.5)	36/268 (13.4)	30/295 (10.2)	18/235 (7.7)
Safety - Most frequent (≥15% of patients) non-ocular adverse events of Grade≥3				
Fatigue	22 (61.1)	7 (58.3)	8 (66.7)	7 (58.3)
Diarrhea	8 (22.2)	2 (16.7)	3 (25.0)	3 (25.0)
Rash	6 (16.7)	2 (16.7)	2 (16.7)	2 (16.7)
Safety - Fatal events				
COVID-19	4 (11.1)	1 (8.3)	1 (8.3)	2 (16.7)
Pneumonia	2 (5.6)	1 (8.3)	1 (8.3)	0 (0.0)
Sudden death	1 (2.8)	0 (0.0)	0 (0.0)	1 (8.3)
Intracranial hemorrhage	1 (2.8)	0 (0.0)	0 (0.0)	1 (8.3)
OSDI responses, Total number of assessments	764	253	282	229
Worst OSDI responses regarding ocular symptoms (Q1-Q5)¶				
All/Most of the time	23 (3.0)	7 (2.8)	8 (3.2)	8 (3.5)
Half of the time	334 (43.7)	124 (49.0)	114 (40.4)	96 (41.9)
Some/None of the time	407 (53.3)	122 (48.2)	160 (56.7)	125 (54.6)
Worst OSDI responses regarding activities of daily living (Q6-Q9)¶				
All/Most of the time	13 (1.7)	6 (2.4)	4 (1.4)	3 (1.3)
Half of the time	48 (6.3)	18 (7.1)	12 (4.3)	18 (7.9)
Some/None of the time	692 (90.6)	227 (89.7)	261 (92.6)	204 (89.1)
Not applicable	11 (1.4)	2 (0.8)	5 (1.8)	4 (1.7)
Efficacy				
IMWG response category				
Stringent complete response	8 (22.2)	4 (33.3)	2 (16.7)	2 (16.7)
Complete response	11 (30.6)	3 (25.0)	4 (33.3)	4 (33.3)
Very good partial response	13 (36.1)	3 (25.0)	5 (41.7)	5 (41.7)
Partial response	4 (11.1)	2 (16.7)	1 (8.3)	1 (8.3)

*Data are n (%) or n/N (%) patients, unless otherwise shown. *High-risk cytogenetics defined as Del 17p13, t(14:16), or t(4:14). §Percentages are based on the number of planned doses. ^Patients with baseline BCVA worse than 20/50 are excluded from this analysis. ¶Ocular Symptoms: sensitivity to light, gritty eyes, painful or sore eyes, blurred vision, poor vision. Activities of daily living: reading, driving at night, working with a computer or bank machine [ATM], watching TV. Ocular symptoms and activities of daily living are assessed by the OSDI questionnaire, completed on Day 1 of each cycle. BCVA, best corrected visual acuity; belamaf, belantamab mafodotin; IMWG, International Myeloma Working Group; N, total number of patients/assessments; n, number of patients/assessments; OAE, ocular adverse event; OSDI, ocular surface disease index; Q, question; Q4W, once every 4 weeks; R-ISS, revised International Staging System.*

atopathy Visual Acuity scale, while ocular symptoms and non-ocular adverse events by CTCAE v5.0. Dry eye disease severity and activities of daily living (ADL) are assessed by the Ocular Surface Disease Index (OSDI). Herein, we present safety/efficacy results over an extensive follow-up period from Part 1 (data cut-off: 15/11/2023). All Part 1 pts (n=36; median age: 73.0; male: 19 [52.8%]) were included in this analysis, of whom 27 (75.0%) are ongoing and 9 (25.0%) discontinued (8 [22.2%] due to belamaf-unrelated fatal events; 1 [2.8%] withdrew consent). Of 157/162/133 planned belamaf doses, 43.3%/34.6%/29.3% were skipped due to OAEs in the 2.5/1.9/1.4 mg/kg cohorts. Following a dose hold, the median times for belamaf re-administration were 8.0/4.6/4.6 weeks. The respective median belamaf dose intensities were 0.8/0.6/0.5 mg/kg/Q4W. Of 268/295/241 ophthalmological assessments, Gr2 and ≥ Gr3 OAEs were observed in 40.3%/33.9%/35.3% and 21.3%/13.6%/11.2%. The median times to first ≥Gr2 OAE were 3.9/4.5/5.9 months. The respective rates of Gr2 and ≥Gr3 BCVA change from baseline were 42.2%/30.2%/33.6% and 17.9%/13.2%/10.8%, while a meaningful BCVA decline (Snellen score <20/50) and ≥3 lines drop in the better-seeing eye was recorded in 13.4%/10.2%/7.7% ophthalmological assessments. Gr2 and ≥Gr3 keratopathy were recorded in 12.3%/12.5%/11.2% and 4.9%/0.3%/0.4% assessments. Of 764 OSDI assessments, the rates of ocular symptoms and ADL with 'all/most of the time' responses were <3.5% across cohorts. Dose-limiting toxicities (DLTs) were reported in 8 pts: 2/4/2 in cohorts 2.5/1.9/1.4, respectively, and included fatigue Gr3 (n=6) and rash Gr3 (n=2), all related to lenalidomide. No hematological or ocular DLTs were recorded. Most common (≥15% of pts) Gr≥3 non-OAEs were fatigue, diarrhoea, and rash, occurring in 58.3%/66.7%/58.3%, 16.7%/25.0%/25.0%, and 16.7%/16.7%/16.7% of pts. Across cohorts, the overall response rate was 100.0%, overall median PFS was not reached and no disease progression was observed; median time to first response was 1.0 month. In TI NDMM pts, belamaf-Rd produced rapid, deep and durable responses, with no disease progression observed over a median follow-up of 24.8 months. Additionally, the prolonged dosing schedule for belamaf successfully mitigated the risk for OAEs and had minimal impact on vision-related functioning. These results suggest that the triplet regimen, with the extended belamaf dosing schedule, may be a valid upfront treatment option for this vulnerable pt population.

B06

DISSECTING THE MULTICELLULAR ECOSYSTEM IN EXTRAMEDULLARY MYELOMA USING SPATIAL TRANSCRIPTOMICS

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Extramedullary multiple myeloma (EMD) is a hallmark of high-risk disease and is associated with increased proliferation and poor outcome. Importantly, EMD remains a negative prognostic marker in the era of novel immunotherapies, and both BCMA CAR T cells and bispecific antibodies show lower response rates and survival in this setting. Indeed, EMD has emerged as one of the major challenges in the treatment of relapsed refractory MM. However, there is a paucity of knowledge about the underlying biology of EMD. Investigating the spatial architecture and microenvironment of EMD lesions is pivotal for understanding disease progression and therapy responses. Recent technological advancements, such as spatial whole transcriptome sequencing (10X Visium), tomography for spatially resolved transcriptomics (TOMO-seq), and single-cell RNA sequencing (scRNAseq), have enabled probing solid tumors at spatial and single-cell levels. Leveraging these multi-omics technologies, our study investigated EMD biopsies obtained from eight extensively treated patients. To elucidate the spatial and cellular architecture, we performed TOMO-seq, utilizing an entire EMD lesion and cutting it into 43 slices, 30 µm thick and 60 µm apart combined with bulk RNA sequencing. We identified inter-sectional heterogeneity shown by low correlations between every pair of sections. Scores derived from gene signatures, indicated enrichment of immune and stromal cells in the first and middle part of the lesions. Cell type deconvolution using gene expression of sorted cell types indicated further that plasma cells (PCs) had the highest cell type abundance in all sections; however, other cell types, such as T cells, dendritic cells, macrophages, endothelial cells and fibroblasts were part of the microenvironment with varying proportions. We additionally performed scRNAseq and verified the abundance of T, NK, and NKT cells and small clusters of myeloid and stromal cells. In conclusion, these observations refute the past notion that PCs exclusively constitute EMD lesions. Subsequent 10X Visium analysis further delineated cellular niches within EMD biopsies. Upon cell type deconvolution, although PCs were distributed throughout samples, M1 macrophages and cytotoxic T cells were confined to distinct niches with low abundance of plasma cells. In contrast, an exhausted and dysfunctional T cell subset (TIM3+ T cells) colocalized with PCs. In summary, despite the infiltration of EMDs by immune cells, they exhibit dysfunction or they are anatomically confined away from PCs. Furthermore, leveraging 10X Visium allowed us to infer the spatial distribution of copy number variations (CNVs), unveiling spatial heterogeneity of CN*vs.* We found previously reported alterations such as del(13q) alongside gains at 1q21, 22q, and 17q. When examining mean residual expression values per spot for genes on chromosomes or chromosome arms, we observed distinct patterns illustrating a snapshot of genomic heterogeneity within EMDs. In summary, our study presents a detailed spatial and cellular characterization of EMD microenvironments using advanced multi-omics techniques, shedding light on immune cell dynamics and CNV distributions within MM lesions.

B07

ELOTUZUMAB PLUS POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: EXTENDED FOLLOW-UP OF A MULTICENTER, RETROSPECTIVE REAL-WORLD EXPERIENCE WITH 305 CASES OUTSIDE OF CONTROLLED CLINICAL TRIALS

E.A. Martino[1], S. Palmieri[2], M. Galli[3], D. Derudas[4], R. Mina[5], R. Della Pepa[6], R. Zambello[7], E. Vigna[1], A. Bruzzese[1], S. Mangiacavalli[8], E. Zamagni[9,10], C. Califano[11], M. Musso[12], C. Conticello[13], C. Cerchione[14], G. Mele[15], N. Di Renzo[16], M. Offidani[17], G. Tarantini[18], G. Margiotta Casaluci[19], A. Rago[20], R. Ria[21,22], G. Uccello[23], G. Barilà[24], G. Palumbo[25], L. Pettine[26], I.D. Vincelli[27], M. Brunori[28], F. Accardi[29], V. Amico[30], A. Amendola[31], R. Fontana[32], V. Bongarzoni[33], B. Rossini[34], E. Cotzia[35], A. Gozzetti[36], R. Rizzi[37,38], N. Sgherza[37], G. Reddiconto[16], A. Maroccia[39], L. Franceschini[40], G. Bertuglia[41], D. Nappi[14], M.T. Petrucci[42], F. Di Raimondo[13], A. Neri[43], F. Morabito[44], P. Musto[37,38], M. Gentile[1,45]

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In the ELOQUENT-3 trial, the combination of elotuzumab, pomalidomide, and dexamethasone (EloPd) proved a superior clinical benefit over Pd with a manageable toxicity profile, leading to its approval for relapsed/refractory multiple myeloma (RRMM), who had received at least two prior therapies, including lenalidomide and a proteasome inhibitor (PI). Recently, we reported a real-world experience involving 200 RRMMs treated with EloPd outside of clinical trials. The results of this cohort confirmed the treatment's effectiveness and safety. This updated analysis includes a larger cohort of 305 RRMM patients accrued in 39 Italian centers, with an extended follow-up, thereby providing a more comprehensive perspective on the outcomes and implications of the EloPd regimen in real-world clinical settings. At the EloPd start, 169 (55.4%) were males, with 24.3% of patients presenting stage III ISS. The median prior therapies were 2, and 35.1% had refractory disease. Approximately half of the patients (50.5%) underwent autologous stem cell transplant (ASCT), while roughly three-quarters (76.7%) were exposed to daratumumab. FISH analysis data were available in 123 patients, with 57.7% of patients exhibiting favorable cytogenetic abnormalities, while 42.3% were categorized as high risk, harboring one of the following aberrations: t(4;14), t(14;16), and del(17p). The overall response rate (ORR) was 54.4%, including 1 (0.3%) stringent complete response (sCR), 9 (3%) CR, and 53 (17.4%) very good partial response (VGPR). Major adverse events included grade 3/4 neutropenia (30.2%), anemia (13.1%), lymphocytopenia (20.3%), and thrombocytopenia (9.2%). Infection rates and pneumonia were 24.6% and 13%, respectively. After a median follow-up of 12 months (range 0-38), 204 patients experienced disease progression or death, with a median progression-free survival (PFS) of 7.5 months (Figure 1A). Age (<70 *vs* >70 years), gender, creatinine clearance (>60 *vs* <60 ml/min), LDH (normal *vs* elevated), number of previous lines of therapy (2 *vs* >2), previous ASCT, cytogenetic abnormalities (standard *vs* high-risk), and disease status (relapse *vs* refractory) failed to significantly impact on PFS in univariable analyses. Interestingly, advanced ISS stage (I-II *vs* III) (HR=1.67; P<0.001) and previous daratumumab exposure (HR=1.74; P=0.002) were associated with a significantly shorter PFS (Figure 1B). Notably, in the Cox multivariable analysis, both parameters maintained an independent prognostic impact on PFS (advanced ISS stage, HR=1.57; P=0.005; previous daratumumab exposure, HR=1.65; P=0.004). Median overall survival (OS) was 19.3 months (Figure 1C), with advanced ISS stage (I-II *vs* III) (HR=2.27; P<0.0001) and a higher number of previous lines of therapy (2 *vs* >2) (HR=1.4; P=0.05) identified as adverse prognostic factors in univariable analyses. Cox multivariable analysis confirmed both parameters as independently associated with a higher risk of death (advanced ISS stage, HR=2.3; P<0.0001; higher number of previous lines of therapy, HR=1.47; P=0.028). In conclusion, our extended real-world study reaffirms the safety and feasibility of EloPd as a therapeutic option for RRMM with a history of at least two prior therapies. However, the negative impact of previous daratumumab exposure and advanced ISS stage on the efficacy of the EloPd triplet regimen warrants consideration in clinical decision-making.

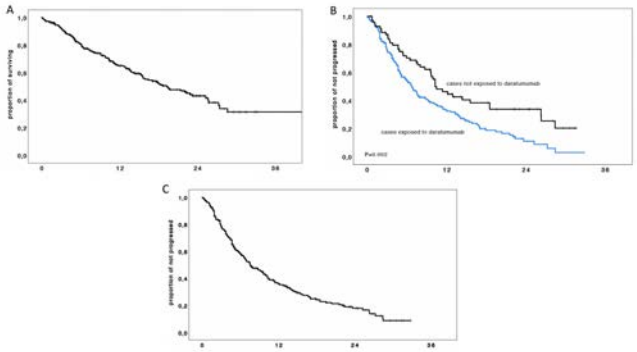

Figure 1.

B08

[18F]-FLORBETABEN PET IN AL AMYLOIDOSIS, A NEW PROMISING TECHNIQUE

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AL amyloidosis is haematological disease chacaterized by clonal population of plasma cells that produces monoclonal light chains and extracellular deposition of amyloid insoluble fibrils.The misfolded proteins interfere with organs functions,frequently heart and kidney;the involvement could be unknown for years before diagnosis,due to the asymptomatic deposition until disfunction. Different techniques were introduced to detect amyloid deposition like Congo Red staining, immunochemistry,electronic microscopy on Periombelical Fat or on tissues biopsies involved,or cardiac imaging,echocardiography, MRI or PET. Cardiac deposits in amyloidosis are major determinants of clinical presentation and may be present in AL amyloidosis or ATTR amyloidosis; often differential diagnosis is difficult. Concerning ATTR, sensitive diagnostic tool, as diphosphonate scintigraphy, was introduced, instead of no imaging approach is as accurate in AL. Cardiac ultrasound and circulanting biomarkers may raise the clinical suspicion of AL, but often endomyocardial biopsy remains the only option to obtain diagnosis. In this retrospective study, we aimed to explore the sensitivity of this new imaging technique, *i.e*. 18F-Florbetaben PET/CT, respect to common blood tests or POF, cardiac or other tissues biopsies in a cohort of 33 patients, referred to Cardiovascular Unit of Fondazione Monasterio and Haematology Unit in Pisa from July 2016 to January 2023. PET was performed by dynamic reconstruction from list-scan during iv infusion of 300MBq/mL of 18F-Florbetaben, followed by a 10 mL saline flush,acquiring static cardiac scans 110 min after injection. PET was performed at time of diagnosis in 19patients and during the follow up in 11.

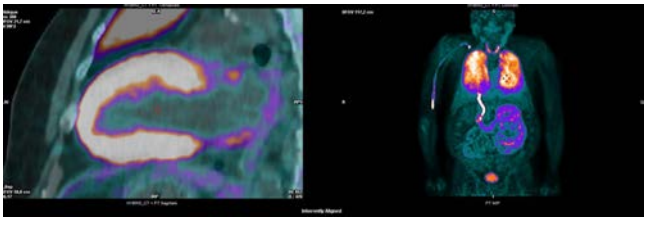

Figure 1. Left, [18F]-florbetaben cardiac positron emission tomography scan in patient with AL and on the right side,scan of other localizations of amyloidotic fibrils in the same patient. The [18F]-florbetaben PET scan shows pathological positivity in lung and thyroid, histological site of AL detection, and normal hepatic, urinary and intestinal uptake.

In our cohort,amyloid fibrils were detected in 17/17 endomyocardial biopsies, 18POF and in 10BM Biopsies. Blood tests performed at the time of PET showed in 87,8% patient high NT-proBNP and elevated Troponine levels in all study cohort, as a cardiac damage sign, that anyway could be not only related to AL cardiac involvement, but also depends on other cardiological conditions. 24hs Proteinuria could not be considered as a significative parameters in our study, due to low number of patients who collected urine in 24 hours (24,2%); even though the number of patients with renal impairement, creatinine levels in 60,6% of patients with renal involvement were normal. Concerning the most relevant parameter, FLC ratio was normal in 3 patients,suggesting a lower sensitivity of dosing FLC compared to PET. Notably, 18F-Florbetaben PET uptake was also consistent in extra cardiac tissues of amyloid histological deposition. Earlier diagnosis is challenging in AL amyloidosis with a relevant impact on life expectancy.Despite an increase in serum levels of FLC anticipates the development of AL, we demonstrate that 18F-Florbetaben PET positive patients could present normal levels of FLCratio, suggesting more relevance to performe this promising imaging technique, in heart failure patients if AL amyloidosis is suspected, instead of only bood exasms or B-Mode US/MRI. Therefore, 18F-Florbetaben PET/CT can be able to explore all sites of amyloid deposits.

POSTERS

Biology and preclinical

P01

LIPID METABOLIC DYNAMICS CONVEYS RESISTANCE TO ANTI-BCMA IMMUNOTHERAPY IN MULTIPLE MYELOMA VIA FERROPTOSIS

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Decreased cholesterol levels in multiple myeloma (MM), as consequence of increased LDL clearance and lipid handling, have been investigated in the development of drug resistance, leading to clinical relapse. Precise regulation of lipid droplet (LD) turnover is essential for polyunsaturated fatty acid (PUFA) distribution, needed to reduce membrane lipid peroxidation, preserve organelle function and cellular homeostasis and prevent cell death, including ferroptosis. Our previous work showed a decrease in LDs in OPM2 cell line higher than in U266 cell line, associated to a differential sensitivity to Belantamab Mafodotin (BeMa), a BCMA-targeted antibody–drug conjugate currently under investigation for the treatment of patients with relapsed or refractory MM (RR-MM). Since the PUFA/MUFA ratio regulates ferroptosis, with PUFA oxidation is pro-ferroptosis, while MonoUnsaturated Fatty Acids (MUFA) synthesis promotes a ferroptosis-resistant cell state, we investigated how ferroptosis and lipid handling could affect BeMa sensitivity in MM. Thus, we combined RNAseq and lipidomic profiles with in vitro assays and FACS analysis, to evaluate the response to BeMa in human MM cell lines (HMCLs) while plasma obtained from matched bone marrow and peripheral blood of 9 RRMM patients at first-MM diagnosis and later at relapse, were investigated by LS-MS/MS. To validate the clinical relevance of in vitro observations, we interrogated 767 RNA sequencing (RNA-Seq) from NDMM patients enrolled in the CoMMpass study, comparing patients with different expression of each gene (subdivided on median value or quartiles) by log-rank test. STRING protein analysis on MM patient plasma highlighted a dysregulation in lipid metabolism with an increased amount of apoliproteins APO-A1 (key component of HDL particle and cofactor for lecithin—cholesterol acyltransferase (LCAT) which is responsible for the formation of most plasma cholesteryl esters), A2, C2 (which hydrolyzes triglycerides to provide free fatty acids for cells), confirming a deranged lipid handling in RR-MM patients. RNAseq analysis under basal conditions revealed in BeMa sensitive cell line U266.S higher levels of ACSL4, a key positive regulator of lipids peroxides (LOOH) production from PUFA. In BeMa resistant cell line OPM2.R we found upregulation of genes involved in fatty acid uptake (CD36, VLDLR and FABP4), fatty acid biosynthesis (ACSL4, LPCAT3, ALOX, SREBP) and key negative regulators of ferroptotic cell death (GPX4, SLC7A11). Among the identified upregulated genes, ALOX12 catalyzes the regio and stereo-specific incorporation of a single molecule of dioxygen into free and esterified PUFA generating LOOH. To validate the clinical meaning of this finding, overexpression of ALOX12 was associated to inferior progression free survival (HR=1.4, p=0.01) and overall survival (HR=1.6, p=0.0012). Supplementation with palmitic acid (a MUFA precursor) rescued ferroptosis resistance upon BeMa exposure in OPM2.R. In accordance, lipidomics analysis confirmed higher MUFA/PUFA ratio in BeMa OPM2.R resistant cells. Combination of GPX4 inhibitor with BeMa sensitized OPM2.R to ferroptosis. Taken together, our findings suggest differential intrinsic vulnerability to ferroptosis cell death which inhibition may contribute to the onset of BeMa-resistance opening a new scenario about the molecular machinery underlying anti-BCMA immunotherapy resistance.

P02

SINGLE MASS SPECTROMETRY ASSAY TARGETTING M-PROTEIN, THERAPEUTIC ANTIBODIES, AND POLYCLONAL IMMUNOGLOBULINS PROVIDES UNIQUE INSIGHT INTO THERAPY RESPONSE KINETICS IN PATIENTS WITH MULTIPLE MYELOMA

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Detecting Minimal Residual Disease (MRD) in multiple myeloma (MM) typically relies on invasive bone marrow aspirates. This poses challenges for frequent monitoring and introduces potential sampling bias due to tumor heterogeneity. Our team introduced an innovative MS-MRD blood test, utilizing targeted mass spectrometry. This patient-tailored solution, targeting clonotypic peptides from the M-protein variable region, exhibits heightened sensitivity compared to serum protein electrophoresis (SPEP) and immunofixation (IFE). In this work, we demonstrate the added value of a multiplex MS-MRD assay designed to target the clonotypic peptides derived from the M-protein, as well as daratumumab, isatuximab, teclistamab, talquetamab, tocilizumab, and the constant regions of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE. This comprehensive approach not only enhances the sensitivity of M-protein monitoring but also allows for the simultaneous assessment of multiple therapeutic agents, providing a holistic view of therapy response kinetics in patients with MM. Employing a multi-enzyme de novo protein sequencing strategy facilitated by bioinformatics, the M-protein sequence was obtained using M-inSight (Sebia). This comprehensive approach not only involved bioinformatics in sequencing the M-protein but also played a crucial role in guiding the selection of clonotypic peptides. Linearity of all selected peptides was evaluated within a dilution series of therapeutic monoclonal antibodies spiked in a pooled control serum. The case series comprised of two individuals producing free light chain (FLC) kappa and one patient with an IgA-Kappa M-protein. Preceding monoclonal antibody treatment, all patients had received multiple lines of other treatments. The analysed

pilot sample set (n=3) included samples collected between 2012 and 2023. Personalized M-protein targets were identified in all three patients using M-inSight de novo sequencing. Linearity testing demonstrated sensitivities down to 1 mg/L, and thereby exhibited a 1000-fold increase in sensitivity compared to SPEP. MS-MRD allowed M-protein quantification long after normalized IFE and free light chain ratios in all three patients. MS-MRD analyses in patient 1 demonstrated that the best response since diagnosis in 2016 was achieved with teclistamab monotherapy as 8th line of therapy (figure 1). Remarkably, also the second patient tested reached the deepest clinical response with teclistamab as 6th treatment line. In the third patient monitored in this case series, the multiplex MS-MRD showed early relapse during sequential monotreatment with daratumumab and also teclistamab. Therapeutic monoclonal antibody monitoring revealed a 1000-fold lower concentration of teclistamab compared to anti-CD38 antibodies (daratumumab and isatuximab) in all three patients, which corresponds to the significantly different dosing of these drugs. The multiplex MS-MRD assay revealed the fast and deep immunoglobulin depletion caused by teclistamab, followed by a selective increase of solely IgG attributed to intravenous immunoglobulin administration in these patients. This series of three cases shows our ability to comprehensively monitor the M-protein, five distinct therapeutic monoclonal antibodies, and all immunoglobulin subclasses within a singular targeted mass spectrometry assay. This allows a dynamic monitoring or novel treatment performance.

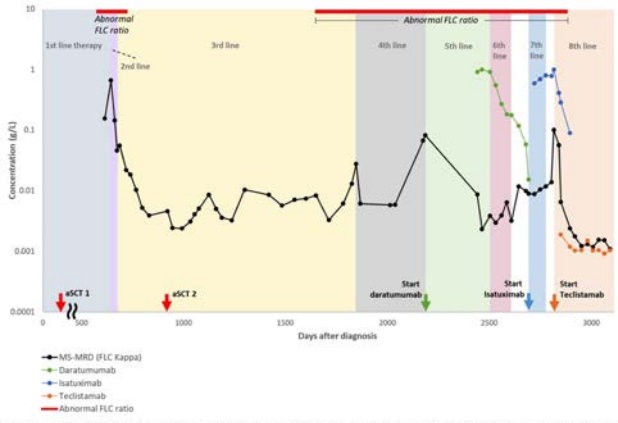

Figure 1. Multiplex MRD monitoring of myeloma patient receiving eight lines of therapy. MS-MRD monitoring started at relapse of the 1st line therapy. Deepest response (still ongoing) was achieved at 8th line therapy. Multiplex MS-MRD allows simultaneous monitoring of polyclonal antibodies and biologics. Nb, not all samples of this patient were biobanked, which leaves several monitoring gaps. aSCT, autologous stem cell transplantation.

Figure 1.

P03

ARGININE DEPRIVATION INDUCES DNA DAMAGE AND CHROMOSOMAL INSTABILITY: THE SEED AND SOIL IN MULTIPLE MYELOMA

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In multiple myeloma (MM) a supportive tumor microenvironment (TME) plays an active role in selecting an array of multiple clones, each potentially associated with different clinical behaviour. Our previous work disclosed how the reduction of arginine (arg) concentration in the TME triggers metabolic reprogramming in PCs, enhancing their survival in vitro (Romano, 2020) and in vivo (Trudu, 2022). Thus, we combined RNAseq with in vitro assays and FACS analysis, to investigate the adaptive response to acute and chronic arg deprivation, in two human myeloma cell lines (U266 and NCI-H929) cultured up to 10 days in arginine deprivation, correspondent respectively to 100%, 25% and 10% of the arg concentration in MM bone marrow. Nuclear DNA leakage started at around 24 hours from arg starvation and increased afterwards, as assessed by fluorescence microscopy and by an increase of cytosolic chromatin-DNA species by ELISA. Confocal immunofluorescence microscopy analysis showed that γH2AX, a marker for DNA double-strand breaks, was increased and appeared as punctate spots in the cell nucleus and enriched in leaked DNAs, in a time-dependent manner. Consistently, we also found that several DNA repair-associated molecules, including p-DNA PKcs, p-53BP1, PARP, and p-ATM, were recruited to leaked DNAs. Upon prolonged arg starvation at 10 days, we found the reduction of the Histone H3 lysine K4 (H3K4) and the increase of histone variant macro H2A1, recruited to DNA double-strand breaks to promote gene silencing and hampering DNA-repair mechanisms, as shown by a significant down-regulation of Fanconi Anemia (FA) pathway members FANCD2 and FANCI, master regulators of efficient replication DNA fork damage recovery. The direct pairwise comparison identified, respectively in U266 an NCI-H929, a total of 1656 and 2214 differentially expressed genes (DEGs) upon 48 hours of arg deprivation. Among 888 DEGs in common in both cell lines, gene set enrichment analysis (GSEA) showed that 48 hours of arg deprivation significantly down-regulated biological processes involved in chromosome organization (GO:0051276), mitotic cell cycle (GO:0000278), chromosome segregation (GO:0007059), regulation of cell cycle process (GO:0010564), DNA repair (GO:0006281) and cellular response to DNA damage stimulus (GO:0006974). To validate the clinical relevance of in vitro observations, DEGs identified in both cell lines were further investigated in 767 RNA-Seq obtained from NDMM patients enrolled in the CoMMpass study, comparing patients with different expression of each gene (subdivided on median value or quartiles) by log-rank test. After setting p-adjusted <0.01, we found that 39/888 DEGs associated to reduced progression-free survival and overall survival, listed in the attached Table 1. Among identified DEGs, FANCB is the only known X-linked component of FA core complex needed for DNA repair in S-phase, where FANCB forms a protein subcomplex to monoubiquitinate FANCD2 and FANCI. Overexpression of FANCB

was associated to inferior progression free survival (HR=2.0, p<0.001) and overall survival (HR=1.4, p=0.006). Taken together, our findings suggest that arg deprivation in TME conveys chromosomal instability, providing new insights to induce synthetic lethality in MM.

Table 1.

	Overall survival analysis		Progression free survival analysis		
DEG	HR	adj p-value	HR	95% CI	adj p-value
GRB10	1.98	<0.001	1.66	1.3-2.2	<0.001
NCAPH	2.24	<0.001	1.79	1.4-2.3	<0.001
LAMP3	0.56	0.005	0.62	0.5-0.8	<0.001
FNDC3B	0.49	0.002	0.53	0.4-0.7	<0.001
TACC3	2.16	<0.001	1.73	1.3-2.3	<0.001
NDC1	1.58	0.04	1.61	1.2-2.1	<0.001
TIMELESS	2.05	0.001	1.65	1.3-2.2	<0.001
GSDMB	1.75	0.01	1.46	1.1-1.9	<0.001
POLA1	2.14	<0.001	1.74	1.3-2.3	<0.001
DNAJB9	0.52	0.003	0.54	0.4-0.7	<0.001
RRM1	1.96	0.002	1.73	1.3-2.3	<0.001
TEDC1	1.97	0.001	1.57	1.2-2.1	<0.001
ARHGEF37	0.58	0.01	0.67	0.5-0.9	<0.001
CSE1L	1.72	0.01	1.7	1.3-2.2	<0.001
IL32	1.66	0.01	1.47	1.1-1.9	<0.001
BTNL9	1.69	0.01	1.58	1.2-2	<0.001
CCDC146	0.45	<0.001	0.65	0.5-0.9	<0.001
HMGN5	1.92	0.003	1.72	1.3-2.2	<0.001
SOX30	0.49	0.001	0.59	0.5-0.8	<0.001
MYO1C	0.54	0.006	0.54	0.4-0.7	<0.001
IQCD	1.92	0.003	1.43	1.1-1.9	<0.001
FAM110A	1.71	0.019	1.52	1.2-2	<0.001
FANCB	2.1	<0.001	1.46	1.1-1.9	<0.001
RAD54B	1.96	0.002	1.84	1.4-2.4	<0.001
PDCL3	1.79	0.01	1.51	1.1-2	<0.001
SNAPIN	2	0.003	1.72	1.3-2.3	<0.001
IL24	1.66	0.02	1.54	1.2-2	<0.001
SFXN3	0.56	0.01	0.61	0.5-0.8	<0.001
INTU	1.77	0.01	1.47	1.1-1.9	<0.001
SELL	1.83	0.008	1.5	1.2-2	<0.001
TCF19	2.04	0.002	1.73	1.3-2.3	<0.001
CRIP2	1.79	0.008	1.66	1.3-2.2	<0.001
BAIAP2L2	2.32	<0.001	1.46	1.1-1.9	<0.001
KLHDC1	0.5	0.001	0.63	0.5-0.8	<0.001
H4C8	1.76	0.02	1.46	1.1-1.9	<0.001
SERPINA6	2.21	0.002	1.75	1.3-2.4	<0.001
CRISPLD1	1.79	0.009	1.58	1.2-2.1	<0.001
TMEM97	1.99	0.002	1.77	1.3-2.4	<0.001
OLFM2	1.77	0.01	1.58	1.2-2.1	<0.001

P04

EMN PROSPECTIVE SAMPLE COLLECTION PROJECT (EMN36): AN INTERNATIONAL UNIFORM SAMPLE REPOSITORY FOR PATIENTS WITH PLASMA CELL DYSCRASIAS TO ENABLE CORRELATIVE RESEARCH

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Background. The EMN36 project is an observational, non-interventional, multicenter study for the prospective collection, storage and analysis of biological samples of patients (pts) with plasma cell dyscrasias. This study establishes a common international infrastructure to uniformly collect and store biological samples and associated clinical data at baseline and during treatment, in order to enable correlative research.

Methods. Previously untreated pts with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), newly diagnosed (ND)MM, or primary plasma cell leukemia (pPCL), with or without extramedullary disease (EMD), were enrolled. Peripheral blood (PB) and bone marrow (BM) aspirates of the enrolled pts were collected and sent to European Myeloma Network (EMN)-associated central laboratories at baseline and at the time of each subsequent progression. A pipeline to uniformly process and stock biological material in the central laboratories was defined. Additional blood and marrow sampling during treatment, BM biopsies and biopsies of EMD sites were collected as well, if the procedures were performed according to clinical practice. Local data about baseline disease characteristics, prognostic factors, treatment received, response and progression and survival status of pts were longitudinally collected.

Results. At data cut-off (Dec 5, 2023), 107 of 132 screened pts were confirmed to be eligible and had baseline clinical data. Median age was 70 years (IQR 61.5-76.5). The majority of pts had IgG isotype (73%) and kappa light chain (55%). Among the 107 pts with baseline clinical data, 17 (16%) were diagnosed with MGUS, 25 (23%) with SMM, 62 (58%) with NDMM and 3 (3%) with pPCL. Among NDMM pts, 32% had International Staging System (ISS) stage I disease, 39% ISS II and 29% ISS III; lactate dehydrogenase was above the upper limit of normal in 15% of pts; the ECOG performance status was ≥2 in 20%. Locally performed fluorescence *in situ* hybridization (FISH) was available in 37/62 (60%) NDMM pts. High-risk cytogenetics (t(4;14), t(14;16), or del(17p)) was present in 27% of evaluable pts, while ≥2 high-risk lesions (among t(4;14), t(14;16), del(17p) and 1q+) were present in 19% of evaluable pts. Treatment details were available for 51/62 NDMM pts: 73% received upfront regimens containing daratumumab (Dara): the most frequent regimen was Dara-VTd (39%), followed by Dara-Rd (14%) and Dara-VMp (12%). Central laboratories received baseline samples from all screened pts. At data cut-off, stock details were available for 91 pts. 872 vials from BM aspirate samples, 950 vials from PB samples and 93 slides/microsection from BM biopsies were stocked (Table 1). CD138+ enrichment was performed on BM aspirates from 61/91 (67%) pts. The median plasma cell purity of CD138+ fraction was 92% (IQR 83%-98%).

Conclusions. EMN36 provides a unique platform to enable correlative research in a cohort of pts with uniformly stocked samples, full clinical data annotations and subsequent follow-up. This study aims to enroll 2000 pts in the next 4 years, with a study duration of

15 years. The analysis of prognostic models and the elucidation of mechanisms of disease initiation/progression and of resistance to specific agents are some of the potential projects that can be performed analyzing the stocked samples. EMN36 will also serve as a repository of baseline samples from MM pts who will be enrolled in future EMN trials.

Table 1.

Table. Samples in stock within the project

	Material	No. of patients with at least 1 vial	Average No. of vials/patient	Average quantity/vial
Bone marrow aspirate material	WBCs (dry pellet)	91	1	6.6 × 10^6 cells
	WBCs (viable)	32	1.7	24.6 × 10^6 cells
	BMMCs (viable)	64	1.5	17.4 × 10^6 cells
	CD138+ (RLT pellet)	60	1.3	1.2 × 10^6 cells
	CD138+ (viable)	41	1.3	2.15 × 10^6 cells
	CD138+ (dry pellet)	6	1	1.3 × 10^6 cells
	CD138+ (Carnoy-fixed)	22	1	0.5 × 10^6 cells
	CD138+ (cytospins)	3	1.7	0.7 × 10^6 cells
	CD138- (viable)	61	2	39.9 × 10^6 cells
	Plasma	89	4	0.5 ml
Peripheral blood material	PBMCs (viable)	84	2.0	22.2 × 10^6 cells
	Granulocytes (dry pellet)	84	1.0	12 × 10^6 cells
	Serum	86	3.7	0.5 ml
Bone marrow biopsy material	Slides	29	2	--
	Macrosections	29	1.2	--

Abbreviations. BMMCs, bone marrow mononuclear cells; No., number; PBMCs, peripheral blood mononuclear cells; WBCs, white blood cells.

P05

NOVEL PROXIMITY LABELLING ASSAY FOR MONITORING DYNAMIC INTERACTIONS BETWEEN MULTIPLE MYELOMA AND CAR T-CELLS

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The recognition of surface proteins on myeloma cells by chimeric antigen receptor (CAR) expressing T-cells is the ultimate prerequisite for subsequent tumor elimination. It is generally accepted that the CD8+ T-cells exhibit the greatest killing activity. However, a little is known about the involvement of the specific T-cells subtypes in the cytotoxic process. Similarly, diverse CARs, hybrid T-cell receptors (hTCR) and bispecific antibodies might engage different T-cell populations. Therefore, the choice of CAR/hTCR and T-cell subsets ratio might have dramatic consequences on the therapy efficiency. In order to quantitatively and qualitatively analyze the T-cells subsets that transiently interact with myeloma cells, we optimized and extensively validated the PUP-IT proximity labelling method. The technology is based on non-selective ligase PafA that covalently attaches short peptides to cell surface proteins. Using various tags and modified antibodies we anchored PafA on CD19 or BCMA expressed on myeloma cells to allow labeling of the interacting T-cells with fluorescent peptide. The marked T-cells were characterised using spectral flow cytometry and RNAseq. Finally, to validate the functional relevance of the cellular interactions, we performed cytotoxic assays with the isolated T-cell subpopulations based on their labelling profile (effective *vs* non-effective binders). Besides, we are optimizing the protocol to distinguish T-cells with various frequencies of binding to myeloma cells. The presented methodology provides a novel, easy to use tool for detailed characterization of CAR T-cells on the single cell level. The labelling protocol can be applied also to other interacting cell types of both immune and non-immune origin in the context of tumor mass.

Newly diagnosed multiple myeloma

P06

ISATUXIMAB-CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE *vs* CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE AS PRE-TRANSPLANT INDUCTION AND POST-TRANSPLANT CONSOLIDATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: RESULTS OF THE PHASE III RANDOMIZED EMN24 ISKIA TRIAL

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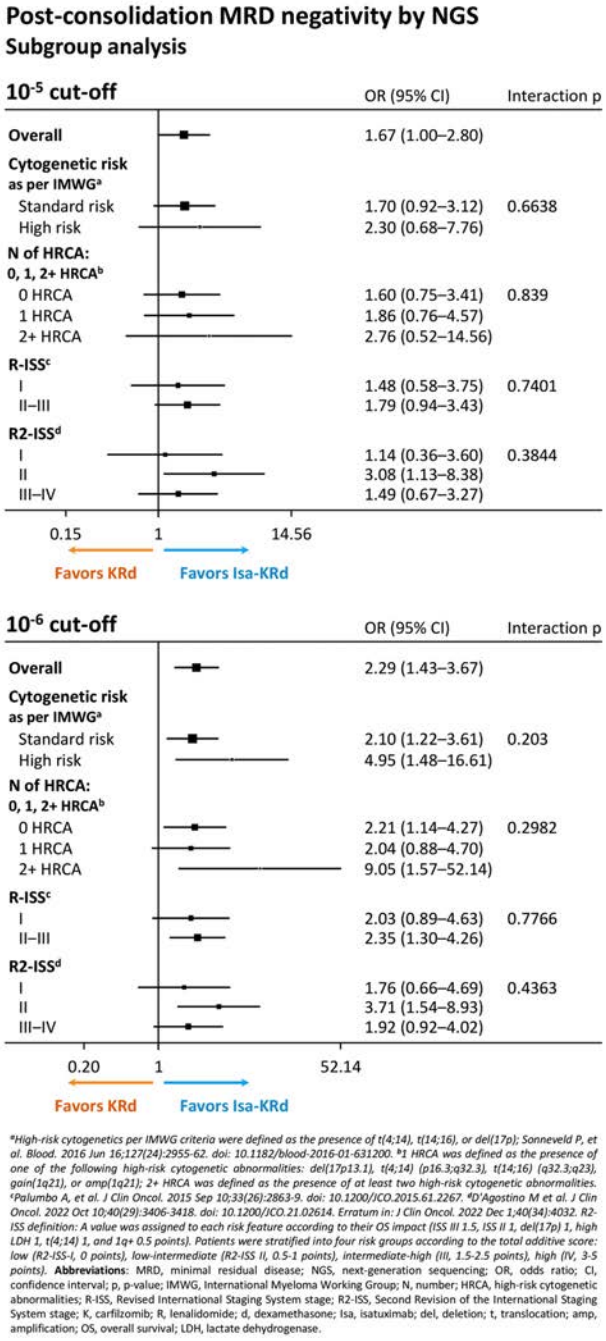
Background. The phase III IsKia trial assessed isatuximab-carfilzomib-lenalidomide-dexamethasone (Isa-KRd) as pre-ASCT induction and post-ASCT consolidation *vs* KRd in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM).

Methods. TE NDMM pts aged <70 yr were randomized to Isa-KRd induction, MEL200-ASCT and Isa-KRd consolidation *vs*. KRd induction, MEL200-ASCT and KRd consolidation. Primary endpoint was MRDneg rate (NGS; 10^{-5}) after consolidation in ITT. MRD was tested in all pts who achieved ≥VGPR. Key secondary endpoints were the NGS MRDneg rate (10^{-5}) after induction and PFS. MRD rates were evaluated in an ITT analysis. Data cut-off was May 22, 2023.

Results. 151 pts were enrolled and randomized in both the Isa-KRd and KRd arms. Pt characteristics were well balanced between the two arms: median age was 61 *vs* 60 years, respectively; 18% *vs*

19% of pts had high-risk (HiR) cytogenetic abnormalities (CA) [del(17p) and/or t(4;14) and/or t(14;16)]; 9% *vs* 8% had ≥2 HiR CA [double hit; including del(17p), t(4;14), t(14;16) and gain/amp(1q)]. In ITT analysis, the rates of MRDneg at the 10^{-5} cut-off after consolidation (primary endpoint) were 77% *vs* 67% (OR 1.67, p=0.049) with Isa-KRd *vs* KRd; the respective rates of MRDneg at the 10^{-5} cut-off were 67% *vs* 48% (OR 2.29, p<0.001); consistent MRD results were detected by next-generation flow. ≥VGPR after consolidation was 94% in both arms; ≥CR 74% *vs* 72% and sCR 64% *vs* 67% in the Isa-KRd *vs* KRd arms.



[a]High-risk cytogenetics per IMWG criteria were defined as the presence of t(4;14), t(14;16), or del(17p); Sonneveld P, et al. Blood. 2016 Jun 16;127(24):2955-62. doi: 10.1182/blood-2016-01-631200. [b]1 HRCA was defined as the presence of one of the following high-risk cytogenetic abnormalities: del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21); 2+ HRCA was defined as the presence of at least two high-risk cytogenetic abnormalities. [c]Palumbo A, et al. J Clin Oncol. 2015 Sep 10;33(26):2863-9. doi: 10.1200/JCO.2015.61.2267. [d]D'Agostino M et al. J Clin Oncol. 2022 Oct 10;40(29):3406-3418. doi: 10.1200/JCO.21.02614. Erratum in: J Clin Oncol. 2022 Dec 1;40(34):4032. R2-ISS definition: A value was assigned to each risk feature according to their OS impact (ISS III 1.5, ISS II 1, del(17p) 1, high LDH 1, t(4;14) 1, and 1q+ 0.5 points). Patients were stratified into four risk groups according to the total additive score: low (R2-ISS-I, 0 points), low-intermediate (R2-ISS II, 0.5-1 points), intermediate-high (III, 1.5-2.5 points), high (IV, 3-5 points). **Abbreviations**: MRD, minimal residual disease; NGS, next-generation sequencing; OR, odds ratio; CI, confidence interval; p, p-value; IMWG, International Myeloma Working Group; N, number; HRCA, high-risk cytogenetic abnormalities; R-ISS, Revised International Staging System stage; R2-ISS, Second Revision of the International Staging System stage; K, carfilzomib; R, lenalidomide; d, dexamethasone; Isa, isatuximab; del, deletion; t, translocation; amp, amplification; OS, overall survival; LDH, lactate dehydrogenase.

Figure 1.

The MRDneg advantage, both at 10^{-5} and 10^{-5}, was retained in all subgroups analyzed (Figure 1), with similar benefit in pts with standard-risk (SR) and HiR features. In particular, the 10^{-5} MRDneg rates with Isa-KRd were 76% in HiR and 77% in double-hit pts, comparable to the one in SR pts (79%). In the KRd arm, the 10^{-5} MRDneg rates were 58% in HiR and 53% in double-hit pts, inferior to the one in SR pts (70%). The 10^{-5} MRDneg rates with Isa-KRd were 72% in HiR, 77% in double-hit pts and 67% in SR pts. The post-induction MRDneg rate (first key secondary endpoint) was also significantly higher with Isa-KRd *vs* KRd (10^{-5}: 45% *vs* 26%, OR 2.34, p<0.001; 10^{-5}: 27% *vs* 14%, OR 2.36, p=0.004), with a consistent benefit in all subgroups. The post-induction MRDneg rates in HiR and double-hit pts treated with Isa-KRd were: 10^{-5} HiR 60%, double-hit 54%; 10^{-5}, HiR 40%, double-hit 31%. The post-ASCT MRDneg rates were also significantly better with Isa-KRd *vs* KRd (10^{-5}: 64% *vs* 49%, OR 1.93, p=0.006; 10^{-5}: 52% *vs* 27%, OR 3.01, p<0.001), with a consistent advantage in all subgroups. At the current follow-up (median, 20 months, IQR 18–23), there was no difference in PFS (95% at 1 year in both arms). 55% of pts had ≥1 hematologic adverse events (AEs) with Isa-KRd *vs* 43% with KRd; main grade 3–4 hematologic AEs in Isa-KRd *vs* KRd were neutropenia (37% *vs* 22%) and thrombocytopenia (15% *vs* 17%). 41% of pts had ≥1 non-hematologic AEs with Isa-KRd *vs* 37% with KRd, including infections (16% *vs* 12%), gastrointestinal (7% *vs* 5%), vascular (2% *vs* 7%) and cardiac events (1% *vs* 4%). Discontinuation for toxicity was 6% in Isa-KRd *vs* 5% in KRd arms; treatment-related deaths were 4 with Isa-KRd (2 COVID, 1 pneumonia, 1 pulmonary embolism) and 1 with KRd (septic shock).

Conclusions. In TE NDMM pts, Isa-KRd induction and consolidation significantly increased MRDneg rates in every treatment phase as compared to KRd, with no new safety concerns. This benefit was retained in HiR pts.

P07

CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE (KRD) *VS* LENALIDOMIDE-DEXAMETHASONE (RD) IN NEWLY DIAGNOSED FIT OR INTERMEDIATE-FIT MULTIPLE MYELOMA PATIENTS INELIGIBLE FOR AUTOLOGOUS STEM-CELL TRANSPLANTATION: ANALYSIS OF SUSTAINED UNDETECTABLE MINIMAL RESIDUAL DISEASE (MRD) IN THE PHASE III EMN20 TRIAL

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Background. The EMN20 trial (NCT04096066) is a randomized, multicenter study comparing weekly carfilzomib-lenalidomide-dexamethasone (KRd) *vs* Rd in fit or intermediate-fit transplant-ineligible (NTE) patients (pts) with newly diagnosed multiple myeloma (NDMM).

Methods. Fit or intermediate-fit NTE NDMM pts (according to the International Myeloma Working Group [IMWG] frailty score) were randomly assigned to receive KRd (28-day cycles [cc], once-weekly K 56 mg/m² on days [dd] 1,8,15 for 12 cc and on dd 1,15 from cc 13 onwards for 5 years (yrs), R 25 mg orally on dd 1–21 continuously and d 40 mg on dd 1,8,15,22 continuously) or continuous Rd (28-day cc, R 25 mg on dd 1–21, d 40 mg on dd 1,8,15,22). Pts were stratified based on International Staging System (ISS) stage and fitness status, using a web-based procedure completely concealed from study participants. Patients in the KRd arm sustaining minimal residual disease (MRD) negativity after 2 yrs of treatment will discontinue K at 2 yrs and continue Rd. The primary endpoints were MRD negativity (clonoSEQ™ assay, sensitivity of $\geq 10^{-5}$) after 2 yrs of treatment and progression-free survival (PFS). The protocol was prematurely stopped on Nov 23, 2021, after the introduction of frontline daratumumab-Rd.

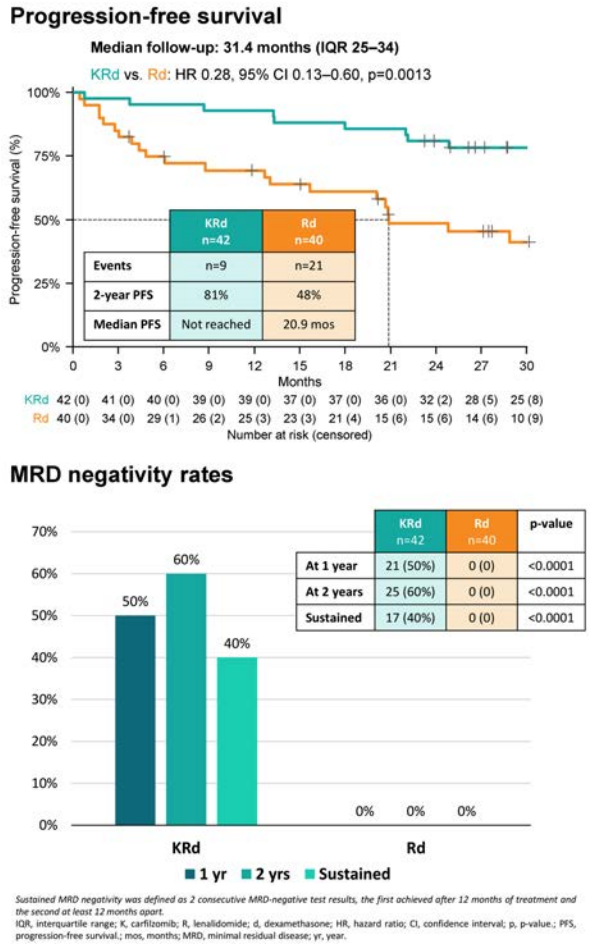

Figure 1.

Results. A total of 82/101 enrolled pts were randomized (KRd 42 *vs* Rd 40); 17 pts were not randomized due to screening failure and 2 due to consent withdrawal. Pt characteristics were well balanced between the KRd and Rd arms: median age was 73 (IQR 70-76) *vs* 74 (IQR 72-76) yrs, 62% *vs* 55% of pts were fit, 33% *vs* 30% had ISS III and 22% *vs* 22% had high-risk cytogenetics, respectively. In the KRd *vs* Rd arms, 30/42 (71%) *vs* 16/40 (40%) pts are still under treatment; reasons for discontinuation were medical decision (1 *vs* 2), death (2 *vs* 5), adverse events (AEs; 3 *vs* 2), progressive disease (3 *vs* 12), lost to follow-up (1 *vs* 0) and consent withdrawal (1 *vs* 3). After a median follow-up of 32 months (IQR 27-35), 76% of KRd and 45% of Rd pts were alive and progression-free. In the ITT population, MRD negativity rates (at 10^{-5}) were observed in 21/42 (50%) KRd *vs* 0 Rd pts at 1 treatment yr (p<0.0001) and in 25/42 (60%) KRd and 0 Rd pts at 2 yrs (p<0.0001). 17/42 (40%) KRd and 0 Rd pts sustained MRD negativity at 2 yrs (p<0.0001; Figure 1). Median PFS was not reached with KRd *vs* 20.9 months with Rd (HR 0.26, 95% CI 0.12-0.58, p=0.0010; Figure 1). In multivariable analysis, no significant effect modification was observed in terms of ISS or frailty status. 2-yr overall survival (OS) was 88% with KRd *vs* 75% with Rd (HR 0.39, 95% CI 0.13-1.20, p=0.10). The most frequent grade 3-4 AEs with KRd were neutropenia (22%), thrombocytopenia (10%), cardiac AEs (7%), infection (7%) and hypertension (5%), while with Rd they were neutropenia (12%) and dermatologic AEs (10%). Second primary malignancy was observed in 1 pt (2%) in the Rd arm. 85% of pts in the KRd and 65% in the Rd arms had ≥1 dose reductions of any drug.

Conclusions. To our knowledge, an unexpectedly high rate of MRD negativity was observed for the first time in NTE NDMM pts. Half of pts treated with KRd achieved MRD negativity, improving over time with therapy (50% at 1 yr and 60% at 2 yrs), and 40% of KRd patients sustained MRD negativity at 2 yrs; this was associated with prolonged PFS. Toxicities were predictable and manageable.

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ABSTRACT NOT PUBLISHABLE

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IBERDOMIDE MAINTENANCE AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: FIRST RESULTS OF THE PHASE 2 EMN26 STUDY

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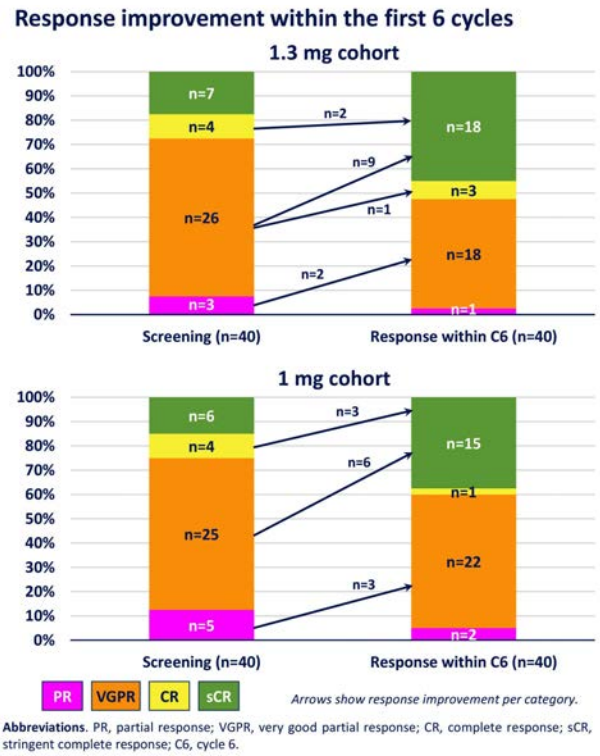
Background. We aimed to evaluate the safety and clinical activity of three different doses of iberdomide as a novel, post-transplant, maintenance treatment in newly diagnosed multiple myeloma (MM) patients (pts). Here we report the first interim analysis for patients who have been treated with ≥6 treatment cycles (cc) or discontinued treatment earlier.

Methods. MM pts aged ≥18 years, who had achieved at least a partial response (PR) after induction therapy containing a proteasome inhibitor (PI) plus an immunomodulatory drug (IMiD) followed by single or double autologous stem-cell transplantation (ASCT) ± consolidation, were enrolled into one of three different cohorts (iberdomide 0.75, 1.0, or 1.3 mg on days 1-21 of each 28-day cc; treatment continued until progression or unacceptable toxicity; 40 pts in each cohort). The primary outcome was response improvement, and secondary outcomes included safety and progression-free survival (PFS). Response was evaluated at screening and after every cc (bone marrow analysis was done at screening, at 6 and 12 months [mo] after treatment initiation, and to confirm (s)CR). This trial is ongoing and is registered with ClinicalTrials.gov (NCT04564703).



Abbreviations. PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; C6, cycle 6.

Figure 1.

Results. At the data cut-off (Sept. 29, 2023), 120 pts were enrolled, 40 in each cohort. In this analysis, we considered the 1.0 and 1.3 mg cohorts (the 0.75 mg cohort was initiated later, and mature data for this cohort have not yet been attained). Median age was 59 years, and 54% of pts were male. At diagnosis, 38% presented with International Staging System (ISS) stage 1 disease, 34% with ISS stage 2, and 28% with stage 3. High-risk disease (del(17p), t(4;14), or t(14;16)) was observed in 19% of pts. All pts received a PI/IMiD-containing induction regimen, which also included daratumumab in 39% of pts. Double ASCT was administered to 20% and post-ASCT consolidation to 9% of pts. Best response at the time of enrollment was PR in 12%, very good (VG)PR in 62%, complete response (CR) in 10%, stringent (s)CR in 15% [≥CR: 25%] in the 1.0 mg cohort, and PR in 7%, VGPR in 65%, CR in 10%, sCR in 17% [≥CR: 27%] in the 1.3 mg cohort. After 6 treatment cc, there was comparable deepening of response in both cohorts (1.0 mg cohort: PR 5%, VGPR 55%, CR 3%, sCR 38% [≥CR: 40%]; 1.3 mg cohort: PR 3%, VGPR 45%, CR 7%, sCR 45% [≥CR: 52%]). Response improvement was reported in 35% (90% CI 22-51%) of pts in the 1.0 mg cohort and in 42% (90% CI 28-58%) of pts in the 1.3 mg cohort (Figure 1) and was thus significantly higher than the null hypothesis of ≤20% response improvement within 6 mo. The most common grade ≥3 adverse events (AEs) during cc 1-12 were neutropenia (42% in the 1.0 mg and 50% in the 1.3 mg cohorts), infections (13% and 10%), fatigue/asthenia (10% and 15%). There were no grade ≥3 thrombocytopenia, anemia, diarrhea, or venous thromboembolism (VTE). Dose reductions during cc 1-12 were used to manage AEs in 38% of pts in the 1.0 mg and 45% in the 1.3 mg cohorts. Treatment discontinuation occurred in 6 pts in the 1.0 mg cohort (2 due to AE, 4 progressive disease [PD]) and in 10 pts in the 1.3 mg cohort (6 due to AE, 2 PD, and 2 death). PFS at 12 mo was 90% and 91% in the 1.0 and 1.3 mg cohorts.

Conclusions. Iberdomide represents a novel effective post-ASCT maintenance strategy, with a favorable safety profile and superior response improvement at 6 mo than what has been observed with lenalidomide maintenance (26% at 6 mo in the EMN02 study).

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ENHANCED DETECTION OF MINIMAL RESIDUAL DISEASE IN MULTIPLE MYELOMA THROUGH CD138 ENRICHMENT

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Background. Euroflow next-generation flow (NGF) cytometry sensitively assesses minimal residual disease (MRD) in multiple myeloma (MM), serving as a global standard for disease monitoring and treatment decision making. Despite Euroflow MRD diagnostic's widespread adoption in trials with advanced in anti-cancer approaches like BiTEs, CAR-T cells, and ADCs, challenges persist in aligning blood-based methods with bone marrow plasma cells (PC) analysis, necessitating heightened sensitivity to detect residual malignant cells post-therapy. The BloodFlow method, a recent innovation, achieves remarkable sensitivity up to 10^{-8} by enriching $CD138^+$ PCs from 50 mL peripheral blood, presenting a unique opportunity to enhance MRD evaluation. Therefore, this study compares conventional Euroflow BM-MRD with an ultrasensitive approach using CD138 enrichment of bone marrow cells before analysis.

Methods. BM-MRD followed Euroflow group guidelines. For ultrasensitive assessment, $CD138^+$ plasma cells were isolated using MACSprep™ CD138 MicroBeads and AutoMACS® Pro system.

Data analysis was performed with Infinicyt software. Automatic gate and identification tool was used for conventional MRD, while data was manually analyzed for ultrasensitive MRD assessment.

Results. We compared conventional and ultrasensitive MRD in bone marrow samples randomly collected of 128 MM patients. All positive MRDs identified using conventional NGF remained positive with the ultrasensitive MRD approach. Notably, among 71 patients with negative conventional NGF-MRD, 7 cases turned positive after ultrasensitive MRD. These included 5 newly diagnosed (ND) MM and 2 relapse refractory (RR) MM, with the ultrasensitive method detecting aPCs ranging from 0,00015 to 0,0018% in all nucleated cells in the bone marrow. From the ND cohort, patient 2, 3 and 6 had high-risk MM and patient 1 and 7 had standard risk cytogenetics. Patients were diagnosed between 2019 and 2022 (Table 1), treated with standard regimens during induction, followed by autologous stem cell transplantation, and were in CR at the time of ultrasensitive MRD. Further investigations, including FDG-PET/CT or WB-MRI studies, corroborated the absence of active myeloma manifestations, in aligning with the results from conventional MRD assessments. During consolidation therapy, patient 7 achieved VGPR, but after serological progress this patient was subjected to anti-BCMA CAR-T therapy. Currently, patients 1, 3, 6 and 7 remain in CR. Patient 2 displayed positive immunofixation with detectable M-protein in a follow up control 5 months after ultrasensitive MRD, but was then lost to follow-up. Patient 4 in PD (according to WBI-MRI) and patient 5 in CR at the time of ultrasensitive MRD, had penta-refractory multiple myeloma including an allogeneic hematopoietic cell transplant for patient 5 and anti-BCMA directed therapies (CAR-T and ADC respectively) for both patients as prior lines of therapy. Imaging results from WB-MRI studies of patient 4, showed several vital medullary myeloma manifestations, contradicting the results from conventional MRD method, but supporting the positive ultrasensitive MRD result. Two months later, this patient presented serological progress and relapsed.

Conclusions. Our study advocates for the adoption of CD138 enrichment in MRD assessment, as it provides heightened sensitivity at detection levels of 10^{-8} cells, allowing for the detection of residual malignant cells that may be missed by conventional methods. This approach holds promise in improving disease monitoring and treatment decision-making for MM patients, particularly in identifying those at risk of relapse or progression.

Table 1.

Table 1. Patient characteristics.

Patient	Age	Diagnosis	Cytogenetics	Therapy	Time from sampling to progression (months)	Time since ultrasensitive MRD (months)
1	59	2020	SR	Sampling after ASCT in 1st line of treatment prior Len maintenance	No serological progression	12
2	76	2021	HR	Sampling after ASCT in 1st line of treatment prior Lenalidomide maintenance	5	11
3	53	2022	HR	Sampling after ASCT in 1st line of treatment prior Len maintenance	No serological progression	11
4	72	2016	SR	Sampling following CAR T (ABECMA) in 6th line of therapy	3	9
5	49	2014	SR	Sampling following Talquetamab in 11th line of therapy	2	7
6	65	2022	HR	Sampling after ASCT in 1st line of treatment prior Len maintenance	No serological progression	7
7	80	2019	SR	Sampling after CAR T (ABECMA)	No serological progression	1

EARLY RESULTS OF TANDEM AUTOLOGOUS STEM-CELL TRANSPLANTATION AFTER DARATUMUMAB VTD INDUCTION IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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Background. Newly diagnosed multiple myeloma patients with high-risk features (HR-NDMM) still have inferior outcomes despite the introduction of anti-CD38 monoclonal antibodies in frontline treatment. Whereas CASSIOPEIA trial included Daratumumab/Bortezomib/Thalidomide/Dexamethasone (Dara-VTd) induction followed by single autologous stem-cell transplantation (ASCT) and consolidation, previous studies clearly showed a survival advantage with tandem ASCT in HR-NDMM and several ongoing trials still include tandem ASCT after anti-CD38-based quadruplet induction.

Methods. we report a retrospective collaborative multicenter analysis of HR-NDMM who underwent tandem ASCT following Dara-VTd induction as per clinical practice. Criteria for definition of HR-NDMM included either the presence of high-risk FISH abnormalities as del17p13, t(4;14), t(14;16), gain/ampl1q21, advanced disease stage (R-ISS stage 3, R2-ISS stage 3-4), extramedullary disease (EMD) or less than complete response (CR) after I ASCT.

Results. From 1st December 2021 to 30th September 2023, 40 HR-NDMM consecutively received Dara-VTd induction followed by tandem ASCT at our institutions. Median age at diagnosis was 52 years (range: 32-70), 15% were R ISS 3 and 35% were R2-ISS 3-4. Twenty-two patients (55%) had high-risk FISH abnormalities and 3 patients (8%) had EMD. After a median of 4 Dara-VTd cycle (range: 4-6) overall response rate (ORR) was 100%, with 40% VGPR and 31% CR/sCR. Patients underwent stem-cell mobilization with cyclophosphamide and G-CSF, followed by leukapheresis. Median total amount of collected stem-cells was $10{,}3x10^6$ CD34+cells/kg (range: 6,5-34); 33% required Plerixafor. After a median of 207 days from start of induction (range: 168-310), 40 patients underwent I ASCT. Median number of infused CD34+cells was $4{,}6x10^6$/kg (range: 2,6-8). Neutrophils and platelets engraftments were obtained after a median of 12 days (range: 9-14) and 15 days (range: 7-21), respectively. Transplantation characteristics and toxicities are reported in Table 1. After I ASCT, response rates deepened, with 38% VGPR and 55% CR/sCR. After a median of 129 days from I ASCT (range: 82-242), 40 patients underwent tandem ASCT because of either high-risk FISH abnormalities (n=17; 42%), advanced disease stage (n=3, 8%), EMD (n=2, 5%), less than CR after I ASCT (n=12, 30%) or other (n=6, 15%). Median number of infused $CD34^+$cells was 4,6 x106/kg (range: 2,1-8,5). Patients obtained stable neutrophils and platelets engraftments after a median of 11 days (range: 7-14) and 14 days (range: 7-22), respectively. Transplantation characteris-

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tics and toxicities are reported in Table 1. Response rates further improved after tandem ASCT, with 25% VGPR and 68% CR/sCR. Twenty patients (50%) also received 2 cycles of Dara-VTd consolidation without relevant toxicities, whereas 30 patients (75%) already started maintenance. At last disease assessment, one patient had disease progression and ORR was 98% (VGPR 20% and CR/sCR 76%). After a median follow up of 573 days (range: 350-745), all patients were alive.

Conclusions. For the first time to our knowledge and in real-life setting, tandem ASCT proved feasible in HR-NDMM who received Dara-VTd induction. Transplantation outcomes were favorable, with both limited hematological and non-hematological toxicities. Although longer follow-up is required to further elucidate its benefit, tandem ASCT proved effective to increasing the depth of response in HR-MM.

Table 1.

Table 1. Characteristics of autologous stem-cell transplantations (ASCT)

	I ASCT	II ASCT
Days from start of induction to ASCT: median (range)	207 (168-310)	342 (279-453)
Conditioning regimen: n (%)		
– Melphalan 200 mg/m^2	37 (92%)	37 (92%)
– Melphalan 140 mg/m^2	3 (8%)	3 (8%)
Number of infused CD34+cells x10^6/kg: median (range)	4,6 (2,6-8)	4,6 (2,1-8,5)
Days to neutrophils engraftments: median (range)	12 (9-14)	11 (7-14)
Days to platelets engraftments: median (range)	15 (7-21)	14 (7-22)
Bacterial adverse events: n (%)		
– Febrile neutropenia (grade 3)	12 (30%)	7 (18%)
– Sepsis (grade 3)	2 (5%)	4 (10%)
– Pneumonia (grade 3)	0 (0%)	4 (10%)
– Soft tissue infection (grade 2)	1 (2%)	0 (0%)
– Urinary tract infection (grade 2)	1 (2%)	1 (2%)
Viral adverse events: n (%)		
– CMV viremia (grade 2)	4 (10%)	3 (7%)
– CMV viremia (grade 3)	0 (0%)	1 (2%)
– HHV6 viremia (grade 2)	0 (0%)	2 (5%)
– Respiratory syncytial virus infection (grade 2)	0 (0%)	1 (2%)
Fungal adverse events: n (%)		
– Probable IFI (grade 3)	0 (0%)	1 (2%)
– Candidemia (grade 3)	0 (0%)	1 (2%)
Other adverse events: n (%)		
– Atrial fibrillation (grade 3)	2 (5%)	2 (5%)
– Pulmonary edema (grade 3)	0 (0%)	1 (2%)
– Deep vein thrombosis (grade 2)	0 (0%)	1 (2%)
Late hematological adverse events: n (%)		
– Neutropenia (grade 3)	0 (0%)	1 (2%)
– Platelet count decreased (grade 3)	0 (0%)	1 (2%)

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MOBILISATION OF HEMATOPOIETIC STEM CELLS WITH G-CSF BEFORE AUTOLOGOUS STEM CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH DVRD VERSUS DVTD

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Autologous stem cell transplantation (ASCT) is the standard of care in transplant-eligible newly diagnosed multiple myeloma patients. Mobilization of hematopoietic stem and progenitor cells (HSPCs) is a requirement for high-dose melphalan followed by ASCT. Previously this was accomplished through cyclophosphamide priming followed by granulocyte colony-stimulating factor (G-CSF), however during the COVID pandemic patients received G-CSF alone without cyclophosphamide priming. Mobilization with G-CSF alone did not result in a lower success rate in patients treated with Bortezomib, Thalidomide and Dexamethasone (VTd) or Bortezomib, Lenalidomide and Dexamethasone (VRd). Since 2022 Daratumumab, Bortezomib, Thalidomide and Dexamethasone (DVTd) was approved and reimbursed. In January 2023 Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) was reimbursed as first-line treatment in the Netherlands. In this retrospective analysis, we analyzed a clinical database of 48 newly diagnosed multiple myeloma patients who underwent HSPC mobilization in 2023. We compared mobilization results using only G-CSF in patients treated with either DVRd (n=25) or DVTd (n=23). We observed a failure to mobilize any HSPCs in 24% of DVRd treated patients while there were no failures to mobilize HSPCs in DVTd patients. The number of CD34+ cells after one day of mobilization and in total was significantly reduced in DVRd treated patients compared to DVTd treated patients. Moreover, the need for plerixafor use was strongly increased in DVRd patients (48%) compared to DVTd (17%). From this analysis we observe that patients treated with DVRd have a lower success rate in HSPC mobilization with G-CSF alone compared to DVTd patients, with a higher need of plerixafor use. More data will be added to the analysis and presented at the meeting.

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PROGNOSTIC IMPACT OF T(11;14) IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA

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Translocation t(11;14) has emerged as a crucial genetic aberration and is one of the most common primary translocations in multiple myeloma (MM). One of the key features linked with t(11;14) is the BCL2 dependency, which is a druggable target with BCL2 inhibitors such as venetoclax. In the era of the novel anti-myeloma agents, the exact prognostic role of t(11;14) remains to be determined. We analyzed data from 1011 consecutive patients with newly diagnosed MM (NDMM), who were diagnosed and treated in the Department of Clinical Therapeutics, Athens, Greece, from 1997 to 2023. The data are prospectively collected and maintained in our institution's database. An approval for the analysis and data publication was obtained by the institutional ethics committee. All patients were tested for t(11;14) at diagnosis using standard fluorescent in-situ hybridization in CD138+ selected cells. Positivity was defined as at least 20% of clonal cells harboring t(11;14). The presence of +1q21, t(4;14), t(14;16), del(17p), del(13q), were also determined by FISH at the time of diagnosis. At the time of diagnosis, 89 out of 1011 patients (8.8%) had the t(11;14), whereas 922 (91.2%) were negative. The median age was 68 years for both subgroups (range 37-88 and 34-93, respectively), whereas 42 (47%) and 502 (54%) were males (p=0.35), respectively. Overall, patients with t(11;14) did not have a statistically significant difference in progression-free survival (PFS) compared with those who did not had t(11;14) [hazard ratio (HR) 1.25, 95% confidence interval (CI) 0.92-1.70, p=0.15]. As anticipated, patients with no cytogenetic abnormalities at diagnosis had superior PFS compared with those who were positive for t(11;14) (HR 1.41, p=0.04) or any other cytogenetic aberration (HR 1.39, p=0.001). Interestingly, patients with isolated positivity for t(11;14) did not have a statistically significant difference in PFS compared with those

without any abnormalities (HR 1.28, 95%CI: 0.81-2.03, p=0.282). However, patients with t(11;14) and at least another cytogenetic abnormality had inferior PFS (HR 1.38, p=0.001). More specifically, those with t(11;14) and del17p (HR 3.74, 95%CI: 1.53-9.17, p=0.004) and those with t(11;14) and 1q21 amplification/addition (HR 1.67, 95%CI: 1.00-2.78, p=0.05) had particularly dismal outcomes. Similarly, there was no statistically significant difference in overall survival (OS) between patients with and without t(11;14) (HR 1.31, 95%CI: 0.86-2.00, p=0.21). However, patients who had at least an additional cytogenetic abnormality had inferior OS (HR 1.68, p<0.001). Furthermore, patients with t(11;14) had inferior OS compared with those without any aberrations (HR 1.62, 95%CI: 1.03-2.55, p=0.04). Interestingly, patients with isolated t(11;14) did not demonstrate inferior OS compared with those without any abnormalities (HR 0.61, 95%CI: 0.22-1.67, p=0.33). However, the co-presence of del17p (HR 6.03, 95%CI 2.20-16.52, p<0.001) or 1q21 amplification/addition (HR 2.51, 95%CI: 1.30-4.86, p=0.006) with t(11;14) had a detrimental impact on OS. In conclusion, isolated t(11;14) in patients with NDMM does not seem to be a marker of adverse prognosis, whereas the presence of other high-risk cytogenetic abnormalities confer dismal outcomes. For the latter patient subgroups, BCL-2 targeted therapies represent a promising treatment approach that had to be validated in future studies.

P14

IMMUNE CELL LANDSCAPE WITHIN THE BONE MARROW: A ROADMAP FROM MGUS TO ACTIVE MULTIPLE MYELOMA AND TREATMENT RESPONSIVENESS

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Monoclonal gammopathy of undetermined significance (MGUS) is recognized as a benign precursor condition that may potentially evolve into a multiple myeloma (MM). Predicting the progression of MGUS to MM or determining the stability of the condition at the time of diagnosis is notably challenging. Over the past decade, researchers have shown increased interest in identifying the initiating biological events of MGUS and exploring the sequential immunological alterations associated with progression and resistance to immunotherapy. In this study, we aimed to investigate the composition of immune cells within the bone marrow (BM) of patients with monoclonal gammopathies at various stages and correlate our findings with clinical behavior. Utilizing FlowCT, a semi-automated bioinformatic pipeline for analyzing large datasets, we compared the immune compartment in the BM of 9 MGUS, 14 smoldering MM (SMM), and 83 MM patients, all stained with two commercial diagnostic tubes. Among the MM patients, 65 had treatment data available, and 43 of them received a daratumumab-based regimen (in combination with RD, VTd, or VMP). Disease progression was marked by a significant reduction in BM granulocytes (mean, 74.71% MGUS *vs.* 72.37% SMM *vs* 62.83% MM, p<0.05) and in the BM granulocytes-to-lymphocytes ratio (NLR) (mean, 12.86% MGUS *vs.* 19.50% SMM *vs.* 9.07% MM, p<0.05), coupled with an increase in T cells (mean, 6.59% MGUS *vs* 6.43% SMM *vs* 10.72% MM, p <0.05). Final progression to MM was linked to a reduction in CD38- CD28+ CD27- CD81+dim T cells, CD28- CD117-, CD28- CD117+, and CD28+ CD117+ monocytes (p<0.05). Subsequently, we assessed the progression-free survival (PFS) among MM patients based on identified BM immune cell populations. An increased presence of granulocytes (>64.5%, median value) was associated with an improved PFS (HR=0.33 (95% CI: 0.11 to 1); log-rank test, p<0.05), resulting in 1-year PFS rates of 80% (vs 65% in patients with < 64.5% BM granulocytes). Similar results were found for BM NLR and granulocyte-to-T lymphocyte (NTL) ratio (HR=0.30 (95% CI: 0.10 to 0.95) and HR=0.31 (95% CI: 0.11 to 0.86) respectively; log-rank test: p<0.05), but not for peripheral blood NLR. When focusing on specific treatment groups, these results were notably influenced by the association of neutrophil and lymphocyte composition with the response to anti-CD38 therapies. Indeed, improved outcomes were observed in patients treated with anti-CD38-based regimens with an NTL ratio above the median (HR=0.18 (95% CI: 0.04 to 0.71); log-rank test, p<0.05). Based on these findings, we hypothesized the involvement of BM granulocytes in the mechanism of action of anti-CD38. To explore this, cytotoxicity assays were performed on BM mononuclear cells (BMMCs) from MM patients (n=4), with the increasing addition of autologous BM-derived granulocytes, in the presence or absence of daratumumab. Compared to BMMCs alone, a significant increase in daratumumab-mediated cytotoxicity (45.7% *vs.* 61.5% induced mortality respectively) was observed when BM-granulocytes were added. Neutrophils obtained from peripheral blood were unable to exert cytotoxicity against MM cell lines, demonstrating a BM-granulocytes-dependent mechanism. In summary, this study identifies a specific BM immune composition as predictive of MM evolution from MGUS and the response to anti-CD38 therapy. A new BM-granulocytes-dependent mechanism of action for daratumumab in MM patients has been identified.

P15

EXPLORING CLINICAL FEATURES THAT COULD PREDICT FUNCTIONAL HIGH RISK MULTIPLE MYELOMA PATIENTS: A REAL-WORLD ANALYSIS

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High-risk MM patients, according to Revised International Staging System (R-ISS), have a dismal outcome in terms of PFS and OS. Nevertheless, despite they are not classified as high-risk and having received optimal initial therapy, some patients have poor prognosis, with a PFS shorter than 12-18 months. This group of patients, at functional (dynamic) high-risk (FHR), represents approximately 10-20% of patients in several trials. Really, these patients could be statically identified by genomics or dynamically with MRD assessment. Nevertheless, these methods are not routinely applied in clinical practice due to several reasons. Therefore, clinically identifying these FHR patients represents an unmet medical need. The aim of this study was to describe and compare characteristics of MM patients who were no HR as per R-ISS but had a suboptimal PFS (< 12-18 months) with those of patients with longer PFS. To be defined as a dismal outcome, we chose a PFS cut-off value ≤ 18 months for patients eligible for ASCT (TE) and ≤ 12 months for not-transplant eligible patients (NTE). Kaplan-Meier curves were compared by log-rank test. Clinical factors affecting suboptimal PFS as above classified were searched with logistic regression univariate and multivariate analysis. Overall, among MM patients included in our database

who underwent first line therapy, 271 relapsed after a median follow-up of 56 months. Out of 271 patients, 93 were TE and 178 NTE.

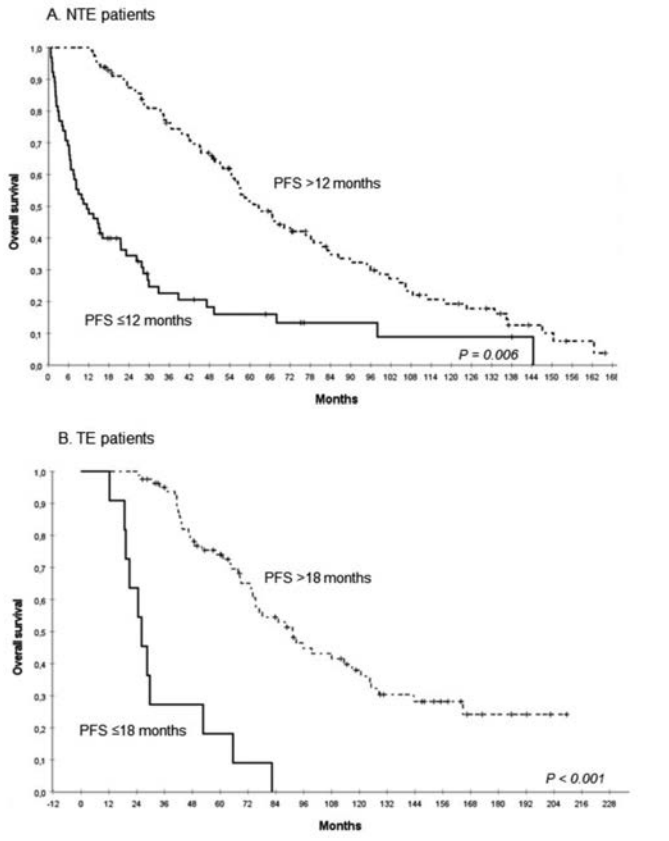

Figure 1.

Regardless of baseline R-ISS stage, 11 TE patients (12%) had a PFS ≤ 18 months and 65 NTE patients (36.5%) had a PFS < 12 months. OS was 91 *vs* 26 months in TE patients having a PFS of > 18 months *vs* shorter, respectively (p<0.001); moreover, it was 48.5 *vs* 11.4 months in NTE having PFS > 12 months *vs* shorter, respectively (p= 0.006) (Figure 1). PFS2 was 20.6 *vs* 56 months in TE (p=0.001) and 16.3 *vs* 42.5 months in NTE, respectively (p=0.002). Out of 47 patients without HR R-ISS stage having PFS ≤ 12 months, 5 (18.5%) was R-ISS low-risk (LR) and 42 (36%) was intermediate-risk R-ISS (IR). In TE group without HR R-ISS stage having PFS ≤ 18 months, 1 (3%) was LR and 8 (16%) was IR R-ISS. The clinical characteristics of these 56 patients with low-intermediate R-ISS stage having poor outcome were compared to the 172 patients with the same R-ISS stage having better outcome according to above definition. Univariate analysis showed as significant factors affecting the worse outcome an ECOG PS ≥ 2 (p=0.106), platelets count <150x10^6/L (p=0.001), renal failure (p=0.181), no continuous therapy (p=0.001) and response to therapy < VGPR (p<0.001). Multivariate analysis selected platelets count <150x10^6/L (OR= 5.1; 95%CI= 1.8-14.4; p=0.002), no continuous therapy (OR= 8.7; 95%CI= 2.4-31.7; p=0.001) and response to therapy < VGPR (OR= 10.9; 95%CI= 4.7-25.1; p<0.001) as factors affecting suboptimal PFS. Our results confirm that at least 20% of patients considered not at high-risk as per R-ISS could have poor outcome after first-line therapy. Our analysis showed that patients at L-I R-ISS stage should be evaluated statically for platelet count at the beginning of first-line therapy, being those with low platelets count at higher risk of suboptimal PFS. Moreover, being fixed therapy and response < VGPR two dynamical parameters to define FHR, continuous therapy and deep response should be considered the goals also in patients with L-I R-ISS risk in order to have the highest probability of achieving an optimal PFS.

P16

EFFICACY AND SAFETY OF IDECABTAGENE VICLEUCEL (IDE-CEL) WITH LENALIDOMIDE (LEN) MAINTENANCE VERSUS LEN MAINTENANCE ALONE IN ADULT PATIENTS (PTS) WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM) WHO HAVE SUBOPTIMAL RESPONSE TO AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT): PHASE 3 KARMMA-9 TRIAL

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Introduction. Despite advances in treatment (Tx) options for transplant-eligible NDMM with triplet and quadruplet induction Tx including immunomodulatory (IMiD®) agents, proteasome inhibitors (PI), and anti-CD38 antibodies followed by ASCT, pts who achieve <CR post-ASCT have poorer prognosis than pts who achieve ≥CR. LEN maintenance post-ASCT is the standard of care in NDMM, but risk of disease progression is higher in pts who have a suboptimal response to ASCT. Therefore, Tx optimization is warranted to reduce residual disease post-ASCT and extend duration of response in these clinically high-risk pts. Ide-cel, a BCMA-directed chimeric antigen receptor (CAR) T cell therapy, significantly improved median progression-free survival (PFS) and overall response rate *vs* standard regimens in pts with triple-class-exposed early line relapsed and refractory MM (Rodríguez-Otero. *NEJM* 2023). Ide-cel also demonstrated deep and durable responses in pts with NDMM who had inadequate response to frontline ASCT in cohort 2c of the phase 2 KarMMa-2 trial at a median follow-up of 39.4 months (Dhodapkar. ASH 2023). Of 8 pts who received LEN maintenance after ide-cel at investigator's discretion in this cohort, 6 achieved ≥CR and 2 achieved very good partial response (VGPR); none experienced progressive disease (PD) or death at data cutoff and the safety profile of LEN maintenance after ide-cel was favorable. There were no second primary malignancies in pts who received LEN maintenance after ide-cel. In the multicenter, randomized, controlled, phase 3 KarMMa-9 trial (NCT06045806), we will compare the efficacy and safety of ide-cel+LEN maintenance *vs* LEN maintenance in adults with NDMM who had suboptimal response (PR or VGPR) to ASCT.

Methods. Eligible pts are adults with NDMM who have received 4–6 cycles of induction Tx, including an IMiD agent and a PI, followed by high-dose chemotherapy and a single ASCT, and have achieved PR or VGPR post-ASCT. Pts must not have had PD since commencing induction and must not have received consolidation or maintenance Tx. Approximately 618 pts will be randomized 1:1 to receive ide-cel+LEN maintenance or LEN maintenance (Figure 1). Randomization will be stratified by revised International Staging System stage III disease at diagnosis (yes *vs* no/unknown), anti-CD38 induction (yes *vs* no), and response post-ASCT (VGPR *vs* PR). Pts randomized to the ide-cel+LEN arm will receive 1 cycle (28d) of LEN at 10mg daily ≤7d after randomization followed by leukapheresis (14-42d after last dose of LEN) and lymphodepleting chemother-

apy prior to ide-cel infusion. Ide-cel target dose range is 300-460 x 10^6 CAR+ T cells. LEN maintenance will resume as early as 1 month after ide-cel infusion, contingent on blood cell count recovery. For the first LEN cycle post-infusion, pts will receive 5mg LEN once daily; if well tolerated, LEN will be administered per prescribing information at the next cycle. Pts randomized to LEN maintenance will receive LEN at the dose indicated by prescribing information until PD or unacceptable toxicity. The primary endpoint is PFS, per Independent Review Committee (IRC). The key secondary endpoint is overall survival. Other secondary endpoints include sustained minimal residual disease (MRD)-negative CR for 12 months, MRD-negative CR rate, event-free survival, duration of response, CR rate by IRC, time to progression by IRC, PFS on next line of Tx, safety, pharmacokinetics, and health-related quality of life.

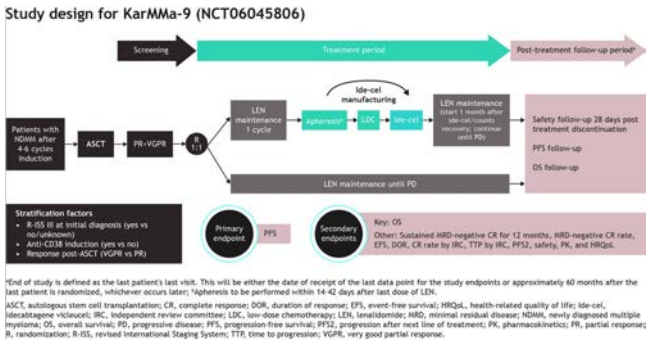

Figure 1.

P17

PROFILE AND OUTCOME OF MULTIPLE MYELOMA WITH AND WITHOUT HIV TREATED AT A TERTIARY HOSPITAL IN KWAZULU-NATAL, SOUTH AFRICA

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Objectives. To profile the outcome of multiple myeloma (MM) patients treated at a South African tertiary hospital in KwaZulu-Natal (KZN) and to compare MM in HIV-negative patients and MM in people living with HIV (PLWH).

Methods. A retrospective analysis of patients with MM was conducted over 5 years (2015-2020). Patient demographics, presenting complaints, symptom duration, disease stage, molecular profile, treatment, and survival data were captured. Statistical analysis was conducted using R Statistical software of the R Core Team, 2020, version 3.6.3.

Results. 135 patients; 79% (n=106) HIV-negative and 21% (n=29) PLWH were investigated. 54% (n=74) females and 57% (n=76) 51-70-year-olds. The 40-50-year-old patient group had a significantly higher proportion of PLWH (p=0.032). Pathological fractures were the commonest presenting complaint, 47% (n=57 and 49% (n=49) had International Staging System, stage III disease. Fluorescent *in situ* hybridization (FISH) MM profiling was completed in 58% (n=78). Positivity for del 11q22 was found in 23.7% (n=14) with significantly more HIV-negative patients having the mutation (p=0.027). Overall, 42.2% (n=57) achieved 2-year overall survival (OS). There were no significant differences in treatment (p=0.926) and 2-year survival outcome (p=0.792) between the two groups.

Conclusions. The incidence of HIV in newly diagnosed MM patients in KZN was increasing. KZN patient profile differed from other reports by showing female predominance but was similar in advanced-stage presentation and bone fracture predominance. Statistically significant differences between the HIV-negative patients and PLWH were observed in age distribution and mutational landscape. Further studies are required in this area.

P18

REAL-WORLD DATA WITH LENALIDOMIDE AS MAINTENANCE THERAPY FOR PATIENTS WITH MULTIPLE MYELOMA AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION: THE EXPERIENCE OF THE "RETE EMATOLOGICA PUGLIESE" (REP)

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Based on the results from four prospective, randomized clinical trials and a large metanalysis, lenalidomide maintenance (LM) therapy until progression or unacceptable toxicity is still considered the current standard of treatment after autologous stem cell transplantation (ASCT) in patients with multiple myeloma (MM). However, real-life evidence of the advantage of LM after ASCT, in terms of progression-free survival (PFS), overall survival (OS) and safety, is quite limited. Thus, we investigated the role of LM in a homogeneous Italian population landscape, by evaluating a series of 257 MM patients not included in clinical trials who underwent ASCT between 2001 and 2020 and treated within the "Rete Ematologica Pugliese" (REP), a network including nine hematology centers active in the Apulia region, in Southern Italy. One-hundred-seven of these patients received LM (LM cohort) after ASCT (10 mg/d for 21-28 days, every 4 weeks), administered for a median time of 19.5 months (range 1-118 months), while the remaining 150 patients did not (non-LM cohort). Age, gender, M-component isotype, comorbidities, ISS stage (R-ISS when available), renal function, serum calcium, hemoglobin levels, cytogenetics, induction treatments (all including bortezomib based regimens, such as VTD, VCD or PAD), conditioning regimens and number of ASCT (1 *vs* 2), were comparable between the two groups. A center-based decision represented the main factor to treat patients with a single or a double ASCT. According to the IMWG criteria, the overall response rate (ORR) after ASCT was 98% in both groups and no difference emerged, in terms of quality of response, between LM group (CR+sCR 47%; ≥VGPR 90%; PR 8%) and non-LM group (CR + sCR 45%; ≥VGPR 89%; PR 9%) (p: NS). With a median follow-up of 47 months (range:13-144) in LM group and 67 months (range: 9-167) in non-LM group, median PFS was significantly longer in the LM cohort (72 *vs* 36 months; P<0.001) (Figure 1). Similarly, median OS was also significantly better in patients receiving LM (142 *vs* 108 months; p=0.01) (Figure 2). ISS stage, induction treatments and number of ASCT (1 *vs* 2) did not influence neither PFS, nor OS. Main adverse events observed in LM-group were leucopenia, skin rashes and diarrhea; they were generally well managed by dose adjustment of lenalidomide and caused the interruption of maintenance before the progression of the disease in a minority of patients. Three secondary primary malignancies (SPM) occurred in the LM-group (one acute myeloid leukemia, one colon carcinoma and one bladder carcinoma). In summary, in our retro-

spective study LM was well tolerated, doubled PFS and significantly improved OS, validating its positive impact in a real-world setting of MM patients who underwent ASCT in the era of novel agents. A slight excess of SPM was also observed. However, the therapeutic scenario of MM is rapidly changing and, in the setting of transplant eligible patients, achievement of sustained measurable residual disease and the use of daratumumab in the induction treatment have substantially modified the objectives and the potential effects of possible novel maintenance therapies with daratumumab as single agent or combined with lenalidomide, or those of other associations, such as carfilzomib plus lenalidomide, as reported in recently published CASSIOPEIA, PERSEUS and FORTE studies, respectively.

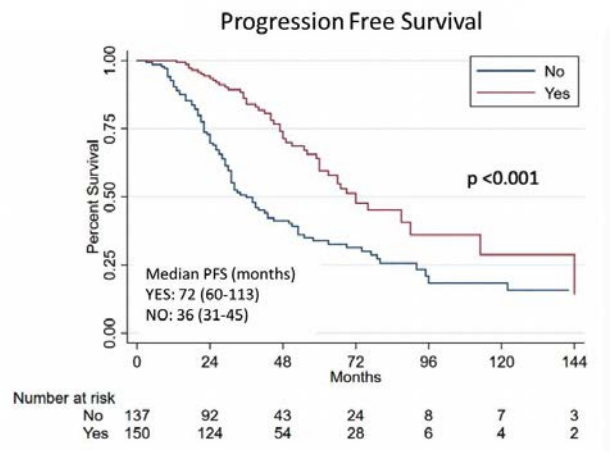

Figure 1

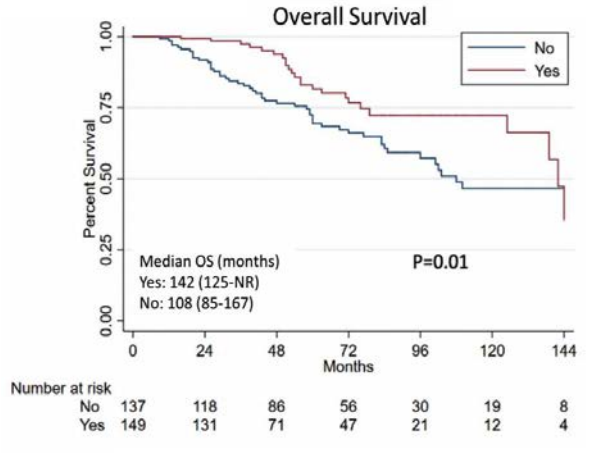

Figure 2

Figures 1 and 2.

P19

IMPACT OF DARATUMUMAB ON HEMATOPOIETIC STEM CELL MOBILIZATION WITH G-CSF AND ON-DEMAND PLERIXAFOR IN NEWLY-DIAGNOSED MULTIPLE MYELOMA PATIENTS

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Introduction. Autologous stem cell transplantation (ASCT) is a SOC in transplant eligible, newly diagnosed Multiple Myeloma (NDMM) patients (pts). Patients treated with upfront daratumumab who underwent chemotherapy-based hematopoietic stem-cell (HSC) mobilization had lower hematopoietic stem cell (HSC) yield and higher rates of plerixafor (PLX) use as compared to daratumumab-naïve pts. We report the results of a multicentre, observational study, aiming to evaluate HSC collection and engraftment with G-CSF+on-demand PLX in pts treated with VTd or VTd plus daratumumab (DVTd).

Methods. NDMM pts undergoing a 1st HSC mobilization attempt with G-CSF (10 mcg/kg/day) were enrolled. PLX was administered in patients with <20 $CD34^+$ cells/μL after ≥4 days of G-CSF or in case of $<1\times10^6$ $CD34^+$ cells/kg collected on the 1st apheresis day. The primary endpoint of the study was the rate of poor mobilizing pts defined as $\leq2x10^6$ $CD34^+$ cells/Kg collected or need for PLX to reach adequate HSC yield.

Results. 217 NDMM pts, (DVTd, n=83, VTd, n=134) were enrolled in 2 Italian centres (IRCSS Istituto Clinico Humanitas and Città della Salute e della Scienza di Torino) and analysed. The median number of induction cycles was 4 in both groups. The rate of poor mobilizing patients was 64% (53/83) in the DVTd and 30% (40/134) in the VTd group (p=0.002), due to a higher rate of PLX use in the DVTd group compared to the VTd one (56.6% *vs* 26.1%; p=0.007), without significant differences in the rate of pts who failed to collect $\geq2x10^6$ $CD34^+$ cells/kg (7.2% *vs* 3.7%; p=0.6). The median number of CD34+/Kg collected was similar in the DVTd (7.04) and VTd group (7.84; p=0.1). No difference in the rate of pts who collected 2-4 (5% *vs* 6%; p=0.7) and ≥4 $CD34^+$ cells/Kg (88% *vs* 92%; p=0.4) was observed in the DVTd and VTd groups. The median number of CD34+/L on the first day was lower in the DVTd as compared to the VTd group (18 *vs* 24; p=<0.002). The median increase of CD34+/L after the 1st PLX dose was 45 $CD34^+$/μL in the DVTd group and 55 CD34+/μL in the VTd group (p=0.4). No significant differences were observed in the median number of apheresis between the DVTd and VTd groups (2 *vs* 1; p=0.6). A second mobilization was attempted in 17 pts (8%, 9 in the DVTd arm and 8 in the VTd arm) with either Cy+G-CSF (8 pts) or G-CSF only (4 pts). Of these, 16 (94%) pts successfully collected $\geq2x10^6$ $CD34^+$ cells/kg. 51 pts in the DVTd and 57 in VTd group received post-transplant G-CSF starting at day +3 to 5; the median number of $CD34^+$/kg re-infused was 3.28 and 3.63, respectively (p=0.4). The time to neutrophil recovery was 12 and 13 days in both groups (p=0.02) and the median time to platelet recovery was 13 and 15 days in the DVTd and VTd groups, respectively (p=0.1).

Conclusions. GCSF+on-demand PLX is an effective HSC mobilization strategy resulting in low rates of mobilization failures irre-

spective of the use of daratumumab during induction. Despite a higher PLX use, upfront daratumumab did not negatively impact neither the possibility to achieve an optimal HSC collection nor the HSC engraftment. Our results, along with the lack of chemotherapy-associated toxicity, support the use of G-CSF and on-demand PLX for HSC mobilization in pts receiving daratumumab upfront.

Table 1. Mobilization characteristics and harvesting outcomes.

Variables		D-VTd	VTd	p
Poor mobilizing N (%)	No	30 (36%)	94 (70%)	0.002
	Yes	53 (64%)	40 (30%)	
PLX administration N (%)	No	36 (43.4%)	99 (73.9%)	0.007
	Yes	47 (56.6%)	35 (26.1%)	
Successful mobilization N (%)	No	6 (7.2%)	5 (3.7%)	0.56
	Yes	77 (92.8%)	129 (96.3%)	
CD34+ cells/µL on the first day of count	Median	18	24	<0.001
CD34+ cells/µL increase after first PLX administration	Median	45	55	0.4
CD34+ cells/Kg	Median	7.04	7.84	0.08
Optimal collection	Optimal * N (%)	73 (88%)	123 (92%)	0.4
Suboptimal collecion	Suboptimal** N (%)	4 (5%)	8 (6%)	0.7
Apheresis sessions	Median	2	1	0.6

*PLX, plerixafor. * Optimal collection: Total HSC collected over 4 $CD34^+$/Kg, **Suboptimal collection: Total HSC collected between 2 and $4x10^6$ CD34/Kg*

P20

EFFICACY AND SAFETY OF DARATUMUMAB-BASED COMBINATION THERAPIES IN TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: A REAL-LIFE POPULATION ANALYSIS ACCORDING TO IMWG FRAILTY SCORE

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Introduction. daratumumab combinations with lenalidomide and dexamethasone (DRD) and with bortezomib, melphalan and prednisone (DVMP) represent current effective treatment options for transplant-ineligible (NTE) newly diagnosed multiple myeloma (NDMM) patients, based on the results of MAIA and ALCYONE trials. However, few data are available in real- life populations outside clinical trials, raising the question of how much the addition of daratumumab can really provide a long-term benefit even in frail older patients. With this aim, we present our single center experience since the Italian approval of the two regimens.

Patients and Methods. We retrospectively analyzed the outcome of 89 unselected NTE NDMM patients (median age 75 years) diagnosed at our institution from April 2021 to September 2023 and treated with DRD or DVMP. Response rates, progression free survival (PFS), overall survival (OS) and safety were analyzed. The International Myeloma Working Group (IMWG) frailty score was also evaluated: due to the small number of fit patients, we merged fit and intermediate-fit into "non-frail" category and compared the outcome according to frailty status.

Results. Out of 89 patients, 22 (24.7%) were ISS stage 3 and 33 (37%) showed high risk cytogenetics. According to IMWG frailty score, 2 (2.2%) patients were stratified as fit, 53 (59.5%) intermediate-fit and 34 (38.2%) as frail. Seventy-two (81%) patients were treated with DRD, of which 39% were frail, whereas 17 (19%) patients received DVMP, of which 41% were frail. Dose reduction of lenalidomide, dexamethasone, melphalan and prednisone, as well as once-weekly bortezomib administration were applied upfront at the beginning of treatment in 48% of the overall cohort and in 100% of frail patients according to clinical judgement. Overall response rate was 86.5% (≥ VGPR 69.7%, CR 19.1% and sCR 1%). After a median follow up of 18 months, the median PFS and OS were not reached in the overall population (2-year PFS: 86%, 2-year OS: 97%). Two-year PFS was 86% and 80% in patients treated with DRD and DVMP, respectively, with no significant difference between the two cohorts. No difference in PFS and OS was observed between non-frail and frail patients (2- year PFS 88% *vs* 84%, p 0.28; 2-year OS 100% *vs* 94%, p 0.07). The most frequent grade ≥3 adverse events (AEs) were neutropenia (43%) and pneumonia (12%); infections of any grade occurred in 49% of patients, with recurrent infections observed in 8% of cases. Temporarily drug discontinuation due to AEs occurred in 53% of patients, of which 49% were frail. Overall, rates of AEs were comparable between frail and non-frail patients within the two treatment cohorts, except for increased infections observed in frail patients respect to non-frail patients treated with DVMP (72% *vs* 20%, p 0.04).

Conclusions. We confirmed the efficacy of DRD and DVMP in a real-life population of NTE NDMM patients, with no new safety concerns. The IMWG frailty score can help the physician in applying a dose reduction strategy, which could allow obtaining a comparable long-term outcome between frail and non-frail patients in clinical practice by reducing severe toxicities and treatment discontinuations. Longer follow up is needed in order to confirm our preliminary data.

P21

IDENTIFICATION OF CLINICAL-BIOLOGICAL FEATURES OF NEWLY DIAGNOSED EARLY RELAPSE MULTIPLE MYELOMA PATIENTS ELIGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION

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Despite the introduction of new therapeutic regimens, the proportion of newly diagnosed multiple myeloma (NDMM) transplant-eligible patients relapsing early after first-line treatment is stable over time at about 15-20% with a median overall survival (OS) less than 3 years. Consequently, clinical and/or biological features that could identify early relapse (ER) patients at diagnosis represent an unmet medical need. In the literature, multicenter studies identified possible predictive markers for ER, however, most of them lacking to report cytogenetic data with the limitations of the different cut-offs used to identify MM patients with high-risk cytogenetic features. Our study is a retrospective-observational and single center study analyzing a cohort of 74 NDMM consecutive patients eligible for high dose therapy that underwent upfront autologous stem cell transplantation (ASCT) between 2011 and 2021. The end point of the study included the assessment of predictive markers for ER defined as a progressive disease that occurred within 18 months from autologous stem cell transplantation (ASCT) in patients who did not have primary refractory disease. All 74 NDMM patients included in the study received an intensive therapy with either a doublet-based induction (n=7, 9.5%) including PI or a triplet-based (n=67, 90.5%) including a PI and an IMiD. A total of 19 (25.5%) patients experienced ER, with median time to relapse of 15.6 (range: 3-18) months versus 55.5 (range: 19-115) months of the non-ER cohort (n=55; 74.5%). Most of the ER patients (n=18; 94.7%) had induction therapy with dexamethasone in combination with thalidomide and borte-

zomib; among these 9 (47.4%) patients received further 2-3 cycles of consolidation by same regimen as induction. Fourteen (73.6%) ER patients received the standard conditioning regimen as melphalan given at 200 mg/m^2. Regarding maintenance therapy, 5 (26.3%) ER patients continued with lenalidomide but in 6 (31.5%) ER patients bortezomib-based maintenance was preferred in view of high-risk disease features. Univariate statistical analysis identified as predictive markers for ER at diagnosis: IgA MM ($p<0.05$), elevated serum LDH level ($p<0.05$), C-CRAB criteria ($p<0.05$), high risk cytogenetic aberrations ($p<0.05$), stage R-ISS III ($p<0.001$), gain/amplification of chromosome 1q ($p<.05$) and stage R2-ISS III or IV ($p<0.001$). First, bivariate logistic analysis and then Cox regression confirmed IgA isotype ($p<0.05$) and higher stage according to R2-ISS ($p<0.001$) as effectively independent predictive risk factors for ER. Furthermore, according to Cox regression analysis both IgA isotype ($p<0.05$) and stage R2-ISS III or IV ($p<0.05$) with the presence of gain or amplification of chromosome 1q ($p<0.05$) and the presence of increase in serum LDH ($p<0.05$) were all associated with shorter PFS from ASCT. Time-to-event analysis displayed a median progression free survival (PFS) from transplant of 24.7 (range: 11-106) months and 32.5 (range: 3-106) months for those with IgA MM and stage R2-ISS III or IV, respectively. In the ER cohort the median OS from diagnosis was 47.1 (range: 17-135) in comparison with the 75.0 (range: 28-154) months of non-ER cohort. In conclusion, this study was able to identify the IgA isotype and the R2-ISS score system, that include the role of gain/amp 1q, as the main predictive prognostic factors for ER in NDMM patients underwent to ASCT.

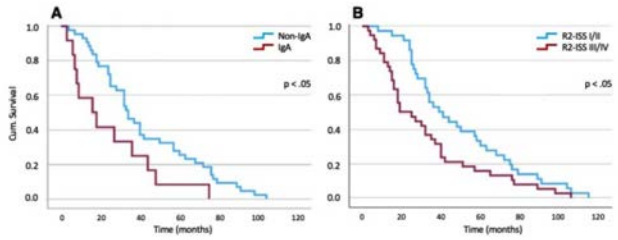

Figure 1.

P22

HIGH RATE OF RESPIRATORY TRACT INFECTIONS AFTER COVID19 WAVES IN TRANSPLANT ELEGIBLE MULTIPLE MYELOMA PATIENTS TREATED WITH DARATUMUMAB

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Patients (pts) with multiple myeloma (MM) are at high risk of infective complications because of the T depletion and the immunosuppressive status caused by therapies (tp) and the disease itself. Infections in newly diagnosed (ND) MM were reported in 65% of pts in the phase III randomised clinical trial CASSIOPEA (Moreau *et al*., Lancet 2019). We performed a retrospective and single□centre analysis to evaluate the real life impact of infection in NDMM pts at Haematology, IRCCS San Raffaele Hospital, Milan after the reduction of COVID19 restrictive social measures. We analysed 32 consecutive at risk pts treated with Daratumumab-based first line tp from AIFA approval. We collect all the infectious complications in last winter period from 1st October 2022 to 30th April 2023. Median time from start of treatment and observation period is 1 year (range 26-500 days). Pts were treated according to institutional standard of care, upon written informed consent for chemotherapy and transplant procedures and use of medical records for research. In this period, cumulative incidence of all grades of infections, rather than neutropenic fever after Melphalan conditioning, was 29 episodes in 20 pts (20/32, 62.5%). Median age is 66 years (range 40-78 years) and according to the Charlson Comorbidity Index, 7/32 (22%) and 1/32 pts were moderately and severe respectively. All pts were vaccinated for seasonal influenza and were on acyclovir prophylaxis; while, as per local policy, cotrimoxazole prophylaxis was commenced only after ASCT. 6/32 (19%) pts received periodical prophylactic intravenous immunoglobulin (IV Ig) as supportive tp for immunoparesis during winter season. There were 1 pneumococcal pneumonia during Daratumumab-bortezomib-thalidomide and dexamethasone (DaraVTD) consolidation, 2 COVID19 paucisymptomatic infections after autologous stem cell transplant (ASCT) and 26 symptomatic respiratory tract infections (RTI). Of whom 21 episodes had a microbiological documented viral cause detected by nasal swab in a total of 14 pts. Pts had suffered of RTI in different phases of tp: 11 during DaraVTD as induction and 5 as consolidation, 4 pts were inpatient for ASCT with Melphalan conditioning and 1 was on lenalidomide maintenance. Distance between RTI and the first day of treatment was 337 days (range 10-495 days). Positive swabs isolated various viruses: 3 Coronavirus OC43/HKV1, 2 Metapneumovirus, 6 parainfluenza, 6 rhinovirus and 6 respiratory syncytial virus (RSV). There were 2 co-infections with RSV and 1 parainfluenza and 1 rhinovirus. There were 3 RSV superinfections: 2 with pulmonary aspergillosis and 1 with bacterial pneumonia. Most cases (17/20, 85%) of RTI were mild and did not require hospitalization or tp (grade 1-2 CTCAE v5.0). 7 pts were treated with pre-emptive IV Ig. In 18/29 (62%) cases there was a delay in the anti-MM tp for RTI that was resumed after a median of 7 days without progression of the disease or drugs' dose reductions. After 30-days follow up 26/29 (90%) infections were solved and pts were on MM-treatment. This analysis confirmed in the real life, the incidences of infections reported in trials and a major impact of RTI especially after the reduction in social measures for COVID19 pandemic. However, all the infections were mild and did not impact the response to anti-MM tp. Further analysis may help developing a risk-stratified approach to preventive and prophylactic measures in pts with NDMM during first line tp.

P23

IMPACT OF DARATUMUMAB, BORTEZOMIB, THALIDOMIDE DEXAMETHASONE INDUCTION THERAPY ON STEM CELL MOBILIZATION: A REAL WORLD EXPERIENCE

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Background. The clinical benefit in adding daratumumab to the VTD-induction-therapy in the newly-diagnosed-multiple-Myeloma (NDMM) was widely demonstrated in the phase-III-CASSIOPEIA-study. The emerging concern related to the addition of daratumumab to a triplet backbone is its negative impact on stem cell mobilization. Data from the largest phase-3 trials CASSIOPEIA-(DaraVTD-vs-VTD) and phase-2-MASTER (DaraKrd) and GRIFFIN-(DaraRVD-vs-RVD) showed a lower stem cell yield and higher plerixafor use, independently from the type of mobilization therapy used (cyclophosphamide + GCSF or only G-CSF). The aim of this multicentric, retrospective study was to describe our experience on stem cell mobi-

lization with DARA-VTD in a real life setting.

Methods. Patients with NDMM treated with DARA-VTD were included in this analysis. Stem cell mobilization performed with G-CSF 10 mg/day with leukapheresis planned at day +5. The minimum target of CD34+cells was 2.5x10 cells/kg for 1 ASCT and 5.0x10 cells/kg when 2 ASCT were planned. Plerixafor was used on demand when the number of circulating $CD34^+$ cells was less than 20 mcl/L at day +5 or when the number of CD34 harvested was less than 2.5x10 cells after the first leukapheresis. Categorical data are presented as count with percentage, and continuous data are presented as median with range. Statistical comparisons were done using the chi square or Fisher exact test for categorical variables and the Mann-Whitney-U-test for continuous variables. NCSS-2019-version was used for statistical analysis, and a $p<.05$ was considered to indicate statistical significance.

Results. From January 2022, 40 patients were included. Median age was 61 (41-71). Most of the patients were mobilized after the third (52%) and fourth course (42%). Before mobilization, 31 (77%) patients were in VGPR and 9 (23%) in CR. The median number of CD34+ cells harvested was 4 (0-11) $x10^6$/Kg. 10% of patients failed the first mobilization attempt. 50% and 45% of patients collected stem cells with 1 and 2 apheresis respectively. 22% patients required plerixafor use. Stem cell mobilization was performed after a median of 21 days after last daratumumab administration. There was no difference in total CD34 yield between patients mobilized after more and less of 21 days after last daratumumab infusion (p=0,57). Median CD 34/Kg total yield was 4.7 and $3.7x10^6$/Kg for patients harvested after 3 and 4 cycles of induction respectively (p=0.07). After high dose Melphalan, the median day to achieve ANC more than 500 and PLTS>20.000 was 12 (6-24) and 13,5 (7-26) respectively. With a median follow up of 175 days, 1 year OS was 94%. 6 patients had planned two ASCT before mobilization and only 4 patient underwent second ASCT.

Conclusions. Our retrospective analysis showed a low rate of mobilization failures after DaraVTD induction. We furthermore found no difference on CD34 total collection after 3 or 4 cicles of Dara-VTD and when mobilization was performed after more or less of 21 days after last daratumumab administration. Prospective trials are needed to confirm feasibility of chemo free G CSF stem cell mobilization after Dara-VTD induction.

P24

PROGNOSTIC PROFILING OF PATIENTS WITH MULTIPLE MYELOMA: REAL WORLD APPLICABILITY

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Background. The variety of different scoring models are used in risk stratification of patients (pts) with multiple myeloma (MM).

Aim. The aim of study was to analyze prognostic impact and real worl applicability of different scoring systems in newly diagnosed multiple myeloma (NDMM) pts.

Patients and Methods. The study included 271 NDMM pts, diagnosed during period 2017-2022 (141 male; 128 female, mean age 63 yrs, range 37-82). The IgG myeloma was diagnosed in 164pts (61%), IgA in 57 (21%), and BJ in 49 (18%). According to the Revised ISS (R-ISS) score, R-ISS1 was found in 66pts (24,4%), R-ISS2 in 172pts (63,5%), while R-ISS3 was present in 33pts (12,1%). According to R2-ISS score, R2-ISS1 had 66pts (24,4%), R2-ISS2 had 61 (22,5%), R2-ISS3 128 (47,2%) and R2-ISS4 had 16pts (5,9%). Double and Triple hit myeloma was found in 16pts (6,8%). Considering Response-Adjusted ISS (RaISS) score the distribution was: low risk 37 (13.8%), intermediate 118 (43.7%) and high risk 116 (42.7%) pts. Frailty analysis according to IMWG Frailty score (IMWG-FS) was following: frail-133pts (49%), 83pts (30.8%) of intermediate-fitness, and 55pts (20.2%) were fit. Treatment with thalidomide-based (Thal) triplets was applied in 81pts (29,9%), while bortezomib-based (Bz) triplets were applied in 189pts (69,7%). High-dose treatment and autologous stem cell transplantation (ASCT) were applied in 77 pts (28,4%).

Results. Overall response rate (ORR ≥PR, IMWG criteria) was achieved in 215pts (79,3%%). There was significant difference between transplant-eligible and non-eligible pts in PFS (Log Rank 10.44, p=0.001) and OS (Log Rank 25.39, p=0.000). Patients with double and triple hit myeloma, had significantly shorter PFS (Log Rank 6.37, p=0.012) and OS (Log Rank 6.57, p=0.010), compared to standard risk pts. Patients with R2-ISS 4 score had the worst prognosis regarding PFS (Log Rank 9.60, p=0.002) and OS (Log Rank 13.86, p=0.000). Considering RaISS score, pts with RaISS 0-3 significantly had longer PFS (Log Rank 7.04, p=0.008), as well as OS (Log Rank 18.58, p=0.000). Frail pts with IMWG-FS 2 had significantly OS (Log Rank 19.16, p=0.001). The multivariate analysis pointed out poor prognostic impact to PFS of following variables: R2-ISS 4 score (HR 5.07, 95% CI 1.37-18.8), RaISS 2 (HR 1.67, 95% CI 1.02-2.74), and transplant ineligibility (HR 0.45, 95% CI 0.26-0.79). Similarly, the OS was strongly influenced by R2-ISS 4 (HR 6.53, 95% CI 1.81-23.54), RaISS 2 (HR 1.75, 95% CI 1.06-2.89), and transplant eligibility (HR 0.23, 95% CI 0.11-0.49).

Conclusions. R2-ISS score represents simple and applicable tool for risk stratification and consequent treatment choice in the real world settings. R2-ISS score 4 has the most significant impact on the course of disease, as well as achievement of CR, represented by Ra-ISS score.

P25

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P31

ABSTRACT NOT PUBLISHABLE

Relapsed/refractory multiple myeloma

P32

IMPACT OF COVID-19 ON OUTCOMES WITH TECLISTAMAB IN THE PHASE 1/2 MAJESTEC-1 STUDY IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Introduction. The COVID-19 pandemic had a disproportionate impact on patients (pts) with multiple myeloma (MM), including higher risk of infection, higher excess mortality rate, and decreased survival (Martinez-Lopez *Blood Cancer J* 2021;11:198). Teclistamab is the first approved B-cell maturation antigen (BCMA)×CD3 bispecific antibody for the treatment of triple-class exposed relapsed/refractory MM (RRMM). The phase 1/2 MajesTEC-1 study of teclistamab in RRMM enrolled the majority of pts between Mar 2020 and Mar 2021, concurrent with the start of the COVID-19 pandemic and overlapping with peak death rates worldwide. At the pandemic onset, there was no approved COVID-19 treatment and vaccines were unavailable until ≥9 months into MajesTEC-1 recruitment. Further, there were no consensus guidelines on infection management with bispecific antibodies and varied implementation of preventive strategies such as IgG replacement. To evaluate the potential impact of COVID-19 on outcomes with teclistamab, we undertook a post-hoc analysis of MajesTEC-1.

Methods. Pts with triple-class exposed MM (N=165; median 5 prior lines of therapy [range 2-14]) received subcutaneous teclistamab 1.5 mg/kg weekly following step-up dosing. COVID-19 infection was managed per institutional guidelines and/or teclistamab interruption. COVID-19 vaccination, including booster doses, was recommended when available.

Results. As of Jan 4, 2023 (median follow-up 22.8 months), COVID-19 positivity was reported in 48 pts (29.1%), with grade 3/4 infection in 35 pts (21.2%) and 18 (10.9%) deaths. Supportive therapies (*e.g.*, glucocorticoids or monoclonal antibodies) were used in 24.2% of cases, with teclistamab interruption in 60.4%. Prior to the first teclistamab dose, 13 pts (7.9%) received ≥1 COVID-19 vaccination, including 1/18 pts who died of COVID-19. On-study, 99 pts (60.0%) received ≥1 COVID-19 vaccination dose, including 13/18 pts who died of COVID-19 (1 dose, n=4; 2 doses, n=4; 3 doses, n=2; 4 doses, n=3). Pts who were never vaccinated tended to die of COVID-19 earlier on-study than vaccinated pts (between 0.7-5.9 and 2.4-25.9 months after starting teclistamab, respectively), corresponding with broader vaccine rollout globally in early 2021. In the ITT population, median progression-free survival (mPFS) was 11.3 months (95% CI 8.8-16.4), median duration of response (mDOR) was 21.6 months (16.2-not estimable [NE]), and median overall survival (mOS) was 21.9 months (15.1-NE). When censored for COVID-19 deaths, mPFS was 15.1 months (9.9-22.8), mDOR was 26.7 months (21.6-NE), and mOS was 28.3 months (21.9-NE). Further details on outcomes will be presented.

Conclusions. MajesTEC-1 enrollment coincided with the onset of the COVID-19 pandemic, with most pts unvaccinated prior to study start. Pts with RRMM may have suboptimal responses to vaccination and emerging data suggest that BCMA-directed therapy may affect vaccine response, indicating that even when available, on-study vaccination may not have provided full protection from COVID-19. There is now increased awareness of the infection profile of bispecific antibodies, with evolving recommendations on COVID-19 vaccination, monitoring, and management. While survival with teclistamab was longer when censored for COVID-19 deaths than in MajesTEC-1 overall, more data from pts treated with teclistamab in the era of both innate and vaccine-induced immunity are needed to further understand the potential impact of COVID-19 on outcomes.

P33

TREATMENT OUTCOMES OF TRIPLE CLASS REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED BY APPROACHING TARGETABLE MUTATIONS

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Introduction. During the clonal evolution of Multiple Myeloma(MM) frequently observed mutations can be acquired. Herein, we aimed to present the mutational profile and targeted treatment results among triple class refractory MM (RRMM) patients.

Materials and Methods. A total of 32 consecutive triple-class refractory MM and two newly diagnosed MM patients between November 2018 and October 2023 were included in the analysis. DNA extracted from bone marrow or extra-medullary plasmacytoma magnetic bead CD138 enriched cells or smears were subjected to NGS on the İllumina Miseq platform (USA) by using QIAseq targeted DNA panel (12)- Human myeloid neoplasm panel covers exons and exon-intronic regions of 141 genes. Data analysis, was performed by QCI Analyze Universal 1,5.0.

Results. Patient characteristics are Female/male: 12/22; age: median 57 (range, 39-87) prior lines of treatment: median 4 (range; 1-13) extramedullary disease (EMD) (+/-): 14/18. NGS results were as follows: 59 mutations in 26 genes were detected. Among these recurrent genomic abnormalities, concomitant missense protein coding alterations were detected in all patients. Mutations of RAS/MAPK pathway genes were the most frequently detected ones. The hotspots of mutation in KRAS, NRAS, and BRAF were codon 61; codons 61, and 13 as well as codon 600 respectively. In addition, we detected novel myeloproliferative, and myelodysplasia-associated mutations previously not described in MM. Both of the NDMM patients were found to carry mutations in KRAS and they responded with continuous CR following VCD induction-ASCT-Lenalidomide maintenance. The frequency of TP53, NRAS, KRAS, and BRAF mutations differed according to the presence/lack of EMD: 43% *vs* 27%, 28.5% *vs* 22.2%, 21.4% *vs* 38.8%, and 11% *vs* 7%, respectively. Furthermore, among five EMD samples we were able to detect mutation of TP53 (n: 2), NRAS (n:1), KRAS (n: 1), and BRAF (n :1) specimens. Of these, two patients had simultaneous marrow samples none of which shared the same mutation.

Treatments. Based on these results seven patients were able to receive off-label approval for treatment with Everolimus (Evo) (for PTEN) (Patient 1 & 11) or Trametinib (Tra) (for KRAS) (Patient 3,5,6 & 9) in combination with Pomalidomide (PomDex) w/wo Daratumumab. Two patients received vemurafenib (for BRAF mutation) alone or in combination with dabrafenib. Responses are summarized

as follows: Patient-1 had extensive EMD in the skin, which responded completely to Dara-EvoPomDex combination with a VGPR duration of only two months. Patients-3,9 and 11 could not survive enough to observe the benefit of Tra-or EvoPomDex. Patient-5, plasma cell leukemia, achieved the deepest response of VGPR in only three months duration following Tra-PomDex treatment. Patient-6, also presenting with EMD, was treated with TraPomDex as the seventh treatment line achieving VGPR, lost during interruption secondary to an infectious episode. Patients-20 and -32 both with EMD have received vemurafenib. Vemurafenib controlled the disease for 12 months then dabrafenib was added due to the progression of EMD which still expressed BRAF mutation (patient-20). However, PR was not sustainable beyond three months. Patient-32 has been on vemurafenib monotherapy for three months now with ongoing CR.

Conclusions. Detection of clonal mutations in our experience has shown the more frequent incidence of p53 mutations among EMD and has led us to design novel treatment options achieving transient at least VGPR responses.

P34

LONG-TERM OUTCOMES FROM THE PHASE 3 OCEAN (OP-103) STUDY: MELFLUFEN AND DEXAMETHASONE (DEX) VERSUS POMALIDOMIDE (POM) AND DEX IN RELAPSED REFRACTORY MULTIPLE MYELOMA (RRMM)

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Background. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that utilizes increased peptidase expression to selectively release alkylating agents inside tumor cells. Melflufen is approved in Europe in patients (pts) with triple-class refractory RRMM with ≥3 prior lines of therapy (LoTs) and time to progression (TTP) >36 mo after prior autologous stem cell transplant (ASCT), if received. In the OCEAN study (NCT03151811), melflufen+dex showed superior PFS *vs* pom+dex (6.8 *vs* 4.9 mo; HR 0.79; P=0.032), which was mainly driven by pts without prior ASCT. Overall survival (OS) trended in favor of melflufen+dex in pts without prior ASCT and favored pom+dex in pts with prior ASCT (Schjesvold, *Lancet Haematol* 2022). Posthoc analyses of OCEAN and HORIZON showed that a TTP <36 mo post ASCT was a negative prognostic factor for OS with melflufen+dex (Sonneveld, *Clin Lymphoma Myeloma Leuk* 2023). Here, we present long-term OS and safety data from the final analysis of OCEAN.

Methods. RRMM pts (2-4 prior LoTs including lenalidomide [len] and a proteasome inhibitor) refractory to len and last LoT were randomized 1:1 to receive 28-day (d) cycles of melflufen 40 mg IV on d1 or pom 4 mg PO daily on d1 to 21. All pts received dex 40 mg (20 mg for pts ≥75 y) PO on d1, 8, 15, and 22. Pts received therapy until disease progression or unacceptable toxicity.

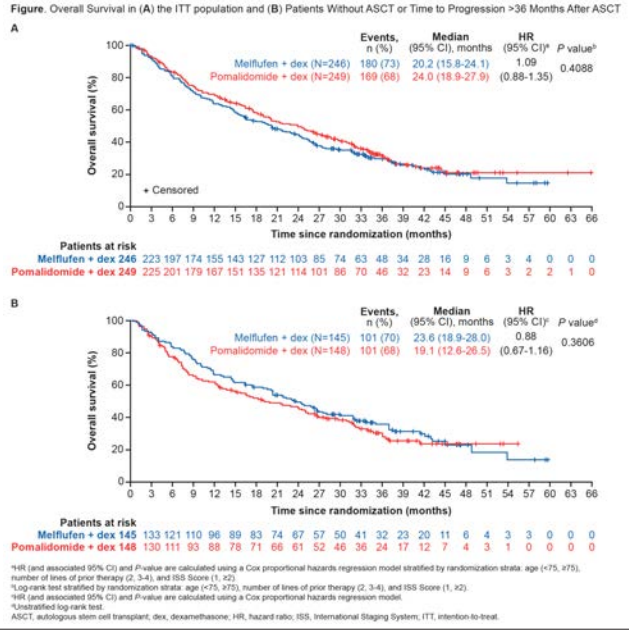

Figure 1.

Results. As of 3 Feb 2023, 495 pts were randomized (melflufen: 246; pom: 249); median age was 68 y (range, 39-91), and median prior LoTs was 3. In the intent-to-treat (ITT) melflufen and pom arms, median OS was 20.2 mo *vs* 24.0 mo (HR 1.09 [95% CI, 0.88-1.35]), at a median follow-up of 40.3 mo and 38.1 mo, respectively (Figure 1). In the target subgroups (no prior ASCT or TTP >36 mo after ASCT), median OS was 23.6 mo for melflufen *vs* 19.1 mo for pom (HR 0.88 [95% CI, 0.67-1.16]; Figure 1); in the non-target population (TTP <36 mo after ASCT), median OS was 15.7 mo *vs* 27.5 mo (HR 1.60 [95% CI, 1.15-2.21]), respectively. Any grade hematologic toxicities were more common with melflufen; non-hematologic toxicities were similar in the 2 arms. G3/4 TEAEs in the safety population (melflufen: n=228; pom: n=246) occurred in 90% *vs* 76% of pts, respectively (thrombocytopenia [78% *vs* 13%; occurring with G3/4 hemorrhage in 1% *vs* 0%], neutropenia [64% *vs* 50%; occurring with G3/4 infections in 4% *vs* 7%], anemia [43% *vs* 19%], and infection and infestations [14% *vs* 24%]). Serious AEs occurred in 43% *vs* 50% of pts (pneumonia [6% *vs* 9%], COVID-19 pneumonia [5% *vs* 6%], and anemia [4% *vs* 2%]), and fatal AEs in 14% *vs* 15% (COVID-19 pneumonia [4% *vs* 2%] and pneumonia [2% *vs* 2%]), respectively. With melflufen and pom, TEAEs led to dose reductions

in 52% *vs* 28% of pts (most frequently thrombocytopenia [32% *vs* 2%] and neutropenia [12% *vs* 8%]), and discontinuations in 30% *vs* 24% of pts, respectively. Deaths occurred in 74% *vs* 68% of pts with melflufen and pom, with AEs being the primary cause in 8% and 11%.

Conclusions. Long-term results were consistent with those of previous analyses. While OS trended in favor of pom in the ITT population, it continued to be more favorable with melflufen in pts with no prior ASCT or with TTP >36 mo after ASCT. No new safety signals were reported; AEs were manageable with dose modifications. This long-term follow-up of OCEAN confirms the favorable safety and OS outcomes of melflufen+dex in the target population and supports its continued use as a treatment choice for pts with RRMM.

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PRACTICAL CONSIDERATIONS ON MANAGEMENT OF INFECTION IN PATIENTS RECEIVING BISPECIFIC ANTIBODIES: A SINGLE CENTER EXPERIENCE

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Background. Patients with multiple myeloma are at increased risk of infection, particularly when relapsed or refractory to therapy. Infections during treatment with bispecific antibodies are common, particularly in the respiratory tract, followed by urinary, skin and gastrointestinal tract.

Methods. We analyzed clinical outcomes of 5 patients treated with two different bispecific antibodies (BA) at our center. Patients were previously exposed to a median of 6 lines of therapy (range 5-9), all of them were penta refractory and had also received prior anti-BCMA exposure, (antibody-drugconjugate belantamab mafodotin) Patients received subcutaneous anti BCMA BA alone teclistamab (3 patients) 1.5 mg/kg weekly after a step-up dosing schedule (0.06 mg/kg and 0.3 mg/kg, each separated by 2-4 days), or anti GPRC5D BA alone talquetamab 0.8 mg/kg weekly after a step up dosing schedule (0.01 mg/kg, 0.06 and 0.4 mg/kg, each separated by 2-4 days) (2 patients). Patients were monitored frequently for infections and received; prophylaxis with trimethoprim/sulfamethoxazole bis in die 2 days/week and acyclovir 200 mg daily .

Results. At a median follow-up of 2 months (range 1-12), infections were reported only in 2 patients (40%) and were two grade 1 infections (in patients treated with teclistamab). Overall,2/5 patients had immunoglobulin G (IgG) level <400 mg/dL before bispecific antibodies therapy, and 60% of patients had a reduction of immunoglobulin G (IgG) level <400 mg/dL that started after first month of treatment. Based on our previous experience we offered early all patients Ig substitution and all patients with IgG <400 mg/dL received ≥1 dose of IgG replacement (range 1-12 doses). Grade 2 neutropenia occurred in 100% of patients and was supported with granulocyte colony stimulating factor according to internal rules. Three out of five patients achieved at least a very good partial response, while one patient, treated with teclistamab, progressed after first cycle and died.

Conclusions. T-cell redirecting BA have revolutioned multiple myeloma armamentarium for remarkable efficacy. Unfortunately, bispecific antibodies are associated with infections. It is therefore recommended that clinicians use preventive measures, such as an appropriate screening, prophylaxis, and management of infections with a large use of Ig replacement in patients with hypogammaglobulinemia

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CLINICAL OUTCOME OF LATENT TUBERCULOSIS INFECTION DETECTED BY QUANTIFERON-TB TEST IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING NOVEL DRUGS: FOCUS ON REACTIVATION PROPHYLAXIS IN A RETROSPECTIVE, SINGLE-CENTER STUDY

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Patients with immunodeficiencies have a greater risk of progressing to overt tuberculosis (TB) disease once infected and this risk is 2-40 times higher compared to that of the general population in patients with hematologic malignancies. Consequently, it could be important to diagnose latent TB infection in these patients and to consider a prophylactic therapy that could avoid a possible reactivation leading to active TB. Regarding this aspect, limited data are available in the setting of patients with multiple myeloma (MM) treated with novel drugs (proteasome inhibitors, IMiDs and monoclonal antibodies). Therefore, we retrospectively evaluated the incidence of latent TB infection by the IGRA Quantiferon®-TB test, in 180 consecutive patients with active MM observed at our Institution since January, 2020, to June, 2023. The test was performed together with other preliminary blood tests, including viral hepatic markers and HIV at diagnosis or at disease progression, before starting treatment. Quantiferon®-TB test was found positive in 26 subjects (14.4%); only three patients were foreign born. Clinical characteristics of patients are summarized in Table 1. The median age was 75 years (range: 42-83), with a male predominance (53.9%). In twenty-two patients (84.6%) the test was positive before starting first line of treatment; in 4 patients (15.4%), it was found positive at switch from first to second line of therapy (not performed before). Twenty-one (80.8%) patients received prophylactic treatment (isoniazid or rifampicin) for latent TB according to indications provided by the infectious disease specialist, while 5 did not (two patients had been treated for active TB several years before; three patients were excluded from prophylaxis due to poor kidney function and other important comorbidities). Fourteen patients (66.7%) received isoniazid, at standard dose of 300 mg/day combined with pyridoxine supplementation for six months, while 7 patients received rifampicin at the standard dose of 600 mg/day for 4 months. In one patient, isoniazid was stopped because of liver toxicity. Eleven patients (HBsAg negative, anti-Hbs positive, total anti-HBc positive, HBV-DNA negative) received concomitant prophylaxis with lamivudine at the dose of 100 mg/day, to avoid reactivation of hepatitis B virus. Regarding specific treatments for MM, all patients enrolled in this analysis received novel drugs, such as proteosome inhibitors, IMiDs and monoclonal antibodies; four of them underwent autologous hematopoietic stem cell transplant too. With a median time of observation of approximately 638 days (range: 109-2562), none of the patients developed TB reactivation during or after MM treatment with novel drugs. Moreover, TB prophylaxis was not associated with any significant toxicity in all but one cases. In conclusion, TB screening using quantiferon-test revealed a not negligible proportion of MM patients with latent TB infection before treatment with new drugs. Specific prophylaxis in these subjects was generally safe (including those also receiving lamivudine) and could have been avoided possible reactivations of latent TB. A comparison with a cohort of similar patients, but not receiving TB prophylaxis, is currently planned.

Table 1. Baseline characteristics of patients with multiple myeloma quantiferon positive.

Median age, years (range)	75 (42-83)
Gender, n. (%)	
Male	14 (53.9)
Female	12 (46.1)
Country of origin, n. (%)	
Italy	23 (88.5)
Eastern Europe	2 (7.7)
Africa	1 (3.8)
MM isotype, n. (%)	
IgG	15 (57.7)
IgA	10 (38.5)
Light chain	1 (3.8)
History of previous active tuberculosis, n. (%)	
Yes	2 (7.7)
No	24 (92.3)
Pharmacological prophylaxis, n. (%)	
Yes	21 (80.8)
No	5 (19.2)
Drugs used for tuberculosis prophylaxis, n. (%)	
Isoniazid with pyridoxine supplementation (6 months)	14 (66.7)
Rifampicin (4 months)	7 (33.3)
Concomitant hepatitis-B virus prophylaxis, n. (%)	
Yes (lamivudine)	11 (42.3)
No	15 (57.7)
MM treatment regimen used, n. (%)	
Contains proteasome inhibitor	
Bortezomib	16 (61.5)
Carfilzomib	4 (15.4)
Contains IMiDs	
Thalidomide	8 (30.8)
Lenalidomide	20 (76.9)
Pomalidomide	4 (15.4)
Contains monoclonal antibodies	
Daratumumab	20 (76.9)
Isatuximab	1 (3.8)
Elotuzumab	4 (15.4)
Autologous hematopoietic stem cell transplant, n. (%)	
Yes	4 (15.4)
No	22 (84.6)
Median duration of follow-up, days (range)	638 (109-2562)

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BURDEN OF INFECTION IN PATIENTS WITH MULTIPLE MYELOMA AND SECONDARY IMMUNODEFICIENCIES: A RETROSPECTIVE COHORT STUDY

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This study aimed to provide insights into the burden of infection in patients with multiple myeloma (MM) with or without secondary immunodeficiencies (SID). In this retrospective cohort study, data were extracted from the Optum-Humedica electronic record database during the period 1 October 2015 to 10 March 2020, which included a 6-month pre-index period (PIP) and 12-month follow-up following patient identification. Patients aged ≥ 18 years with a confirmed diagnosis of MM in the PIP were included in the analysis and stratified into two cohorts: those with (SID cohort) and those without SID (no-SID cohort). If a patient had SID or primary immunodeficiencies in the PIP, they were excluded. The first occurrence of a hypogammaglobulinaemia International Classification of Diseases, Tenth Revision (ICD-10) code, or a low (<5.0 g/L) serum immunoglobulin G level was defined as the SID index date. Of patients with MM, 870 with SID and 3768 without SID were included (mean age: 66.5 and 68.7 years; males: 54.3% and 53.6%; respectively). At 12-month follow-up, significantly more patients in the SID cohort experienced ≥ 1 infection than the no-SID cohort (58.9% *vs* 32.1%, p<0.001). A similar pattern was observed for mean number of infections, patients experiencing ≥ 1 severe bacterial infection or ≥ 1 infection-associated hospitalization (Table 1). The most common infection in both cohorts

was bacterial: SID, mean (standard deviation [SD]) number of bacterial infections 6.83 (8.04) and no-SID, 4.73 (6.57), p<0.001. Kaplan-Meier analysis showed overall survival at 24 months was lower in the SID cohort (74.9% of patients alive) than the no-SID cohort (81.8%). In conclusion, patients with MM and SID have a substantially higher burden of infection and healthcare resource use, and lower overall survival than those without SID. Understanding this burden will allow for earlier targeted treatment of individuals at risk of SID. This abstract was first presented at the European Society for Medical Oncology (ESMO) Congress 2022. Takeda Development Center Americas, Inc. funded this study. Takeda Pharmaceuticals International AG funded writing support.

Table 1. Outcome measures at 12 months.

	SID N = 870	No-SID N = 3768	*p* value SID vs no-SID
Number of infections, mean (SD)	7.07 (9.23)	4.58 (6.45)	< 0.001
Patients with ≥ 1 severe bacterial infection,[a] n (%)	276 (31.7)	510 (13.5)	< 0.001
Patients with ≥ 1 hospitalization associated with any infection, n (%)	231 (26.6)	350 (9.3)	< 0.001
Number of hospitalizations, mean (SD)	6.55 (8.65)	5.47 (6.90)	0.11
Length of hospital stay, mean (SD), days	13.02 (34.95)	9.69 (26.88)	0.22

[a]Defined using ICD-10 codes for bacteraemia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess.

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POOLED ANALYSIS OF SAFETY FROM BIRTAMIMAB PHASE 1-3 TRIALS IN PATIENTS WITH LIGHT CHAIN (AL) AMYLOIDOSIS

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Introduction. AL amyloidosis is a progressive, fatal disease caused by misfolded light chains that aggregate into amyloid fibrils that cause organ dysfunction. Birtamimab – a humanized monoclonal antibody that neutralizes soluble, toxic light chain aggregates and depletes insoluble amyloid deposits – is being investigated in AL amyloidosis. Here we present a pooled safety analysis from Phase 1-3 trials.

Methods. Patients (pts) with AL amyloidosis received intravenous birtamimab up to 24 mg/kg every 28 days in the non–placebo (PBO)-controlled Phase 1/2 trial (NCT01707264) and open-label extension (OLE; NCT02613182), and two randomized controlled trials (RCTs; Phase 2 PRONTO [NCT02632786] with OLE [NCT03154047] and Phase 3 VITAL [NCT02312206]). In PRONTO, pts had received ≥1 previous systemic therapy with at least partial hematologic response and persistent cardiac dysfunction, and received birtamimab or PBO. In VITAL, newly diagnosed treatment-naïve pts with cardiac involvement received birtamimab + SoC or PBO + SoC (SoC was a bortezomib-containing regimen). Pts who received ≥1 dose of birtamimab were included. Pooled median exposure times were calculated, and baseline characteristics and demographics were summarized. For VITAL and PRONTO, pooled rates and severity of adverse events (AEs) were compared between treatment arms. Safety data from the non–PBO-controlled studies were summarized.

Results. The median (range) exposure to birtamimab among 302 pts from Phase 1-3 trials was 12.24 (0.03–57.72) months. In total, 295 pts received at least one 24-mg/kg infusion. Analysis of the two PBO-controlled trials included data from 196 pts treated with birtamimab from PRONTO (n=66) and VITAL (n=130), and 193 pts who received PBO (PRONTO, n=63; VITAL, n=130). Treatment durations were comparable. Rates of AEs, serious and grade ≥3 AEs were similar between birtamimab and PBO arms within trials and between treatment arms in the pooled analysis set (PRONTO and VITAL; Table 1). Higher rates of treatment-related, serious, and grade ≥3 AEs were reported in VITAL *vs* PRONTO, likely due to the treatment-naïve population and concomitant SoC therapy in VITAL. In the pooled analysis set, the most common AEs with greater frequency in the birtamimab *vs* PBO arms in either trial were, respectively, fatigue (36.2%, 34.2%), diarrhea (33.2%, 33.7%), nausea (31.6%, 30.1%), constipation (31.1%, 31.6%), and dyspnea (25.0%, 24.9%). Consistent with the underlying disease, cardiac events (heart failure, syncope, cardiac arrest) were the most frequent (≥5%) serious and grade ≥3 AEs. Infusion-associated AE rates were low and AEs were mild to moderate in the pooled birtamimab and PBO arms (5.1% *vs* 3.6%, respectively). The safety profile in the non–PBO-controlled trials (n=106) was consistent with that of the PBO-controlled trials.

Conclusions. Birtamimab was well tolerated with a favorable safety profile as monotherapy and did not demonstrate additive toxicity with SoC chemotherapy in patients with AL amyloidosis. Rates of AEs were similar in the birtamimab and PBO arms in PRONTO and VITAL. The safety and efficacy of birtamimab is being further investigated in an ongoing, confirmatory, Phase 3 double-blind RCT in pts with Mayo Stage IV AL amyloidosis (AFFIRM-AL; NCT04973137), which is currently enrolling.

Support and Funding. This study was sponsored by Prothena Biosciences Limited, a member of the Prothena Corporation plc group.

Table 1.

Table 1. AE summary for birtamimab placebo-controlled trials to date (PRONTO, VITAL)

	PRONTO		VITAL		Pooled	
Patients reporting ≥1 of the following, n (%)	Birtamimab (N=66)	Placebo (N=63)	Birtamimab (N=130)	Placebo (N=130)	Birtamimab (N=196)	Placebo (N=193)
Any AE	64 (97.0)	59 (93.7)	127 (97.7)	130 (100)	191 (97.4)	189 (97.9)
Treatment-related AE	17 (25.8)	17 (27.0)	41 (31.5)	50 (38.5)	58 (29.6)	67 (34.7)
AE grade ≥3	19 (28.8)	17 (27.0)	96 (73.8)	102 (78.5)	115 (58.7)	119 (61.7)
Treatment-related AE grade ≥3	4 (6.1)	0	6 (4.6)	12 (9.2)	10 (5.1)	12 (6.2)
Serious AE	14 (21.2)	15 (23.8)	88 (67.7)	91 (70.0)	102 (52.0)	106 (54.9)
Treatment-related serious AE	1 (1.5)	0	4 (3.1)	5 (3.8)	5 (2.6)	5 (2.6)
AE leading to study drug discontinuation	3 (4.5)	1 (1.6)	6 (4.6)	14 (10.8)	9 (4.6)	15 (7.8)
AE leading to death	2 (3.0)	2 (3.2)	19 (14.6)	28 (21.5)	21 (10.7)	30 (15.5)
Treatment-related AE leading to death	0	0	0	0	0	0

AE, adverse event.

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DARATUMUMAB-BASED REGIMENS FOR PATIENTS WITH MULTIPLE MYELOMA PLUS EXTRAMEDULLARY PLASMACYTOMAS OR PARASKELETAL PLASMACYTOMAS: INITIAL FOLLOW-UP OF AN ITALIAN MULTICENTER RETROSPECTIVE CLINICAL EXPERIENCE

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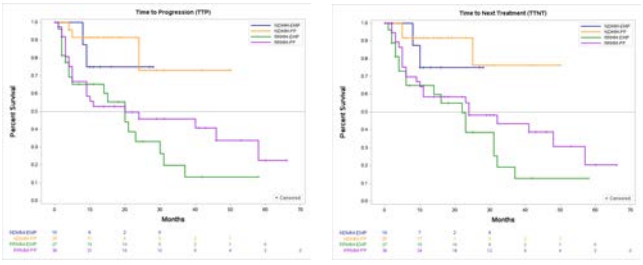
Multiple Myeloma (MM) with extramedullary plasmacytomas not adjacent to bone (EMP) is associated with an extremely poor outcome compared with paraosseous plasmacytomas (PP) as current therapies are unsatisfactory. The role of new molecules and monoclonal antibodies is under investigation. To determine whether daratumumab-based regimens are effective for EMP, 102 patients (43 F, 59 M) (mean age 72 years [45-85]) were included in this initial analysis, and EMP and PP were analyzed separately. Of 38 MM patients with EMP, 26.3% (n=10) had newly diagnosed MM (NDMM) and 73.7% (n=28) had refractory/relapsed MM (RRMM). Of 64 MM patients with PP, 39% (n=25) had NDMM and 61% (n=39) had RRMM. EMP or PP were detected by biopsy and/or imaging (PET, TC, MRI). Using FISH, chromosomal aberrations were evaluated at the time of EMP or PP diagnosis in only 62 patients (61.4%). The common chromosomal alterations were detected in 64.5% of patients valued. All patients with NDMM plus EMP or PP eligible for ASCT (n=13) were treated with D-VTd followed by intensification with single or double ASCT. For transplant ineligible (TIE) patients with NDMM plus EMP or PP, the upfront approach most commonly used was D-Rd (n=19 [86.4%]); only 3 TIE patients (13.6%) were treated with D-VMP as upfront approach. As regards the 67 RRMM patients with EMP or PP, 39 (58.2%) were treated with D-Rd, 20 (29.8%) with D-Vd, 3 (4.5%) with D-Pd, and 5 (7.5%) with D single-agent. Patients with RRMM plus EMP or PP had received a median of 1 previous line of therapy (1-7). About one-third of patients, analyzed separately for each cohort, received local radiotherapy. EMP and PP at diagnosis were associated with higher biochemical (90% *vs* 96%) and instrumental ORR (86% *vs* 83.3%), while at relapse, biochemical (74% *vs* 73%) and instrumental (53% *vs* 59%) ORR were lower. Median OS was inferior in EMP patients compared with patients with PP both at diagnosis (21.0 months *vs* NR) (p 0.005) and at relapse (32.0 *vs* 40.0 months) (p 0.428), although, during relapse, there was no statistically significant difference between the two groups. It is very interesting to observe that, at diagnosis, median TTP and median TTNT were not reached either in EMP patients or PP patients. Surprisingly, during relapse, there were no statistically significant differences in terms of median TTP (20 months for two groups), and median TTNT (24 months for PP patients *vs* 22 months for EMP patients) between the two groups. Median TTR was 1 month in all populations. Among the NDMM patients with EMP, after 27 months of follow-up, 7 patients (70%) are alive and were still receiving daratumumab-based therapy. Among the NDMM patients with PP, after 47 months, 24 patients (96%) are alive. Of the 24 live patients, 82.7% were still receiving daratumumab-based therapy. Among the RRMM patients with EMP, after 61 months, all (n=28) are alive. Of the 28 live patients, 27% were still receiving daratumumab-based therapy. Among the RRMM patients with PP, after 81 months, 19 patients (95%) are alive. Of the 19 live patients, 34.3% were still receiving daratumumab-based therapy. In conclusion, these promising results were documented even in the absence of local aggressive radiotherapy and in TIE patients, suggesting that daratumumab based-regimens could be effective also in critical situations and in frail patients who may not be candidates for aggressive treatment approaches owing to early mortality and high attrition rate.



TTP by cohort:
- **NDMM-EMP**: median TTP not reached
- **NDMM-PP:** median TTP not reached

Log-rank test between the NDMM-EMP cohort vs NDMM-PP cohort: *p* 0.511

- **RRMM-EMP:** median TTP 20 months (95% CI: 4-30 months)
- **RRMM-PP:** median TTP 20 months (95% CI: 5-58 months)

Log-rank test between the RRMM-EMP cohort vs RRMM-PP cohort: *p* 0.284

TNTT by cohort:
- **NDMM-EMP**: median TTNT not reached
- **NDMM-PP:** median TTNT not reached

Log-rank test between the NDMM-EMP cohort vs NDMM-PP cohort: *p* 0.485

- **RRMM-EMP:** median TTNT 22 months, (95% CI: 6-31 months)
- **RRMM-PP:** median TTNT 24 months, (95% CI: 9-57 months)

Log-rank test between the RRMM-EMP cohort vs RRMM-PP cohort: *p* 0.208

Figure 1.

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LIGHT-CHAIN (AL) AMYLOIDOSIS IN THE REAL-WORLD SETTINGS

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Background. Over the past 20 years, improvements in early diagnostics and treatment of AL Amyloidosis significantly changed the course the course of this rare plasma cell dyscrasia. The aim of the

study was to analyze prognostic significance of clinical and laboratory characteristics present in patients (pts) with AL Amyloidosis.

Methods. The study included 60pts with AL Amyloidosis diagnosed during January 2012. - June 2023. (male/female 33pts/27pts, mean age 59yrs, range 29-77yrs). According to the type of M protein, lambda light chains existed in 23pts (70%). The diagnosis was established by the presence of amyloid in soft fat tissue of 42pts (70%), bone marrow biopsies of 21pts (35%), renal biopsies of 11 pts (18.3%), and gingiva in 2 pts (3.3%). The bone marrow plasmocytic infiltration of ≥ 10% (median 34%, range 15-90%) was found in 25 pts (41.7%). iFISH was performed in 15 pts (25%) with ≥10% plasmocytic bone marrow infiltration, pointing out 1q21 amplification present in 6/15pts. Cardiac MRI involvement had 13pts (86.7%). According to the Mayo staging system, I clinical stage (CS) was found in 13pts (21.7%), II in 21pts (25%), while IIIa CS was present in 16pts (26.7%), and IIIb in 10pts (16.7%). Regarding Revised Mayo CS: III CS in 20pts (33.3%), and IV in 10pts (16.7%). In majority of patients was found renal impairement of I or II CS (Palladini et al, I CS 23pts, 38.3%; or II CS 25pts, 41.7%), while 12pts (20%) were characterized by advanced III CS. Treatment was aplied with alkylating based combos in 24pts (40%), and bortezomib (Bz) based triplets in 36pts (60%). High-dose melphalan and autologous stem cell transplantation (ASCT) was performed in 10pts (16.7%).

Results. The overall response rate (ORR, ≥PR) was achieved in 40pts (70%). Patients treated with Bz-based combos had significantly better hematological (71.4% *vs* 36.4%; p=0.013), cardiac (70.8% *vs* 38.1%; p=0.027), renal (80.8% *vs* 42.1%; p=0.007) and composite response (CHOR; 78.6% *vs* 40.9%; p=0.006). There was no difference in PFS (p=0.785) and OS (p=0.07) between pts treated with standard chemotherapy, either with Bz- or Alk-based combos. Patients treated with high-dose melphalan and ASCT had significantly better hematological (100% *vs* 56%; p=0.008), cardiac (100% *vs* 55.6%; p=0.017), renal (100% *vs* 64.4%, p=0.033) and composite response (CHOR; 100% *vs* 62%; p=0.018) compared to ASCT ineligible patients. Treatment with high-dose melphalan and ASCT resulted with significantly longer overall survival (OS: 67.4 *vs* 39.5 months; p=0.036), still, without prolongation of progression free survival (PFS: 59.2 *vs* 47.7 months; p=0.229) compared to non-ASCT group. The OS was strongly influenced by cardiac involvement, presented as Mayo CS (p<0.01; HR 1.79, 95% CI 1.17-2.73) and Revised Mayo stratification (p<0.01; HR 1.80, 95%CI 1.23-2.64), and ASCT eligibility (p=0.05; HR 0.29, 95% CI 0.08-1.00), as well as the hematological (p<0.01; HR 0.15, 95% CI 0.07-0.35), cardiac (p<0.01; HR 0.13, 95% CI 0.05-0.31), renal (p<0.01; HR 0.17, 95% CI 0.07-0.41) and composite response (p<0.01; HR 3.92, 95% CI 3.86-20.61).

Conclusions. In the real-world settings, the cardiac involvement per Mayo and Revised-Mayo staging, ASCT eligibility and achievement of hematological and organ response in AL Amyloidosis, retains its prognostic impact on the overall survival, particularly in the case of limited accessibility to antiCD38 monoclonal antibodies in the first line of treatment.

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ANTIBODY RESPONSE TO BREAKTHROUGH SARS-COV-2 INFECTION IN "BOOSTER" VACCINATED PATIENTS WITH MULTIPLE MYELOMA ACCORDING TO B, T AND NK LYMPHOCYTE ABSOLUTE COUNTS AND ANTI-CD38 TREATMENTS

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Low B-lymphocyte count and treatment with anti-CD38 monoclonal antibodies (MoAbs) correlate with poor antibody response to "conventional" doses of anti-SARS-CoV-2 vaccines in patients with multiple myeloma (MM). Notably, "booster" doses have shown to enhance the humoral response of these patients. In the present study we evaluated a possible relationship between antibody response after SARS-CoV-2 infection in "booster" vaccinated (at least 3 doses) MM patients and main circulating lymphocyte subpopulations at the time of infection; we also investigated the impact of treatments including anti-CD38 MoAbs on antibody titer in the same population of patients. Sixty-two MM patients with breakthrough SARS-CoV-2 infection (men, 58.1%; median age, 65.5 years) followed at our Institution between January 2022 and April 2023 were included in this study. Twenty-seven percent of patients were receiving proteosome inhibitors, 77% IMIDs, 50% anti-CD38 MoAbs (45% daratumumab, 5% isatuximab), 69% steroids, 10% other treatments. All patients had been previously vaccinated against SARS-CoV-2 infection with at least three doses (81% 3, 14% 4 and 5% 5 doses, respectively). Collection of serum samples was performed at first outpatient visit after a median of 22 days (range: 9-162) from positive swab for SARS-CoV-2 infection.

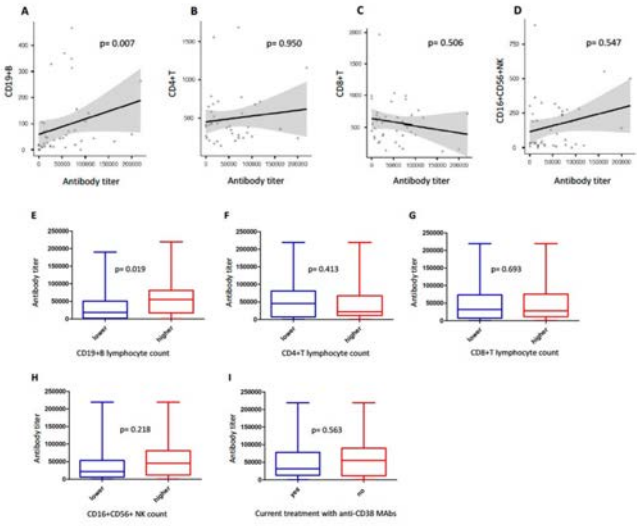

Figure: Correlation between antibody titers after SARS-CoV-2 breakthrough infection and absolute count/µl of CD19+B-lymphocytes (**A**), CD4+ T-lymphocytes (**B**), CD8+ T-lymphocytes (**C**), and CD16+CD56+ NK-lymphocytes (**D**). Comparison of antibody titer after SARS-CoV-2 breakthrough infection according to the median (lower vs higher) absolute count/µl of CD19+ B-lymphocytes (median number 40, range 0-467) (**E**), CD4+ T-lymphocytes (median number 390, range 86-1,688) (**F**), CD8+ T-lymphocytes (median number 527, range 19-1,966) (**G**), CD16+CD56+ NK lymphocytes (median number 47, range 0-886) (**H**). Comparison of antibody titer after SARS-CoV-2 breakthrough infection according to the use of anti-CD38 MAbs (yes vs no) (**I**).

Figure 1.

Determination of anti-spike IgG antibodies was performed using the SARS-CoV-2 IgG II Quant ABBOTT assay; absolute counts of B, T and NK subsets were determined by the software BD FACSCanto™. Correlation between different lymphocyte subpopulations with anti-SARS-CoV-2 antibody titers were investigated using Spearman's Rho criterion, while comparisons between groups were performed by Mann–Whitney U test. Overall, almost all patients (60/62, 96.8%) showed a titer greater than 50 AU/mL, considered as potentially protective by assay's manufactures (median 31,641, range 10.7-219,255). Regarding the antibody response according to the absolute count of $CD19^+$ B-lymphocytes, the presence of a direct correlation between the two variables (Figure 1A) and a significant reduction

associated to a lower B-lymphocyte level when the median value was used as a cut-off level (Figure 1 E) were observed. By contrast, assessing the impact of the absolute count of T ($CD4^+$ or $CD8^+$) and NK ($CD16/CD56^+$) lymphocyte subpopulations on the development of anti-SARS-CoV-2 antibody titer, no correlation was found (Figure 1 B-D). Likewise, no significant differences in terms of antibody titer emerged comparing patients with lower versus higher median $CD4^+$, $CD8^+$ and $CD16/CD56^+$ lymphocyte absolute values, respectively (Figure 1 F-H). Finally, evaluating the antibody response according to concomitant treatments with anti-CD38 MoAbs, no statistically significant difference was identified between 31 patients undergoing these treatments and 31 patients who did not (Figure 1 I). Notably, no death due to COVID-19 occurred in these patients. Our study suggests that, in MM patients who have previously received three or more doses of anti-SARS-CoV-2 vaccines, the absolute number of $CD19^+$ B cells may marginally reduce the production of specific antibodies after breakthrough SARS-CoV-2 infection, without significantly decreasing, however, the percentage of patients with "protective" titers. In this setting, the absolute number of T and NK populations, as well as the use of anti-CD38 antibodies for the treatment of MM, do not show significant effects on humoral response to viral infection.

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REAL-WORLD USAGE OF HYALURONIDASE-FACILITATED SUBCUTANEOUS IMMUNOGLOBULIN 10% IN PATIENTS WITH MULTIPLE MYELOMA DIAGNOSED WITH SECONDARY IMMUNODEFICIENCY DISEASE

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In patients with multiple myeloma (MM), both the underlying disease and immunosuppressive therapy can lead to secondary immunodeficiency disease (SID). SID often manifests in severe, recurrent, or persistent infections that impair health-related quality of life (HRQoL), are a major cause of morbidity and mortality in patients with MM, and result in significant clinical and socioeconomic burden. Hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIG) 10% is a dual-vial unit of IgG 10% and recombinant human hyaluronidase. fSCIG 10% is approved in the USA for the treatment of adults and children aged ≥2 years with PID, and in the EU for patients of any age with primary immunodeficiency disease (PID) or SID. fSCIG 10% is not fully integrated into standard of care for patients with SID in many countries, partly owing to comparatively less familiarity of practitioners with the evidence supporting use of fSCIG 10% than for intravenous (IV) IgG therapy. The HyMMy study (NCT05879757) aims to generate real-world evidence of fSCIG 10% use and outcomes in patients with MM and SID. HyMMy is a prospective, noninterventional, observational study that will be conducted at 31 centres in Europe and South America. One hundred patients are planned to be enrolled and observed over 12 months' follow-up. Eligible patients are aged ≥18 years with a diagnosis of MM who fulfil diagnostic criteria for SID: severe, recurrent, or persistent infection despite appropriate anti-infective treatment, and proven specific antibody failure or a serum IgG trough level of <4 g/L (excluding paraprotein). Patients with a SID diagnosis may enter the study ≤30 days after fSCIG 10% treatment initiation, or after ≤2 doses of fSCIG 10% have been infused (Figure 1).

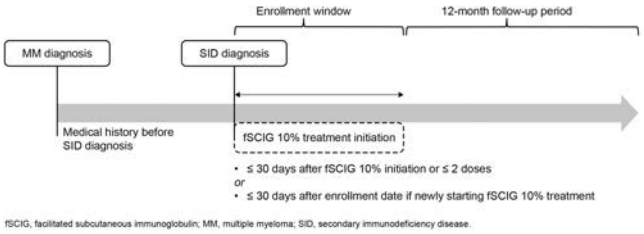

Figure 1. Study design.

Patients newly starting fSCIG 10% have a 30-day window from enrolment to inclusion. Major exclusion criteria include PID, immunoglobulin treatment or prophylaxis within 3 months of enrolment, ongoing serious infection requiring IV antimicrobial therapy, history of malignancy other than MM within 3 years of enrolment, or major surgery within 2 weeks of enrolment. The primary objective is to characterize real-world infusion parameters of fSCIG 10% (including dosing and administration characteristics; treatment interval; infusion volume, sites, rate, and duration; training visits; and reasons for treatment discontinuation, interruption, or switch to other treatment). Secondary endpoints will examine the disease course and clinical management of MM (including overall survival and healthcare resource utilization) in patients treated with fSCIG 10%. Exploratory endpoints include: burden of infection; infection rate, type, duration, and severity; patient-reported outcomes pertaining to HRQoL; and overall physician assessment of fSCIG 10% utilization, tolerability, and effectiveness. Patient recruitment started in June 2023. Interim analysis is planned after enrolment of the first 50 patients. Estimated study end is 2026. HyMMy is the first prospective, observational study focusing on assessment of fSCIG 10% utilization patterns in adults with MM diagnosed with SID. The study will help to improve understanding of treatment patterns and options available for patients with SID and haematologic malignancies, in particular MM. This abstract was first presented at the American Society of Hematology meeting 2023. Study/medical writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

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