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ABSTRACT BOOK

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ABSTRACT BOOK

MAIN PROGRAM

HOW TO DEFINE HIGH RISK SMM?

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High-risk smoldering multiple myeloma (SMM) is defined as multiple myeloma in patients who do not meet the CRAB criteria but have a high probability (approximately 70%) of progressing to symptomatic multiple myeloma within 12 to 24 months, although this threshold is somewhat arbitrary. Accurate identification of these patients is critical to prevent the emergence of devastating MM symptoms. In this population, it is essential to strike the right balance between the benefits of early treatment and the risks of overtreatment. The parameters used to identify high-risk SMM patients should be globally applicable, reproducible, standardized, easy to implement, clinically practical, and highly specific. Why is this identification important? High-risk SMM patients are prime candidates for early intervention in clinical trials, with the goal of delaying or preventing end-organ damage and improving overall survival. In 2008, the Spanish Myeloma Group established criteria based on immunoparesis and the identification of <95% pathological plasma cells by flow cytometry (Table 1). Later, in 2018, researchers from the Mayo Clinic developed a scoring system based on M-protein ≥2 g/dL, bone marrow plasma cells ≥20%, and an FLC ratio ≥20. Patients with ≥2 of these factors were classified as high-risk, with a ~50% probability of progression within 2 years. This model, published by the Mayo Clinic, meets several of the proposed criteria for identifying high-risk SMM. More recently, the International Myeloma Working Group (IMWG) refined this classification by incorporating high-risk cytogenetic abnormalities and introducing a weighted scoring system. High-risk cytogenetics – such as del(17p), t(4;14), t(14;16), +1q, and del(13q) – were added as additional risk factors. In clinical practice, the Mayo 2018 (20/2/20) model has been widely adopted due to its simplicity, while the IMWG 2020 model offers a more granular and comprehensive tool, making it the state-of-the-art for clinical trials and decision-making. To further improve these classifications, other biological factors are being explored. For example, the detection of circulating plasma cells by next-generation flow cytometry has shown promising results. Additionally, factors such as ctDNA, gene expression profiles, immune system status, and the tumor microenvironment are under active investigation. The dynamic of the disease is important. Some patients without meeting the criteria for high-risk smoldering multiple myeloma exhibit an evolving behavior characterized by an increasing M-component. These patients should also be considered at risk for progression. Finally, patient-specific factors such as age and comorbidities should also considered when making treatment decisions.

Table 1. Most scores used to identify high risk smoldering Multiple Myeloma.

Risk Model (Year)	Key Risk Factors (Thresholds)	High-Risk Definition	Progression Risk (High-Risk group)
Mayo Clinic "20/2/20" (2018)	– Bone marrow plasma cells ≥20% – Serum M-protein ≥2 g/dL – Involved serum free light chain (FLC) ratio >20	≥2 of the above risk factors (out of 3)	~44% at 2 years (high-risk group)
IMWG 2020	– **Refined 20/2/20 criteria:** higher M-protein and BMPC thresholds give more points – Serum FLC ratio (continuous) – + **Cytogenetics:** any high-risk chromosomal abnormality (e.g. del17p, t(4;14), +1q, etc.)	Weighted risk score >12 (out of 18)	~73% at 2 years (high-risk); 51% if intermediate (score 9–12)
PETHEMA (Spanish) (2008)	– ≥95% clonal ("aberrant") plasma cells in BM by flow – Immunoparesis (≥1 uninvolved immunoglobulin reduced >25% below normal)	Both risk factors present (2/2)	~73% at 5 years (vs 46% if 1 factor)

DO WE NEED TO TREAT ALL HIGH-RISK SMOLDERING MULTIPLE MYELOMA?

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Smoldering multiple myeloma (SMM) is a plasma cell precursor condition defined by the presence of monoclonal plasma cells in the bone marrow and elevated serum monoclonal proteins but without the symptoms of end-organ damage that define multiple myeloma. The tradition paradigm for the management of SMM has been observation, however, multiple recent studies have evaluated therapeutic interventions for individuals with high-risk disease. Data from the recently published phase III AQUILA study, which was a randomized study comparing three years of single-agent daratumumab to active monitoring, showed that the risk of disease progression or death was 51% lower with daratumumab than with active monitoring (hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.67; p<0.001) at a median follow-up of 65.2 months. The progression-free survival (PFS) at 5 years was 63.1% with daratumumab and 40.8% with active monitoring.[1] This adds to the existing data from two previous phase III studies comparing lenalidomide with or without dexamethasone to observation. In the QuiRedex trials of lenalidomide with dexamethasone (Rd), the median time to progression to MM was 2.1 years in the observation arm and 9.5 years in the Rd arm (HR: 0.28, 95% CI: 0.18-0.44, p< 0.0001) after a median follow-up time of 12.5 years. The median overall survival was 8.5 years in the observation arm and not reached in the Rd group (HR: 0.57, 95% CI: 0.34-0.95, p=0.032).[2] In the ECOG study of lenalidomide versus observation, the PFS was significantly longer with lenalidomide compared with observation (hazard ratio, 0.28; 95% CI, 0.12 to 0.62; p=.002). One-, 2-, and 3-year PFS was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm, respectively.[3] As this growing body of evidence suggests that there may be benefit to treating individuals with high-risk disease, the importance of determining who is of high-risk and if all such patients needs to be treated becomes increasingly important. Further, the question of whether single agent therapy is the best intervention for high-risk disease remains unanswered. We will review existing models for defining risk and explore the question of who should be treated for high-risk SMM.

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MASS-SPECTROMETRY FOR TREATMENT MONITORING OF PATIENTS WITH MULTIPLE MYELOMA

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The monoclonal protein produced by the malignant plasma cell clone is used to assess treatment response in multiple myeloma (MM) patients, as it is usually linked to tumor burden. The standard detection methods (electrophoresis and immunofixation) have remained unchanged for years, except for the recent introduction of serum free light chain analysis by turbidimetry. While these techniques provide valuable clinical information, recent advances in MM treatment have highlighted the need for more sensitive methods to detect residual disease after therapy, known as minimal residual disease (MRD). Although MRD assessment has clear clinical utility, its evaluation in bone marrow samples presents a major limitation, as the procedure is invasive and painful, preventing frequent monitoring. An optimal alternative for MM follow-up would be serum monoclonal protein monitoring using more sensitive and specific detection methods. In recent years, mass spectrometry (MS) has been explored for identifying and quantifying monoclonal proteins. Different MS-based methods target specific analytes: simpler approaches detect intact monoclonal light chains, while more complex ones focus on a specific peptide from the variable region of the immunoglobulin light chain. While the former has already been broadly studied, including its clinical utility, data on the latter remain limited, although the technique achieves higher sensitivity. The Spanish Myeloma Group has evaluated the clinical utility of the EXENT assay, which detects intact monoclonal light chains, in high-risk smoldering MM (GEM-CESAR), transplant-eligible patients during induction (GEM2012) and maintenance (GEM2014), and fit elderly patients ineligible for transplant (GEM2017FIT). These studies confirmed the superior sensitivity of MS over conventional methods and demonstrated its prognostic value, as MM patients deemed negative by standard tests but still detectable by MS had shorter progression-free survival. This subgroup may warrant a new response category beyond conventional complete response, defined by MS detection. Additionally, we compared serum MS results with bone marrow MRD assessment by next-generation flow cytometry (NGF). While MS applied in its current form (it does not include the analysis of the free light chains) appears slightly less sensitive, both methods show comparable clinical value, particularly in later treatment stages when residual monoclonal protein interference is minimal. The potential complementary role of MS in detecting extramedullary disease alongside imaging techniques like PET remains to be determined.

NEW DEFINITION OF HIGH RISK MULTIPLE MYELOMA

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Despite significant improvements in survival outcomes of patients with multiple myeloma (MM) remain heterogeneous, and a significant proportion of patients experience early relapse. Traditional prognostic factors based on data from patients treated with older therapies no longer capture prognosis accurately in the contemporary era of novel triplet/quadruplet therapies. Risk stratification therefore requires refinement in the context of available and investigational treatment options in routine practice and clinical trials, respectively. Identification of high-risk multiple myeloma (HRMM) in current routine practice is based on

the Revised International Staging System, which stratifies patients using a combination of conventional serum biomarkers and chromosomal abnormalities assessed via fluorescence in situ hybridization. In recent years, a substantial body of evidence concerning additional clinical, biological, and molecular/genomic prognostic factors has accumulated, along with new MM risk-stratification tools and consensus reports. The International Myeloma Society (IMS) convened an Expert Panel with the primary aim of revisiting the definition of HRMM and formulating a practical and data-driven consensus definition, based on new evidence from molecular/genomic assays, updated clinical data, and contemporary risk-stratification concepts. The Panel, which met at the July 2023 IMS "*Workshop on Genomics: Defining High-Risk Disease and Developing Targeted Therapies in MM*", proposes the following consensus definition of HRMM: The presence of —del(17p), with a cutoff of >20% clonal fraction, and/or *TP53* mutation; an IgH translocation—t(4;14) or t(4;16) or t(14;20)—along with +1q and/or del(1p); monoallelic del(1p32) along with +1q, or bi-allelic del(1p32); or β2 microglobulin ≥5.5 mg/L with normal creatinine (<1.2 mg/dL). The data supporting this consensus definition will be presented.

GENETIC: GENETIC ASSESSMENT FOR ALL PATIENTS? (EMD PCL CTC AND OTHER FACTORS *VS* GENETIC) – YES

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Newly diagnosed multiple myeloma (NDMM) is characterised by marked variation in an underlying genetic landscape of founder lesions and secondary genetic drivers of disease evolution. A readily accessible component of the diagnostic work up of NDMM is FISH, and where available, NGS approaches. Based on these data the newly described IMS/IMWG criteria for high-risk (HR) disease have been formulated to enable more accurate prognostication and inform risk-stratified clinical trials. While the quantification of the number of circulating tumour cells (CTC) in NDMM is proving to be powerful biomarker for prognostication this approach is not routinely available outside the context of clinical trials and does not provide information in relation to the underlying biological characteristics in individual patients. It is increasingly recognised that a subset of NDMM patients will manifest early disease progression after the initiation of first line therapy, so called functional HR (FHR) disease. Remarkably >50% of the FHR patients manifest no HR cytogenetic abnormalities at diagnosis. It is therefore critical that genetic characterisation of NDMM with NGS be encouraged to enable our understanding and identification of FHR so inform future risk-stratified treatments. Two clinical presentations of MM that manifest drug resistance and unacceptably short survival are extramedullary disease (EMD) and plasma cell leukaemia (PCL). A recent WGS study of EMD has demonstrated that approximately 80% of cases harbour clonal activating driver mutations of the RAS-MAPK pathway while the remainder have no obvious drivers but instead manifest a hyper-mutated genotype. These findings provide a rationale for the use of pan-RAS inhibitors and checkpoint inhibitors, respectively, thus representing potential personalised approaches for these HR clinical variants of MM. Primary PCL manifests t(11;14) in almost 50% of cases thus providing a remarkable opportunity for personalised treatment with BCL2 inhibitors as part of multiagent approaches to the disorder. In summary, the ongoing and expanded use of approaches to genetically characterise MM enables real-time prognostication and treatment stratification, and moreover will continue to increase our understanding of HR subsets of MM such as FHR and provides a powerful rationale for the adoption of genetically guided personalised therapies as has been employed successfully in other haematological malignancies.

DEBATE: GENETIC ASSESSMENT FOR ALL PATIENTS? (EMD PCL CTC AND OTHER FACTORS *VS* GENETIC) – NO

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Nowadays, cytogentic evaluation for identification of high-risk (HR) multiple myeloma (MM) disease is mainly performed with FISH analysis and is obligate for all patients at primary diagnosis. However, beyond this, diagnostic evaluation with extended further diagnostics at primary diagnosis is questionable. The main reason for this is the lack of clear definitions, limited availability, costs as well as the lack of treatment recommendations or approved standard of care treatments for distinct phenotypes. Beyond FISH analysis, genetic assessment with the SKY92 panel is used by several investigators for definition of HR disease. However, the test is provided by a single company, has limited availability and superiority in the identification of HR patients compared to FISH analysis has still to be proven. For PCL, definitions are varying: Whereas PCL was for a long time defined when ≥ 20% circulating plasma cells (CTCs) were detected in the peripheral blood (PB), this threshold was decreased to ≥ 5% in 2021. Most recently it was shown, that patients with ≥ 2%-20% CTCs in the PB had comparable outcomes with those with ≥ 20%, questioning PCL as a separate entity rather than defining CTCs as a marker of ultra HR disease. Even more, clear recommendations whether CTCs should be measured by conventional microscopic analysis or immunophenotyping are still missing. For EMD, definitions also vary: When agreeing on defining EMD as a true organ involvement which is completely separate from the bones and the bone marrow, incidence especially at primary diagnosis is very low and systematic outcome data of these patients under modern standard first line-treatments are lacking. In a number of trials or observations, paraskeletal myeloma manifestations were included in EMD analysis. However, these paraskeletal events are more representing a high myeloma burden rather than a distinct entity and are mainly covered by the initial skeletal CT evaluation. Additional extensive diagnostics *e.g.* with PET-CT for all patients at primary diagnosis would have the risk of delayed staging with a minimum of additional information in the majority of patients and without a direct therapeutic impact. Before it was not been shown that extensive diagnostic work-up beyond FISH analysis is resulting in a better outcome, decision for special diagnostics should be balanced in a careful risk-benefit analysis. (Please note that this is an abstract for a debate and not reflecting the author's opinion).

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE (MGRS)

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Kidney disease is a common complication of monoclonal gammopathies, particularly multiple myeloma, but it can also occur independently of an overt hematologic malignancy. The term MGRS (Monoclonal Gammopathy of Renal Significance) was introduced in 2012 by the IKMG (International Kidney and Monoclonal Gammopathy Research Group) to distinguish these disorders from monoclonal gammopathy of undetermined significance (MGUS), which is not associated with organ

damage. MGRS encompasses a spectrum of renal diseases caused by a monoclonal immunoglobulin secreted by an otherwise indolent but pathogenic plasma cell or B-cell clone. In 2018, the concept was expanded to include diseases caused by a toxic monoclonal immunoglobulin affecting other organs, such as heart, peripheral nerves, skin, and liver, under the broader term Monoclonal Gammopathy of Clinical Significance (MGCS). MGRS-associated renal lesions can be glomerular or tubular and are primarily determined by the molecular characteristics of the monoclonal protein. These lesions may result from direct deposition (organized deposits, such as amyloidosis, or non-organized deposits, as seen in monoclonal immunoglobulin deposition diseases) or indirect mechanisms (autoantibody activity, complement activation) (Figure 1). Progression to end-stage kidney disease is common, and recurrence after kidney transplantation is frequent if the pathogenic clone persists sometimes occurring rapidly and in other cases developing over time. Diagnosis typically requires a renal biopsy, except in AL amyloidosis, which is often diagnosed via peripheral tissue biopsy (fat aspiration or minor salivary gland biopsy). Histologic studies include light microscopy, immunofluorescence, and electron microscopy, along with a comprehensive hematologic workup (serum and urine protein electrophoresis, immunofixation, free light chain assay, and bone marrow analysis with flow cytometry and cytogenetics). Management focuses on clone-directed therapy, proteasome inhibitors and anti-CD38 monoclonal antibodies or anti-CD20 antibodies containing regimens. Achieving a deep hematologic response improves renal function and prevents post-transplant recurrence. In some MGRS-related diseases, a complete hematologic response is mandatory, whereas in others, a partial hematologic response may be sufficient. MGRS should be recognized as a distinct clinical entity requiring targeted treatment to prevent irreversible kidney failure and improve patient outcomes.

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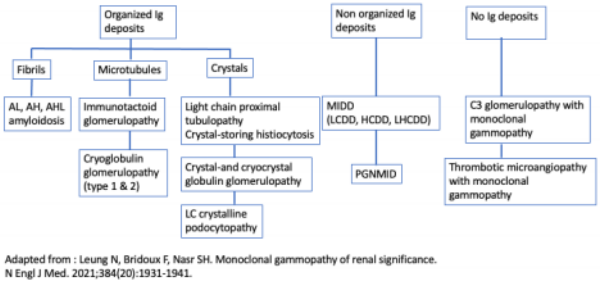

Figure 1. IKMG classification of principal MGRS-related renal diseases.

MGUS WITH OTHER TYPES OF PATHOLOGIES

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Monoclonal gammopathy of Undetermined Significance (MGUS) is a common condition, affecting almost ~5% of the population >50 years and of low malignant potential in most. The small clones in MGUS may occasionally cause a variety of complications and syndromes that are associated with the physicochemical or the immune properties of monoclonal immunoglobulins (MIg) or may be "paraneoplasmatic" related to cytokine secretion. Immunoglobulin light chain (AL) amyloidosis is a disease associated with MGUS clones, the kidneys are common target-organ of MIg derived from MGUS clones either directly or indirectly (termed monoclonal gammopathy of renal significance). Several other systemic syndromes have a causal association with a monoclonal gammopathy, most commonly MGUS, which may affect a single or multiple organs or organ systems and can be included under the term monoclonal gammopathy of clinical significance (MGCS). The diagnostic approach is challenging due to the varying clinical presentations, even among the same "condition", the low index of suspicion, the requirement for advanced technology in some and the varying degree of association with the underlying MGUS. A combination of clinical, laboratory and histologic criteria is required for the diagnosis. Peripheral nervous system is commonly affected, through different mechanisms, either directly by the MIg, as in IgM anti-MAG polyneuropathy, or indirectly, as in POEMS syndrome. Dermatologic conditions have been associated with an underlying MGUS, with or without systemic manifestations (scleromyxedema, necrobiotic xanthogranuloma, Schnitzler syndrome etc); muscles (as in nemaline myopathy) or the eyes (keratopathy) may be involved. Systemic syndromes may be related to specific properties of the MIg (cryoglobulinemia, cold agglutin activity, autoantibody activity) or to cytokine activity.; often 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 MGUS patients 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 anti-clonal therapies; in others, benefits may not be as prominent while in some non-clone-targeting therapies may be indicated.

CHALLENGES IN TREATMENT OF RR AMYLOIDOSIS

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The treatment landscape of AL amyloidosis has changed radically thanks to the introduction of the new standard of care, daratumumab, bortezomib, cyclophosphamide, and dexamethasone (Dara-CyBorD) in the upfront setting. This regimen is now available in many countries but is still not approved for patients with advanced cardiac disease at diagnosis (stage IIIb). Nevertheless, daratumumab-based combinations or single-agent regimens are recommended by the European Hematology Association (EHA) and the International Society of Amyloidosis (ISA) guidelines. Despite the high efficacy reported, some patients eventually attain a suboptimal hematologic response or develop resistance to Dara-CyBorD or other daratumumab-based combinations, requiring a subsequent line of therapy. Due to its recent introduction in the first-line treatment armamentarium, there is limited data regarding the best rescue treatment for patients who have received daratumumab in the upfront setting, and to date, no approved regimen for the treatment of refractory/relapsed AL amyloidosis exists. A study from the Mayo group explored the effectiveness of various treatment approaches, including autologous stem cell transplant (ASCT) and immunomodulatory agents (IMiDs), in a limited group of individuals who had prior exposure to Dara-CyBorD. However, due to the small patient cohort, drawing definitive conclusions remains difficult. The choice of treatment in this context must follow EHA and ISA guidelines. In particular, for the few daratumumab-naïve patients, a regimen containing the anti-CD38 antibody is

recommended. For patients refractory to daratumumab and proteasome inhibitors, IMiDs (i.e., lenalidomide and pomalidomide) remain the best option. For eligible patients, ASCT may be considered. Recently published retrospective case series reported high rates of hematologic response in relapsed/refractory AL amyloidosis patients receiving venetoclax-based therapies, which could represent an option for those harboring t(11;14). The use of belantamab mafodotin has been evaluated in the recently terminated EMN27 clinical trial, and bispecific antibodies (*i.e*. teclistamab, elranatamab) have been studied in small retrospective series. Moreover, a recent study on the CAR-T approach has shed light on its potential role in AL amyloidosis.

In conclusion, future comparative studies are needed to define optimal treatment strategies, which should be carefully tailored based on disease and patient characteristics.

GENERAL OVERVIEW OF UPFRONT TREATMENT

X. Leleu

CHU Poitiers, France

The treatment of newly diagnosed Multiple Myeloma has evolved towards the systematic use of CD38-targeting immunotherapy containing regimens as induction and consolidation, with or without an intensification of ASCT type according to particular transplant eligibility features. The most important objectives of the upfront treatments remain the survival times. Interestingly, the depth of response remains ORR and CR in the real-life use, although it has been replaced by MRD negative status in the context of the research programs. The most effective regimen has become the PERSEUS-type parkour with transplant the gold standard approach for patients eligible. This parkour is challenged in various ways. The recent reports on excellent data using the IMROZ/CEPHEUS/ BENEFIT CD38-targeting immunotherapy containing quadruplet-based regimens in transplant ineligible/deferred newly diagnosed Multiple Myeloma question on the systematic use of the transplant. The use of bortezomib as the preferred/approved/reimbursed proteasome inhibitor in the regimen is also challenge with great data coming from carfilzomib. Whether early MRD analysis could drive the ASCT decision. Whether ASCT could be challenged by CAR t, myeloablative versus immunological intensifications, and for who. Last not least, whether the T-cell redirecting bispecific/trispecific agents, particularly the BCMA/CD3 targeting ones, will challenge the CD38 immunotherapy or will complement its use, again when as induction, to replace ASCT/Car t cells, as a post maintenance treatment, and for whom high-risk MM, MRD positive MM, all comers, remains subject of questions. As a conclusion, the cure of Myeloma will come, if possible, with constantly improving the upfront line of treatment. Once the tumor cells are trained to relapse/resist it is likely too late to hope better than to improve survival times. The presentation will set the stage with PERSEUS as a start and review some of the important scientific questions to answer in the time to come.

DO WE NEED CONTINUOUS DEXAMETHASONE IN FIT PATIENTS?

X. Leleu

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The treatment of Multiple Myeloma is marked by relapse of the disease. No patients can be considered cured, unless to agree upon a functional cure with or without treatments. So, to maintain patients on treatment is absolutely key, and for many patients it would last for years (long run). The demonstration that fixed duration is as good as continuous treatments remains is yet to be seen. Therefore, the safety profile and the quality of life on treatments is a key element. It was showed that CD38-targeting immunotherapy containing quadruplet-based regimens, the new standard of care across most fit patients' populations in newly diagnosed Multiple Myeloma had no specific safety profiles, but the safety profile of each agents. Dexamethasone has been given in Multiple Myeloma for various reasons, including direct anti-Myeloma activity, that can immediately within hours decrease certain complications induced by MM (pain in general, bone pain, anti-inflammatory effect, tumor reduction and therefore tumor mass compression symptoms' reduction), and also immune reaction mitigation, limitations in certain side effects, and also to give a boost to patients that initially suffer from cancer, anemia, pain etc. Although never clearly demonstrated, it is believed that the balance benefit risk changes over time with a decrease antitumor effect initially to an increase side effect frequency profile later on. It is also unclear when and how to identify this change at a patient level. Importantly, many studies have now demonstrated the obvious, that the early decrease of dexamethasone dose or its early interruption was responsible for a significant reduction in side effects profile with no loss of activity of the regimen as a whole. This has been repeatedly demonstrated in frailer patients, least to say it certainly is applicable to fit patients whom receive much more complex regimens and largely more active regimens. As a conclusion, the least effective drug in the 4 drugs-based regimen is likely dexamethasone, rapidly becoming the potential most toxic one over the disease course of treatment. To learn when and when to tap down, then permanently discontinue, the dexamethasone is a need for the patients, an art from the physician point of view and a great improvement in the quality of life and survival time of our patients, our ultimate goal.

SELINEXOR

S. Delimpasi

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Mechanism of action

XPO1, is a protein that regulates the bidirectional movements of various proteins between the nucleus and the cytoplasm of a cell. Overexpression of XPO1 occurs in MM, is essential for myeloma cell survival, and correlates with a shorter survival and increased bone disease. Selective inhibitor of nuclear export (SINE) compounds bind to XPO1 mediating the inactivation of cell-cycle regulators and promoting the export and translation of mRNA for key oncoproteins, including c-MYC, BCL-2, and cyclin D.

Selinexor

Selinexor is an oral SINE that targets XPO1 and the first in class drug to be used in the treatment of R/R MM. The MOA of selinexor mediates the inhibition of XPO1, causing the retention and activation of tumor suppressor proteins, disrupting signaling pathways, and resulting in apoptosis. In myeloma cells, selinexor treatment has been shown to induce apoptosis, reduce levels of proto-oncoproteins, and impair osteoclastogenesis.

Early clinical trial data assessing selinexor/dexamethasone in triple-class R/R MM

<u>STORM: selinexor/dexamethasone (Sd)</u>

In the 2019 phase 2 clinical trial STORM, the oral doublet combination of Sd was given twice weekly to patients with penta-exposed, triple-class R/R MM. The median number of previous regimens was 7 (range: 3, 18). An overall response rate (ORR) was observed in 26% of patients

including 2 stringent complete responses (sCRs) and 39% of patients had a minimal response or better. The median duration of response (DOR) was 4.4 months, median progression-free survival (PFS) was 3.7 months, and median overall survival (OS) was 8.6 months. The most common grade 3/4 adverse events (AEs) were thrombocytopenia (58%), anemia (44%), hyponatremia (22%), and neutropenia (21%). Eighteen percent of the patients discontinued treatment due to a treatment-related adverse event of selinexor or dexamethasone. The phase 2 STORM trial with the oral combination Sd showed a positive response rate in triple-class refractory R/R MM.

Early clinical trial data assessing safety and the maximum tolerated dose (MTD) of selinexor with several backbone agents in patients with MM

STOMP is a phase 1b/2 study evaluating selinexor and low-dose dexamethasone in combination with 1 of several standard approved therapies including lenalidomide, pomalidomide, bortezomib, carfilzomib, or daratumumab in patients with R/R MM. One arm investigated the combination of selinexor and lenalidomide in patients with newly diagnosed multiple myeloma (NDMM).

Phase 3 clinical trial data assessing weekly selinexor/bortezomib/dexamethasone (SVd) vs twice-weekly bortezomib/dexamethasone (Vd) in R/R MM with 1 to 3 prior lines of therapy

BOSTON

The phase 3 BOSTON trial, published in 2020, evaluated the response rates between oral weekly SVd and twice-weekly bortezomib plus dexamethasone (Vd) in R/R MM with 1 to 3 prior lines of therapy.

A significantly longer median PFS was oberseved in the SVd group with 13.9 months compared to 9.5 months in the Vd group; HR 0.70 (95% CI: 0.53, 0.93), P=.0075. The ORR was also significantly higher in the SVd group (76.4%) compared to the Vd group (62.3%); odds ratio 1.96 (95% CI: 1.3, 3.1), P=.0012. The median OS was not reached in the SVd group, but was 25 months in the Vd group. Patients in the SVd arm experienced more frequent grade ≥ 3 AEs compared to the Vd arm including thrombocytopenia (39% versus 17%), fatigue (13% versus 1%), anemia (16% versus 10%); however, the rate of grade ≥ 2 peripheral neuropathy (PN) was significantly lower in the SVd group (21%) compared to the Vd group (34%).

BOSTON subgroup analysis

Several subgroup analyses of the phase 3 BOSTON trial were recently presented at ASH 2020 assessing the effect of prior treatments and frailty on outcomes, as well as rates of PN.

- Cytogenetic Risk Status: Prespecified subgroup analyses from the BOSTON study according to cytogenetic risk status were investigated and resulted in a superiority of SVd to Vd in patients with MM including high-risk patients despite using 40% less bortezomib and 25% less dexamethasone during the first 24 weeks of treatment. The PFS benefit for SVd compared to Vd was particularly notable in patients with del(17p), t(4;14), and amp(1q21) abnormalities -- 12.2 months vs 5.9 months; 13.2 months vs 7.0 months; 13.9 months vs 7.2 months, respectively. The ORR was comparable between the high-risk and standard-risk groups in the SVd arm.
- Effect of Prior PI: A subgroup analysis of treatment outcomes based on prior PI treatment was reported. PFS was prolonged with SVd in both the PI-treated group and PI-naive group compared to Vd. In the PI-treated group, PFS was 11.7 months vs 9.4 months; HR 0.78, P=.057 and in the PI-naive group, PFS was not reached vs 9.7 months; HR 0.26, P=.0003. Grade 2 or greater PN was less frequent in SVd than with Vd (PI-naive [25.5% *vs* 43.8%, P=.03] and the PI-treated groups [19.6% *vs* 31.4%, P=.009]).
- Impact of Prior Therapies and Prior Treatment with Lenalidomide (len): Another subgroup analysis of the BOSTON trial was performed and reported outcomes according to the number of prior lines of therapy (1 prior therapy vs 2 to 3 prior therapies) and prior treatment with len (len-treated vs len-naive). The PFS significantly improved with SVd in patients with 1 prior therapy (16.6 months *vs* 10.7 months; P=.0148) and ≥ 2 prior lines (11.7 months vs 90.4 months; P=.0295). SVd was active with a PFS HR of 0.63 among patients with prior len treatment who received SVd compared to Vd. The ORR significantly improved with SVd in patients with 1 prior therapy (80.8% vs 65.7%; P=.008) and ≥ 2 prior lines (71.9% *vs* 59.3%; P=.029). Finally, SVd was associated with significantly reduced rates of ≥ grade 2 PN in all subgroups compared with Vd; len-treated 21% vs 37%; len-naive 21% *vs* 33%; 1 prior line 21% *vs* 33%; 2 to 3 prior lines 21% vs 36%, respectively.
- Age and Frailty: A subgroup analysis of age (< 65 years and ≥ 65 years) and frailty from the phase 3 BOSTON trial was presented and reported improved PFS in the SVd arm regardless of age and frailty score compared to the Vd arm. The PFS was 21 months in the SVd arm compared with only 9.5 months in the Vd arm for those ≥65 years (HR, 0.55; 95% CI: 0.37, 0.83; P=.0018) . SVd reported a sustained PFS benefit with and comparable results in frail patients: 13.9 vs 9.5 months (HR, 0.69; 95% CI: 0.40, 1.17; P=.08). TREAs in the SVd arm were comparable across subgroups except for a higher incidence of fatigue and pneumonia in those ≥ 65 years and frail groups. PN ≥ grade 2 was lower in the SVd arm, but were still significantly higher in those ≥ 65 years (22% *vs* 37%) and frail patients (15% *vs* 44%).
- Patient-reported outcomes in BOSTON were analyzed to evaluate patterns in therapy-induced PN symptoms, pain, and function. Patients in the twice-weekly Vd group had a more rapid rate of sensory symptom worsening and a trend to more rapid worsening of motor symptoms compared to the SVd group. In the Vd group, 45.7% experienced sensory symptom deterioration with a median time to deterioration of 12.5 months; in the SVd group, 27.7% experienced sensory symptom deterioration with a median time to deterioration of 20.7 months.

The results of the phase 3 BOSTON trial and the subgroup analysis are impactful, indicating that once-weekly oral SVd is effective and a convenient treatment option and results in improved PFS and ORR compared to twice-weekly Vd for patients with 1 to 3 prior lines of therapy in R/R MM regardless of prior therapy, frailty, or age.

Other novel XPO1 inhibitors

Eltanexor is a second-generation XPO1 inhibitor and is currently in phase 1b/2 clinical trials. This study has both escalation and expansion stages to assess the preliminary safety, tolerability, and efficacy of eltanexor in patients with R/R MM and other refractory cancers. Most patients who were enrolled were quad- or penta-refractory. Median duration of treatment thus far is 76 days and the most common TRAEs is thrombocytopenia (43%). Based on preliminary data from NCT02649790, eltanexor is well tolerated and demonstrates promising activity in this heavily pretreated R/R MM population.

ANTIBODY-DRUG CONJUGATES FOR SECOND LINE

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Treatment at second line is challenging, especially for patients who are exposed or are refractory to both daratumumab and lenalidomide. Belantamab mafodotin (belamaf, Bela) is an afucosylated humanized B-cell maturation antigen (BCMA) IgG1 monoclonal antibody (mAb) conjugated to microtubule disrupting monomethyl auristatin F (antibody drug conjugate, ADC). Its combinations with bortezomib and dexam-

ethasone (Vd) or with pomalidomide/dexamethasone (Pd) were recently approved by FDA (approval by EMA is awaited) for patients with relapsed/refractory multiple myeloma (RRMM), who received 1-3 prior lines of therapy. In the DREAMM-7 study, 494 patients were randomly assigned to receive BelaVd (n=243) or DaraVd (n=251). At a median follow-up of 39.4 months, median progression-free survival (PFS) was 36.6 months for the BelaVd group and 13.4 months for the DaraVd group (HR: 0.41; 95% CI: 0.31 to 0.53; p<0.001). Overall survival (OS) at 36 months was superior for BelaVd (74% versus 60%; HR: 0.58; 95% CI: 0.43-0.79; p=0.00023). Ocular events were more common in the BelaVd group than in the DaraVd group (79% vs. 29%); such events were managed with dose modifications, and events of worsening visual acuity mostly resolved. Thus, BelaVd is a new SoC for patients with 1-3 prior lines of therapy, but formal approval by relevant authorities is pending. Notably only 33% of patients were lenalidomide refractory in the BelaVd arm and none were daratumumab refractory. The second study evaluated BelaPd (n=155) as compared with PVd (n=147), in lenalidomide-exposed patients who had RRMM after at least one line of therapy (DREAMM-8 study). At a median follow-up of 21.8 months, the 12-month estimated PFS with BelaPd was 71% versus 51% with PVd (HR: 0.52; 95% CI:0.37-0.73; p<0.001). In lenalidomide-refractory patients median PFS was 25 months (95% CI: 18.1–NR) for BelaPd versus 8.6 months (95% CI: 6.4-13.5) for PVd (HR: 0.31; 95%CI: 0.19-0.48). Ocular events occurred in 89% of the patients who received BelaPd (grade 3 or 4 in 43%) and 30% of those who received PVd (grade 3 or 4 in 2%). The median dose intensity of belamaf was equal to 1.9 mg/kg given every 8-12 weeks, despite the scheduled dose of 2.5 mg/kg every 4 weeks for the first cycle and 1.9 mg/kg every 4 weeks from cycle 2 and after. Ocular AEs led to treatment discontinuation in 9% of the patients in the BelaPd arm. BelaPd approval is pending by the authorities.

TALQUETAMAB BISPECIFIC ANTIBODY: FROM PRECLINICAL INSIGHTS TO COMBINATION THERAPY STRATEGIES

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Talquetamab (TAL) is a first-in-class bispecific antibody (BsAb) targeting G-protein-coupled receptor class 5 member D (GPRC5D) and CD3, providing a novel therapeutic approach for relapsed and refractory multiple myeloma (RRMM) patients (Pts). TAL was approved by the FDA and EMA, for patients who have progressed after ≥4 prior lines of therapy (LOTs). TAL binds simultaneously to GPRC5D on myeloma cells and CD3 on T-cells, forming an immune synapse that enhances T-cell activation and cytotoxicity, by promoting the release of cytotoxic granules and pro-inflammatory cytokines, leading myeloma cell death. GPRC5D gene's ligand and biological function remain largely unknown. Plasma cells exhibit the highest GPRC5D expression, it is minimally/not detected in normal B cells, T cells, natural killer cells, monocytes, granulocytes, and progenitors. Expression in epithelial structures such as the tongue and skin are responsible for the mouth, skin and nail toxicities, there is minimal expression in other tissues. The pivotal MonumenTAL-1 trial evaluated TAL's safety and efficacy in a heavily pre-treated highly refractory population with a median of 5 prior LOTs. Overall response rate was approximately 70%, at the recommended phase 2 dose of 0.8 mg/kg Q2W, median PFS was 11.2 mo, comparable in Pts with high- vs standard-risk cytogenetics, median response duration was 17.7mo and 24mo overall survival was 67%. Safety profile was manageable, with cytokine release syndrome occurring in 77% of Pts, predominantly grade 1-2. TAL's unique on-target off-tumor effects included dysgeusia leading to weight loss, and skin-related toxicities. Notably, rate of infections was lower compared to BCMA targeted T-cell re-directional therapy. Resistance mechanisms remain of concern, Pts may develop biallelic inactivation or epigenetic silencing of GPRC5D, diminishing TAL's efficacy. Ongoing studies are exploring combination therapies to mitigate resistance, investigating TAL in combination with daratumumab, pomalidomide, and teclistamab, aiming to leverage synergistic effects and modulate tumour micro-environment to enhance efficacy, preliminary results are encouraging. Overall, talquetamab represents a promising therapeutic option in the evolving landscape of MM treatment, particularly for Pts with limited options due to therapeutic resistance, highlighting the importance of continued research into combination strategies and resistance mechanisms to optimize its clinical application.

BISPECIFICS IN COMBINATIONS

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T-cell redirecting antibodies have high activity in relapsed/refractory MM. Preclinical studies have shown that combination therapy with IMiDs, CD38 antibodies or checkpoint inhibitors may enhance the activity of bispecific antibodies. In this presentation, an overview will be provided of available clinical evidence from studies evaluating bispecific antibodies in combination with other anti-MM agents

IMPROVING SHARED DECISION-MAKING IN MYELOMA: RECOMMENDATIONS BASED ON THE NEEDS AND EXPERIENCES OF EUROPEAN PATIENTS AND HEALTHCARE PROFESSIONALS

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Myeloma treatment decision-making involves complex trade-offs, including overall survival, side effects, progression free survival, and quality of life. With an increasing number of myeloma treatments, patients need to be as informed as possible when making decisions about their treatment. Patients' personal factors and preferences, and physician preferences and values, all play a role in determining how patients arrive at treatment decisions. However, few studies have investigated how myeloma treatment decisions are made in practice, what is working well, and what might need to be improved. Myeloma Patients Europe's research examined current experiences of patients and health professionals with decision-making, barriers and facilitators to Shared Decision-Making (SDM), and how to improve SDM in myeloma. Our goal was to better understand the patient experience and to inform improvement efforts so that treatment decisions can better reflect patients' needs and preferences. Phase 1 included semi-structured interviews with 39 patients from 9 European countries and 20 healthcare professionals from 5 countries. Phase 2 included an online survey of 558 patients from 21 European countries and 89 healthcare professionals from 15 countries. The research findings highlighted a lack of knowledge on what SDM is. Myeloma patients also reported not having been as involved in the decision-making process as they would ideally have liked to have been, both at diagnosis and in later lines of treatment. Barriers to SDM included a lack of understanding of what healthcare professionals say and patients not feeling they had sufficient knowledge to be involved. The research produced 16 recommendations for healthcare professionals, health systems, and resource development to help improve and expand shared decision-making in myeloma. MPE is now working in partnership with patients, families, health professionals and researchers to realise the recommendations through education, awareness, support and empowerment.

NEW CRITERIA FOR RESPONSE - REVISITING RESPONSE CRITERIA IN MULTIPLE MYELOMA: ALIGNING WITH ADVANCES IN THERAPY AND DIAGNOSTICS

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Multiple myeloma is a rapidly evolving disease, with significant advancements in both therapeutic strategies and laboratory techniques over the past decade. Given these developments, a revision of the current response criteria is imminent. The integration of next-generation flow cytometry into routine practice has facilitated the assessment of minimal residual disease (MRD) in both bone marrow and, potentially, peripheral blood. With the widespread adoption of frontline quadruplet therapies and a high proportion of patients achieving MRD negativity, MRD status should be the ultimate goal of treatment. Furthermore, the necessity of serial bone marrow examinations remains crucial, as patients with sustained MRD negativity experience prolonged, sometimes lifelong, remission. Determining the optimal frequency and timing of MRD assessments is therefore essential. With highly sensitive techniques capable of detecting a single clonal cell among a million, the continued reliance on traditional microscopic evaluation of plasma cells warrants reconsideration. Additionally, novel mass spectrometry techniques suggest that MRD assessment in peripheral blood may soon become a viable alternative to bone marrow evaluation. These advancements allow for superior prognostic stratification compared to conventional bone marrow morphology, which remains the standard criterion for complete response (CR). In light of these changes, the relevance of certain traditional response criteria, such as minimal response, must be reassessed—particularly given the efficacy of modern therapeutic options, even in relapsed patients. Likewise, the necessity of urine M-protein assessment in defining CR is questionable, at least for patients with intact immunoglobulin molecules, as it is infrequently performed in clinical practice and holds limited prognostic value. Other practices, such as serial sample measurements for response assessment and overlooking free light chains in patients with intact immunoglobulin molecules, also warrant reevaluation. In conclusion, given the speed and depth of responses achieved with contemporary treatments, the response criteria for multiple myeloma must be redefined to align with ongoing therapeutic and diagnostic advancements.

REAL WORD DATA

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Real-world evidence (RWE) refers to clinical data collected outside controlled clinical trials (RCTs), including patient registries, electronic health records, and insurance claims. While RCTs provide high-quality data, they often exclude diverse patient populations, making RWE crucial for assessing real-world effectiveness. RWE helps evaluate treatment outcomes in populations usually excluded from RCTs such as elderly patients, those with comorbidities, and those in different healthcare settings. RWE also provides valuable data when RCTs are not feasible, such as rare diseases or long-term treatment outcomes. Regulatory agencies, such as the FDA and EMA, increasingly consider RWE for drug approvals and post-marketing surveillance. RWE plays also a key role in evaluating cost-effectiveness, healthcare utilization.

Real-World Evidence in Multiple Myeloma (MM). MM is a heterogeneous disease with varying progression, making RWE essential for understanding treatment responses in different subgroups. Approximately half of MM patients are excluded from RCTs. MM treatments have rapidly advanced, with novel agents such monoclonal antibodies, bispecific T-cell engagers and CAR-T therapy. RWE helps assess their real-world effectiveness, also provides insights into the optimal order of therapies, particularly in relapsed or refractory MM. RWE contributes to understanding overall survival (OS) and progression-free survival (PFS) beyond RCTs conditions, very frequent weakness of RCTs in MM. Access to modern therapies is one of the critical point for prognosis improvement in MM. RWE highlighting disparities in treatment access, identifying gaps in healthcare systems that affect patient outcomes. Finally, by supplementing RCT data, RWE supports updates to clinical guidelines and real-world treatment recommendations in MM.

Registry of Monoclonal gammopathies (RMG): RMG (https://rmg.healthregistry.org) of Czech Myeloma Group is an international clinical registry established in 12/2006. The RMG is open to collaboration with cancer centres and groups across the Czech Republic, Slovakia, and other European countries. CMG is participating on analysis inside networks that are collaborating to unlock the transformational potential of RWE such as Honeur, Harmony and Ehden. Currently (3/2025) there are total of 16867 patients enrolled to RMG (MGUS, 5278; MM 10 629; WM 364; ALA 172 pts.). Typical as well as remarkable examples of RWE data from RMG will be presented during session.

UPDATE OF EUROPEAN GUIDELINES FOR FIRST-LINE TREATMENT OF MULTIPLE MYELOMA

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Multiple myeloma (MM) is a complex hematologic malignancy, and its management has significantly evolved in recent years due to new therapeutic classes and improved treatment strategies. In this context, the European guidelines for first-line treatment of MM are updated to integrate the latest scientific and therapeutic advances. This update is based on data from phase III clinical trials, cohort reviews, and expert recommendations, with the goal of personalizing treatment according to the clinical and biological characteristics of patients. First-line treatments are now centered on drug combinations, including proteasome inhibitors, immunomodulators, and monoclonal antibodies, which offer more durable responses and better management of side effects. Among these strategies, regimens combining bortezomib (proteasome inhibitor), lenalidomide (immunomodulator), and the anti-CD38 monoclonal antibody daratumumab have proven effective, in both patients eligible or not for autologous stem cell transplantation. The guidelines also emphasize the importance of evaluating the patient's genetic status, and highlight the importance of a personalized approach to optimize therapeutic outcomes, reduce relapse risks, and improve patients' quality of life. Future research should continue to explore the impact of these innovative therapies and combination strategies to refine first-line treatment in MM.

SECOND LINE THERAPY FOR MYELOMA

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Treatment choices at second line are based on the regimens that were given at first line, taking into consideration efficacy, toxicity and refractoriness to previous drugs, as well as patients comorbidities. The new EHA/EMN guidelines provide recommendations based on novel data

from several clinical trials that were published between 2021 and 2024. Thus, patients who had received a bortezomib-based therapy upfront, without lenalidomide or anti-CD38 mAb and are bortezomib refractory, the preferred regimens are DaraRd, DaraKd, IsaKd, or BelaPd [I, A]; other approved regimens include KRd, IxaRd or EloRd [I, A].

Patients who had received a bortezomib-based therapy upfront, without lenalidomide or anti-CD38 mAb and are bortezomib sensitive, should receive preferably DaraRd, DaraKd, IsaKd, BelaVd, or BelaPd [I, A]. Other approved regimens include KRd, IxaRd, EloRd SelVd or Kd [I, A]. PomVd or DaraVd maybe used in the absence of BelaPd or BelaVd, respectively [panel consensus; I, A].

Eligible patients who are refractory to lenalidomide upfront and are anti-CD38 mAb naive or sensitive should receive cilta-cel [I, A] if available. Other options for lenalidomide refractory patients include DaraKd, IsaKd, BelaPd, BelaVd, DaraPd or SelVd [I, A]. The combinations of anti-CD38 mAbs with Kd or BelaPd offer the best results in these, refractory to lenalidomide, RRMM patients and are preferred. PomVd or DaraVd may be used in the absence of BelaPd or BelaVd, respectively [panel consensus; I, A].

Patients who are both refractory to lenalidomide and bortezomib, and are anti-CD38 mAb naive or sensitive, should receive Cilta-cel, BelaPd, DaraKd, IsaKd [I, A] or DaraPd [II, B]. In patients, who are both refractory to lenalidomide and daratumumab, cilta-cel and BelaPd [I, A] are the preferred options, as they are the only regimens that have been tested in patients who received both lenalidomide and daratumumab previously, in the early relapsing setting. SelVd [II, C], BelaVd [V, C] and Kd [V, C] can be used in this setting (only in case of bortezomib sensitive patients) if other options are not available; however, there is no or limited evidence to support this recommendation (almost no daratumumab refractory patients participated in the registrational studies of these regimens; panel consensus).

For patients with limited access to novel regimens, a second-line ASCT can be an option for those who received primary therapy that included an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥36 months (panel consensus).

THIRD LINE TREATMENT AND BEYOND

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The management of relapsed/refractory multiple myeloma (RRMM) in patients receiving third-line treatment and beyond remains a major challenge, as most patients are refractory to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies. The emergence of novel immunotherapies, including chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies (BsAbs), has transformed the treatment landscape for heavily pretreated patients. CAR T-cell therapies, such as ciltacabtagene autoleucel (cilta-cel) and idecabtagene vicleucel (ide-cel), have demonstrated deep and durable responses in triple-class refractory patients, with cilta-cel showing median progression-free survival exceeding two years in some cohorts. BsAbs targeting BCMA, including teclistamab and elranatamab, and the GPRC5D-targeting agent talquetamab, offer off-the-shelf alternatives to CAR-T therapy with promising efficacy, particularly in patients previously treated with anti-BCMA therapies. Treatment sequencing remains a critical consideration, as prior exposure to BCMA-targeted therapies may affect the efficacy of subsequent immunotherapies. While antibody-drug conjugates such as belantamab mafodotin remain an option, their use requires careful management of ocular toxicities. The optimal integration of these novel agents into treatment algorithms is an area of active investigation, with ongoing trials evaluating combination strategies and earlier use of immunotherapies. As therapeutic options expand, individualized treatment decisions based on prior drug exposure, resistance mechanisms, and patient-specific factors are essential to improving outcomes for patients with advanced multiple myeloma.

DEVELOPMENT AND VALIDATION OF A DATA-DRIVEN MACHINE LEARNING RISK STRATIFICATION STRATEGY FOR MULTIPLE MYELOMA: INSIGHTS FROM THE HARMONY ALLIANCE PLATFORM

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The study presents a machine learning (ML)-based risk stratification strategy for multiple myeloma (MM), addressing the limitations of traditional models like ISS, R-ISS, and R2-ISS, which rely on static clinical and cytogenetic parameters. Using data from the HARMONY Consortium (14,345 patients, including 10,843 newly diagnosed MM cases), we developed a strategy that integrates different levels of risk prediction: baseline, treatment-informed, and dynamic models, improving prognostic accuracy across different clinical scenarios. The baseline model, built using Random Survival Forests, included 20 variables, such as hemoglobin, β2-microglobulin, albumin, and key cytogenetic markers (1q gain, 17p deletion). It achieved a c-index of 0.667 for overall survival (OS) and 0.627 for progression-free survival (PFS), outperforming conventional stratification systems. A simplified model with just six variablesmaintained comparable accuracy, ensuring clinical feasibility, while a cytogenetics-free model also performed well, making it applicable in cases where genetic testing is unavailable. Beyond the baseline prediction, the treatment-informed model incorporated initial therapy regimens (proteasome inhibitors, immunomodulatory drugs, or combinations), leading to improved PFS predictions. The dynamic model further refined risk assessment by recalibrating scores based on a patient's response to induction therapy, adapting risk predictions in real-time as disease progression and treatment response evolve. The models showed strong reproducibility in relapsed/refractory MM, including patients treated with daratumumab-based regimens, further supporting their robustness. Importantly, an interactive online risk calculator was developed to integrate these ML-driven predictions into clinical practice, allowing real-time, patient-specific risk assessments (taxonomy.harmony-platform.eu/riskcalculator/). By leveraging large-scale clinical trial data, machine learning, and a multi-layered risk assessment framework, this study proposes amore dynamic, personalized approach to MM risk stratification, with potential applications in treatment decision-making, clinical trial design, and future integration with genomic and minimal residual disease data.

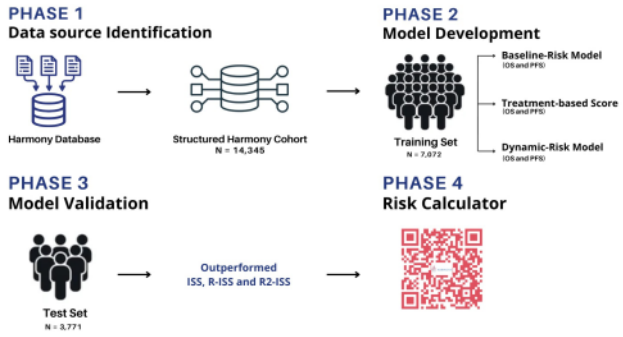

Figure 1.

BEST ABSTRACTS

B01

PREDICTIVE VALUE OF GLUT1 EXPRESSING CIRCULATING NORMAL AND MALIGNANT PLASMA CELLS IN MULTIPLE MYELOMA

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Circulating tumor plasma cells (CTCs) are important biomarkers in multiple myeloma (MM), providing valuable prognostic information about disease severity and progression. Glucose transporter 1 (GLUT1) plays a crucial role in immune cell metabolism and is a prognostic and diagnostic marker in various cancers. However, the expression of GLUT1 on normal and malignant plasma cells (PCs) and its prognostic implications in MM remain unclear. This study explores GLUT1 expression profile on normal and malignant PCs throughout the various stages of MM disease and examines correlations between GLUT1-expressing CTCs and clinical parameters. Bone marrow (BM) and peripheral blood (PB) were collected from 112 patients, including 4 with monoclonal gammopathy of undetermined significance (MGUS), 15 with smoldering MM (SMM), 15 with newly diagnosed MM (NDMM), 59 in complete remission (CR), 19 with relapse refractory MM (RRMM) and 20 healthy controls (HCs). Samples were processed and analyzed using adapted Euroflow protocols and flow cytometry for the surface expression of GLUT1, utilizing receptor binding doming (RBD) reagents from Metafora Biosystems. The study adhered to Good Clinical Practice Guidelines (study n° 7411, prot. n° 0073322) with informed consent obtained from all patients. GLUT1 expression on CTCs was evaluated in 49 patients: 3 MGUS, 13 SMM, 14 NDMM and 19 RRMM. Furthermore, GLUT1 was also evaluated in a cohort of BM matched samples: 3 MGUS, 8 SMM, 6 NDMM, 8 RRMM. Malignant PCs showed a heterogeneous GLUT1 expression in the BM, while in PB, GLUT1 levels increased from MGUS to NDMM and decreased from NDMM to RRMM. NDMM patients exhibited significantly higher GLUT1 expression on CTCs compared to the SMM group (p=0.016). In the NDMM cohort, patients with high-risk cytogenetics defined as t(4;14), del(17p13), t(14;16) or 1qamp/gain had significantly higher GLUT1 levels than those with standard risk (p=0.0160), while no differences were observed in BM. Pearson's analysis revealed correlations between GLUT1 on CTCs and clinical parameters such as CTC counts, calcium, albumin and β2 microglobulin levels in the NDMM group. In the relapsed group, GLUT1+ CTCs correlated with CTC levels, bone marrow infiltration at diagnosis, as well as with hemoglobin, albumin and lactate dehydrogenase (LDH) levels. Furthermore, we assessed GLUT1 expression on circulating PCs in 20 HCs and compared the results with those from patients at various stages of multiple myeloma. GLUT1 frequencies were significantly higher in HCs compared to normal PCs at any MM stage (p=0.0177 for MGUS, p<0.0001 for SMM, p=0.0006 for NDMM, p=0.0004 for CR, and p=0.029 for RRMM), reinforcing the predictive value of GLUT1. Overall, GLUT1 expression on CTCs increased from MGUS to NDMM, correlating with cytogenetic risk factors and clinical parameters such as BM infiltration, calcium, albumin, and β2 microglobulin. Additionally, GLUT1 levels on circulating PCs in HCs were significantly higher compared to normal PCs in different MM stages, highlighting GLUT1 expression on normal PCs as potential predictor of MM development or progression. This study demonstrates that GLUT1 expression on circulating plasma cells holds predictive value and correlates with MM risk factors and clinical parameters. These findings position GLUT1 as a powerful biomarker that, when combined with disease stratification models, could effectively predict active disease and patient outcomes in multiple myeloma.

B02

PATHOGENESIS OF SECONDARY LEUKEMIA IN MULTIPLE MYELOMA THROUGH CAR-T INDUCED EXPANSION OF PRE-EXISTING CLONAL HEMATOPOEISIS

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Background. The approval of chimeric antigen receptor T-cell (CAR-T) therapy has marked a significant advancement in treating hematologic cancers, including multiple myeloma (MM). However, while CAR-T therapy demonstrates exceptional effectiveness, emerging reports have highlighted an increased risk of CAR-T-related myeloid (pt-MN) and lymphoid (pt-LN) neoplasms. In this study, we aimed to examine the prevalence and mutational characteristics of secondary hematologic neoplasms after CAR-T therapy through a multi-center registry analysis of n=179 patients (pts).

Methods. Screening for pt-MN/ pt-LN was performed by whole genome sequencing (WGS) of CD138-negative BM mononuclear cells (BMMCs). Upon pt-MN/ pt-LN detection, targeted DNA sequecing was added to determine variant allele frequency (VAF) expansion over time in retrospective pre- and post-CAR-T samples.

Results. At an extended median follow-up of 17.7 months after CAR-T cell treatment, 10/179 (5.6%) pts were diagnosed with a pt-MN, including 6 pts with secondary AML/ MDS and 4 pts with clonal cytopenia of undetermined significance (CCUS). No cases of pt-LN have been noted thus far, adding to reports on the low incidence of T-cell leukemia after CAR-T. At the same time, onset of pt-MN after CAR-T was accelerated at a median latency of 1.8 months (range 0.0-5.8) after CAR-T infusion. While the pathogenesis of pt-MN in MM is well established, and in part driven by prior drug exposure, this observation suggests that CAR-T mediated inflammation within the bone marrow niche may act as an independent stimulus which leads to accelerated outgrowth of pt-MN after CAR-T cell therapy. Median age in pts with CAR-T associated pt-MN was 67.7 years (range 53.4-78.3). Pts were heavily pretreated with a median of 2.0 prior stem cell transplants (ASCT, range 1-4) and prior exposure to lenalidomide in 10/10 cases. Clonal expansion was tracked in available pre-CAR-T samples from a total of 8/10 pts and revealed rapid expansion of pre-existing clonal hematopoiesis (CH)

mutants after CAR-T cell infusion. Interestingly, clonal dynamics seemed to differ on a qualitative level with *DNMT3A* and *PPM1D* clones leading to more transient CCUS-associated cytopenia suggesting a scenario in which regeneration after CAR-T therapy, with decreasing bone marrow inflammation, removes the competitive advantage of CH and ultimately leads to its decline. In contrast, *TP53* mutants were linked to rapid-onset AML and fatal outcome in 3/10 pts (Figure 1). Lastly, SBS-MM1 melphalan signatures could be tracked in BMMCs at the time of pt-MN manifestation indicating an increased risk for secondary myeloid disorders in pts with prior ASCT.

Conclusions. Although the relationship between pt-MN and CAR-T therapy remains uncertain, our data demonstrates a higher frequency and more rapid expansion of CH clones in CAR-T-treated MM patients. This increased prevalence of pt-MN may be influenced by prior treatment with immunomodulatory drugs and alkylating agents, as evidenced by detectable melphalan signatures in our cohort. In conclusion, incorporating enhanced CH monitoring as a baseline testing measure seems essential to improve the safety and mitigate the risk of secondary leukemias after CAR-T cell therapy in multiple myeloma.

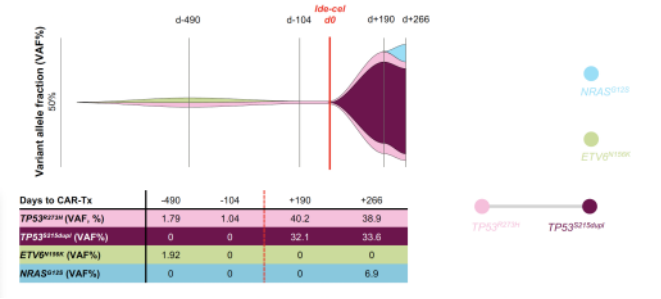

Figure 1.

B03

SUBCUTANEOUS DARATUMUMAB (DARA) + BORTEZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE (VCD) IN NEWLY DIAGNOSED LIGHT CHAIN (AL) AMYLOIDOSIS: OVERALL SURVIVAL AND FINAL MAJOR ORGAN DETERIORATION PROGRESSION-FREE SURVIVAL (PFS) FROM THE PHASE 3 ANDROMEDA STUDY

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Introduction. AL amyloidosis is characterized by CD38+ plasma cell-produced immunoglobulin light chains deposited as insoluble amyloid fibrils in vital organs. ANDROMEDA (NCT03201965) is a randomized, open-label, phase 3 study of VCd ± DARA in newly diagnosed AL amyloidosis. DARA-VCd is the only approved therapy and standard of care for newly diagnosed pts. We report the pre-planned final analysis for major organ deterioration PFS (MOD-PFS; ie, end-stage renal or cardiac disease, hematologic [heme] progression, or death) and OS.

Methods. Eligibility criteria included newly diagnosed AL amyloidosis with measurable heme disease, ≥1 involved organ, cardiac stage (Mayo 2004) I-IIIA, eGFR ≥20 mL/min, and no symptomatic MM. Pts were randomized 1:1 to VCd ± DARA. All received bortezomib (1.3 mg/m^2 SC QW), cyclophosphamide (300 mg/m^2 PO or IV QW), and dexamethasone (20-40 mg PO or IV QW) for 6 28-day cycles. DARA SC (1800 mg; co-formulated with rHuPH20) was given QW in Cycles 1–2, Q2W in C3–6, and Q4W thereafter for ≥24 cycles. Disease status was evaluated Q4W in C1–6 and Q8W in C7+ until major organ deterioration, death, study end, or withdrawal. Primary endpoint was overall heme CR (HemCR) rate. Secondary endpoints were MOD-PFS, OS, organ response rate, and safety.

Results. 388 pts were randomized to DARA-VCd (n=195) or VCd (n=193); baseline characteristics were well balanced. Median treatment duration was 21.3 months (mo) for DARA-VCd vs 5.3 mo for VCd. Of 122 pts in the VCd arm who received subsequent therapy, 82 (67%) received DARA. Median follow-up was 61.4 mo (range 0.0-71.2). Overall HemCR was 59.5% for DARA-VCd vs 19.2% for VCd (odds ratio 6.03 [95% CI 3.80-9.58; P<0.0001]). Significant improvement in MOD-PFS and OS were seen with DARA-VCd vs VCd: MOD-PFS HR 0.44 (95% CI 0.31-0.63; P<0.0001); OS HR 0.62 (95% CI 0.42-0.90; p=0.0121). Median MOD-PFS was not reached (NR) for DARA-VCd vs 30.2 mo for VCd. 112 deaths occurred (DARA-VCd 46; VCd 66). 5-year survival rate was 76.1% for DARA-VCd vs 64.7% for VCd. MOD-PFS and OS were generally consistent across pre-planned subgroups. Time to HemCR with DARA-VCd was 67.5 days vs 85.0 for VCd. HemCR was associated with improved MOD-PFS and OS from 6-month landmark onwards. Pts achieving HemCR had better MOD-PFS (HR 0.30 [95% CI 0.19-0.47]) and OS (HR 0.41 [95% CI 0.23-0.72]) irrespective of treatment. Median duration of HemCR was NR in either arm. Cardiac and renal response rates at 6, 12, 24, 36, and 48 mo were about doubled with DARA-VCd vs VCd. 113/235 cardiac response-evaluable pts achieved cardiac ≥ VGPR (DARA-VCd 76 [64.4%] vs VCd 37 [31.6%]); of these, 64 achieved cardiac CR (DARA-VCd 48 [40.7%] vs VCd 16 [13.7%]). Most common (≥5%) grade 3/4 TEAEs were lymphopenia (DARA-VCd 13%/VCd 10%), pneumonia (8/4%), diarrhea (6/4%), cardiac failure (congestive; 6/3%), neutropenia (5/3%), syncope (6/6%), fatigue (5/3%), hypokalemia (2/5%), and peripheral edema (3/6%). Systemic administration-related reactions with DARA-VCd occurred in 14 (7%) pts; all grade 1/2 and 86% occurred with first injection. Treatment was discontinued due to TEAEs in 5% with DARA-VCd vs 4% with VCd.

Conclusion. Adding DARA to VCd resulted in deeper and more rapid heme responses, significant improvements in OS and MOD-PFS,

and 40.7% cardiac CR vs VCd alone. DARA-VCd had a known and manageable safety profile. These results reaffirm DARA-VCd as the standard of care for newly diagnosed AL amyloidosis.

B04

MODELING LONG-TERM PROGRESSION-FREE SURVIVAL IN TRANSPLANT-ELIGIBLE AND TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH DARATUMUMAB, BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE

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Background. Quadruplet therapy consisting of daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) plus DR maintenance therapy showed superior efficacy to VRd with R maintenance in patients with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM) in the PERSEUS trial. Similarly, the CEPHEUS trial showed superiority of DVRd over VRd in transplant-ineligible (TIE) or transplant-deferred patients with NDMM. In the DVRd arms of both trials (intent to treat [ITT]), median progression-free survival (PFS) had not been reached at median follow-up of 47.5 months (mo; PERSEUS) and 58.7 mo (CEPHEUS); in the VRd arms, median PFS was not reached in PERSEUS and was 52.6 mo in CEPHEUS. With the availability of DVRd to treat both TE and TIE patients, and treatment guidelines focusing on these 2 groups, this analysis aimed to extrapolate PFS data from the PERSEUS trial (ITT) and the TIE subgroup of CEPHEUS to estimate long-term outcomes of DVRd in the frontline setting to help inform clinical decision making.

Methods. Following UK National Institute for Health and Clinical Excellence (NICE) guidance on survival data extrapolation, 7 parametric distributions were fitted to model PFS data: exponential, Weibull, gamma, Gompertz, log-logistic, log-normal, and generalized gamma. Individual parametric curves were fit for the DVRd and VRd groups. Long-term extrapolations were capped by UK general population data for 2020–2022 on disease-specific and all-cause mortality, utilizing the median age of the population and the proportion of male patients in the cohort at the initiation of treatment (per NICE guidance). PFS projections begin at the median age of the population.

Results. In PERSEUS, 709 TE patients were randomized (DVRd, n=355; VRd, n=354), with median age 60 years and 59% male. In CEPHEUS, 289 TIE patients were randomized (DVRd, n=144; VRd, n=145), with median age 72 years and 51% male. Observed Kaplan-Meier estimates of PFS at 48 mo in TE patients in PERSEUS were 84.3% vs 67.7% in the DVRd and VRd groups, respectively; for TIE patients in CEPHEUS, they were 72.3% vs 52.3% (Figure 1). Based on PFS modeling in the PERSEUS TE population, the range of estimated median PFS across all distributions was 158–255 mo (13.2–21.2 years) for the DVRd group and 76–119 mo (6.3–9.9 years) for the VRd group. The exponential distribution (best fit), gave PFS estimates of 205 vs 87 mo (17.1 vs 7.3 years) for DVRd and VRd, respectively. For the CEPHEUS TIE population, the range of estimated median PFS across distributions was 96–118 mo (8.0–9.8 years) for the DVRd group and 52–54 mo (4.3–4.5 years) for the VRd group, with the exponential distribution (best fit) giving estimates of 100 *vs* 53 mo (8.3 vs 4.4 years) for DVRd and VRd, respectively.

Conclusions. Across all 7 distributions, PFS projections were significantly longer with DVRd than VRd in both TE and TIE patients with NDMM. As expected, projected PFS with DVRd was longer for TE patients (205 mo from baseline age of 60 years) than TIE patients (100 mo from age 72 years). These extrapolations provide supportive projections beyond the observed PFS data, helping to inform treatment decisions and reinforcing the benefit of DVRd with a daratumumab-containing maintenance regimen in all patients with NDMM.

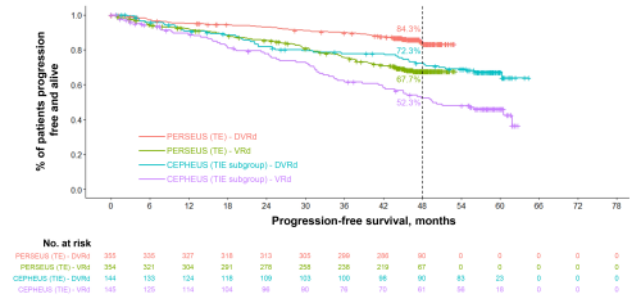

Figure 1. Observed PFS in TE and TIE patients treated with DVRd or VRdin the PERSEUS and CEPHEUS studies.

B05

THE PHASE 3 CEPHEUS TRIAL OF DARATUMUMAB PLUS BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE IN PATIENTS WITH TRANSPLANT-INELIGIBLE OR TRANSPLANT-DEFERRED NEWLY DIAGNOSED MULTIPLE MYELOMA: FRAILTY SUBGROUP ANALYSIS

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Background. Daratumumab, lenalidomide, and dexamethasone (DRd) is a guideline-recognized standard of care for NDMM in patients (pts) who are transplant-ineligible (TIE). The phase 3 MAIA trial in pts with TIE NDMM and median age 73 (range, 45–90) years (y) previously showed that DRd significantly improved PFS vs Rd, with a median OS of 7.5 y with DRd; 46% of pts had an IFM simplified frailty score ≥2 (frail). In the phase 3 CEPHEUS trial, at median 58.7-month (mo) follow-up, DVRd improved overall MRD negativity (neg) rate at 10^{-5} (61% vs 39%; odds ratio [OR], 2.37; 95% CI, 1.58–3.55; $P<0.0001$) and PFS (median not reached vs 52.6 mo; hazard ratio [HR], 0.57; 95% CI, 0.41–0.79; $p=0.0005$) vs VRd in pts with TIE or transplant-deferred (TD) NDMM. We present CEPHEUS subgroup analyses based on frailty status per IMWG criteria (protocol specified) and IFM simplified frailty score (*post hoc*).

Methods. Eligible pts had TIE or TD NDMM, ECOG performance status (PS) 0–2, and an IMWG frailty score of 0 or 1. Pts were randomized (1:1 ratio) to receive DVRd or VRd. The primary endpoint was overall MRD neg rate, defined as the proportion of pts who had ≥CR and MRD neg (10^{-5}) status. Key secondary endpoints included PFS. IMWG frailty score is assessed by age, comorbidities, and pt-reported functional status (activities of daily living); IFM simplified frailty score considers age, comorbidities, and physician-reported ECOG PS.

Results. In total, 395 pts were randomly assigned to DVRd (n=197) or VRd (n=198). Median age was 70 (range, 31–80) y. IMWG frailty score was 0 (fit) in 124 (63%) pts in the DVRd arm and 132 (67%) in the VRd arm; a respective 73 (37%) and 66 (33%) had a score of 1 (intermediate fitness [int fit]). Utilizing the IFM simplified frailty scale, 140 (71%) pts in the DVRd arm and 157 (79%) in the VRd arm had a score of 0–1 (nonfrail), including a respective 115 (58%) and 127 (64%) with a score of 0 (fit) and 25 (13%) and 30 (15%) with a score of 1 (int fit); 57 (29%) and 41 (21%) had a score ≥2 (frail). At median 58.7-mo follow-up, overall MRD neg rate was 64% vs 45% in the DVRd vs VRd arms in the IMWG fit group (OR, 2.17; 95% CI, 1.32–3.59; $p=0.0026$) and 56% vs 29% in the int fit group (OR, 3.17; 95% CI, 1.57–6.42; $p=0.0019$; Table 1). In the fit group, median PFS in the DVRd vs VRd arms was not estimable (NE) vs 60.6 mo (HR, 0.59; 95% CI, 0.39–0.91; $p=0.0149$) and in the int fit group was NE vs 38.7 mo, respectively (HR, 0.56; 95% CI, 0.34–0.91; $p=0.0189$). For IFM simplified frailty groups, overall MRD neg rate in the nonfrail group was 64% vs 42% in the DVRd vs VRd arms (OR, 2.41; 95% CI, 1.51–3.84; $p=0.0003$) and 54% vs 29% in the frail group (OR, 2.88; 95% CI, 1.23–6.75; $p=0.0148$); median PFS was NE vs 60.6 mo in the nonfrail group (HR, 0.58; 95% CI, 0.39–0.86; $p=0.0054$) and NE vs 31.7 mo in the frail group (HR, 0.51; 95% CI, 0.28–0.93; $p=0.0242$).

Conclusions. For pts with TIE or TD NDMM, DVRd demonstrated a consistent benefit vs VRd across frailty subgroups using either the protocol-specified IMWG frailty scale or the IFM simplified scale, supporting its consideration regardless of frailty status. Within treatment arms, MRD neg rates and PFS rates trended lower for int fit or frail pts. These data, along with results of MAIA, help to inform the choice of daratumumab quadruplet or triplet therapy in the non-transplant NDMM setting with the ability to tailor the regimen based on bortezomib eligibility and goals of therapy.

Table: Efficacy in patient subgroups by frailty status

Outcome	IMWG fit		IMWG intermediate fitness	
	DVRd (n=124)	VRd (n=132)	DVRd (n=73)	VRd (n=66)
Overall MRD negativity (10^{-5}) rate, n (%)	79 (63.7)	59 (44.7)	41 (56.2)	19 (28.8)
OR (95% CI)[a]	2.17 (1.32–3.59)		3.17 (1.57–6.42)	
P value[b]	0.0026		0.0019	
PFS				
Median (95% CI), months	NE (NE–NE)	60.6 (50.2–NE)	NE (46.0–NE)	38.7 (31.4–49.2)
HR (95% CI)[c]	0.59 (0.39–0.91)		0.56 (0.34–0.91)	
P value[d]	0.0149		0.0189	
54-month PFS rate, % (95% CI)	72.8 (63.8–80.0)	56.5 (47.0–65.0)	59.7 (46.9–70.4)	34.4 (22.1–47.0)
Outcome	IFM nonfrail		IFM frail	
	DVRd (n=140)	VRd (n=157)	DVRd (n=57)	VRd (n=41)
Overall MRD negativity (10^{-5}) rate, n (%)	89 (63.6)	66 (42.0)	31 (54.4)	12 (29.3)
OR (95% CI)[a]	2.41 (1.51–3.84)		2.88 (1.23–6.75)	
P value[b]	0.0003		0.0148	
PFS				
Median (95% CI), months	NE (NE–NE)	60.6 (49.2–NE)	NE (43.9–NE)	31.7 (24.4–42.2)
HR (95% CI)[c]	0.58 (0.39–0.86)		0.51 (0.28–0.93)	
P value[d]	0.0054		0.0242	
54-month PFS rate, % (95% CI)	71.4 (62.8–78.3)	53.9 (45.2–61.7)	59.8 (45.1–71.7)	29.8 (15.0–46.2)

[a]Mantel-Haenszel estimate of the common OR; value >1 indicates an advantage for DVRd vs VRd.
[b]Fisher's exact test.
[c]HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable; value <1 indicates an advantage for DVRd.
[d]Unstratified log-rank test.
DVRd, daratumumab plus VRd; HR, hazard ratio; IFM, Intergroupe Francophone du Myelome; IMWG, International Myeloma Working Group; MRD, minimal residual disease; NE, not estimable; OR, odds ratio; PFS, progression-free survival; VRd, bortezomib, lenalidomide, and dexamethasone.

B06

BELANTAMAB MAFODOTIN IN COMBINATION WITH DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE IN INTERMEDIATE-FIT AND FRAIL NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA: THE PHASE 1/2 BELADRD STUDY

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MAIA trial established daratumumab with lenalidomide & dexamethasone (DRd) as a preferred regimen in transplant ineligible (TI) patients (pts) with newly diagnosed multiple myeloma (NDMM). Belantamab mafodotin (belamaf) has demonstrated superior efficacy over SoC regimens in relapsed/refractory MM pts in the DREAMM-7/-8 clinical trials. Combination of belamaf & DRd may offer TI pts better outcomes with manageable tolerability. BelaDRd (NCT05280275) is a 2-part, phase 1/2 trial. Part 1 evaluates the safety & efficacy of belamaf 1.9/1.4 mg/kg plus DRd in TI-NDMM pts & established belamaf 1.9 mg/kg Q8W, extended to Q12W to account for Ocular Adverse Events (OAEs, Best Corrected Visual Acuity [BCVA] change from baseline & keratopathy, graded by the Keratopathy Visual Acuity scale) as the recommended phase 2 dose (RP2D). Dosing was guided by ophthalmologist-assessed OAEs. Part 2 assesses the safety/efficacy of RP2D by 2 belamaf dose modification guidelines: In Group A dosing is guided as in Part 1, while in Group B by a novel Vision-Related Anamnestic questionnaire (VRA, a pt-reported, 9-question tool capturing ocular symptoms and their impact on ADL) and ≥Gr3 OAEs. We present safety & efficacy results from both parts of the trial (data cut-off: 25 November 2024). Of all Part 1 pts (n=24; median age: 73; male: 54%), 20 (83%) are ongoing & 4 (17%) discontinued (2 [8%] due to fatal events; 1 [4%] SAE; 1 [4%] withdrew consent). 46%/50% of pts had stage I/II disease per R-ISS & 12.5% high-risk cytogenetics (HRC). 79%/21% of pts were intermediate-fit/frail as per IMWG frailty score. At a median follow-up of 23 months, of 142/145 planned belamaf doses, 44%/22% were skipped due to OAEs in the 1.9/1.4 mg/kg cohorts. The median dose intensity was 0.5 mg/kg/Q4W. The overall response rate (ORR) was 91.7%. Median time to 1st response was ~1 month.

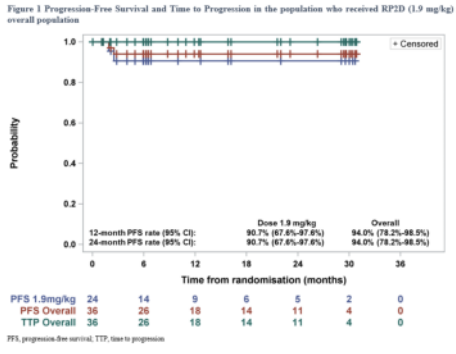

Figure 1.

The 12/24-months Progression Free Survival (PFS) rates were both 83.3% & 100% for cohorts 1 & 2. Meaningful BCVA decline (Snellen <20/50) was recorded in 17% & Gr2/≥Gr3 keratopathy in 9.7%/0.8% of ophthalmological exams. Median time to resolution was ~1 month for both ≥Gr2 BCVA drop from baseline & ≥Gr2 keratopathy. The most common (≥10%) Gr≥3 non-ocular AEs were fatigue & rash. All Part 2 pts (n=12; median age: 74; male: 58%) are ongoing. 8%/83% of pts had stage I/II disease per R-ISS & 17% HRC. 92%/8% of pts were intermediate-fit/frail as per IMWG frailty score. The median dose intensity was 0.9 mg/kg/Q4W. ORR in 10 evaluable pts was 90%. The 6-months PFS rate was 100%. BCVA change ≥Gr3 was reported in 8% of pts. Meaningful BCVA decline was recorded in 8% & Gr2/≥Gr3 keratopathy in 1.9%/0% of ophthalmological exams. Fatigue was the only common (≥10%) ≥Gr3 non-ocular AE. The 12/24-months PFS rates for pts (n=24) who received the RP2D (1.9 mg/kg) in both parts of the trial were constant at 90.7%, while the respective rates for the overall population (n=36) were constant at 94% (Figure 1). BelaDRd demonstrated substantial clinical activity, with rapid and deep responses without compromising tolerability in an unfit population. No progressive disease was observed in either part. Moreover, a low frequency of ≥Gr3 OAEs was observed, that resolved rapidly. The remarkable PFS data may justify a phase 3 study with this quadruplet versus novel quadruplet combinations in this setting.

B07

FIRST RESULTS FROM REALITEC: A MULTI-COUNTRY OBSERVATIONAL RETROSPECTIVE STUDY OF TECLISTAMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA OUTSIDE OF CLINICAL TRIALS

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Background. Teclistamab is the first approved bispecific monoclonal antibody targeting BCMA and CD3 for the treatment of patients with triple class exposed relapsed/refractory multiple myeloma (RRMM). With a median follow up of 30.4 months, the pivotal Phase I/II trial MajesTEC-1 (N=165) showed deep and durable responses in this patient population, with an overall response rate (ORR) of 63%, a complete response or better (≥CR) rate of 46.1% and a median duration of response (DoR) of 24 months. Here, we report the first results of the REALiTEC study, a retrospective observational study of patients receiving teclis-

tamab in a broader population who may not have been eligible for clinical trials.

Methods. REALiTEC is a retrospective, international, non-interventional study that aims to describe the management and outcomes of patients treated with teclistamab outside of the clinical trial setting. Informed consent was obtained for all patients. Data were collected from patient medical records, including demographics, disease characteristics, prior therapies, effectiveness and safety. Treatment outcomes were assessed based on response rates, time to first and best response, DoR, progression-free survival (PFS), and overall survival (OS). Responses were evaluated according to the International Myeloma Working Group (IMWG) criteria.

Results. In total, 113 eligible patients who received teclistamab on/before the 31st of December 2022 from 23 sites in 8 different countries were included in the study. Overall, 88.5% of patients received teclistamab as part of a pre-approval access programs, the remainder of patients received commercial teclistamab. Median age was 66 years, with a median of 6 prior lines of therapy. 78.8% and 44.2% patients were triple and penta-class refractory, respectively, and 33.6% had previously received anti-BCMA treatments. With a median follow up of 20.7 (0.7-35.8) months, median treatment duration was 9.4 (0.3-35.8) months. After a median of 7 (0-18) months, 39.8% of patients switched from weekly to biweekly dosing, mostly due to achieving deep responses (very good partial response or better, ≥VGPR). ORR for all cohort was 60.2%, with 52.2% of patients achieving ≥VGPR. Median time to first response was 1.6 (1.2-1.9) months, with a median time to best response of 3.7 (2.8-5) months. Median DoR was 20.3 (14.8-NE) months, median PFS was 9.7 (5.5-18.8) months and median OS was 26.2 (16.5-NE) months. Patients achieving ≥VGPR had longer DoR (median 26.1 months; 16.7-NE), with median PFS and OS not reached and with 71.2% of patients being progression free and 83.1% alive at 12 months. Patients with no prior BCMA treatments had a median PFS of 14.2 (7.8-NE) months and median OS was not reached (26.2-NE). Most common adverse events were infections (all grade 71.7%; G3-4: 40.7%), CRS (all grade 55.7%; G3-4: 1.8%), neutropenia (all grade 35.4%; G3-4: 32.7%) and anemia (all grade 25.7%; G3-4:16.8%). No new safety signals were identified.

Conclusions. REALITEC study shows similar clinical outcomes as those observed in MajesTEC-1 study. These results provide additional validation of the activity of teclistamab in this hard-to-treat heavily pretreated patient population. They also support the importance of reaching a deep response with teclistamab, which is associated with longer DoR, PFS and OS.

B08

TOLERABILITY AND CLINICAL ACTIVITY OF NOVEL FIRST-IN-CLASS ORAL AGENT, INOBRODIB (CCS1477), IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Aims. We report an update on safety (primary objective) and efficacy (secondary) data for inobrodib, a first-in-class potent, selective, and oral inhibitor of p300/CBP in combination with pomalidomide and dexamethasone from relapsed/refractory multiple myeloma (RRMM) patients treated in the Phase I/IIa trial (NCT04068597).

Methods. Eligible patients (pts) had confirmed RRMM and had exhausted available or suitable standard of care treatment options. Three dose escalation combination cohorts were completed; inobrodib 25mg, or 35mg, bid on a 4 days on/3 days off intermittent schedule with 4mg pom; or inobrodib 25mg bid 4 days on/3 days off with 3 mg pom. All regimens were 28-day cycles and included a standard dose of dex, 20-40mg depending on age. Each cohort was further expanded to include up to 10 patients. Adverse events were graded by CTCAE v5.0. Responses were investigator assessed per IMWG.

Results. Dose escalation cohorts have enrolled 48 RRMM pts to date with a median age of 68 yrs (range 41-82). Median prior lines of therapy was 6 (range 2-10), all were triple-class exposed, 39 pts (81%) were triple class refractory, and 16 pts (33%) received prior BCMA therapy. In addition, 31 pts (65%) were pomalidomide-refractory. Median duration of treatment for 36 evaluable patients to date was 177 days (range 35-601), with a median of 6 cycles (range 1-21). Over 1/3rd of patients continue on treatment. Almost 1/3rd of patients have died in the survival follow-up, mainly due to disease progression, but a number of patients remain in follow-up for overall survival. At the data cut-off (04June2024), Grade (gr) 3/4 treatment-emergent adverse events (TEAEs) were reported in 35 of 48 (73%) pts. The most frequent gr 3/4 events were hematological (56%); neutropenia (27%: 19% gr 3, 8% gr 4), thrombocytopenia (27%: 21% gr 3, 6% gr 4) and anemia (13%, all gr 3). Frequency of gr 3/4 infections was 29%. This is in line with the anticipated profile of pom/dex only. The main potential for overlapping toxicity is thrombocytopenia however no significant increase in frequency or severity has been seen with the triplet. Inobrodib as monotherapy has not been shown to cause neutropenia. One patient died due to an unrelated cardiac event at the end of cycle 2. Five pts (10%) discontinued due to TEAEs. The pattern of TEAEs considered related to study treatments is consistent with the known safety profile of the individual agents, with the majority of events gr 1/2 and the most common gr 3/4 events being hematological toxicities. Objective responses were seen across all dose levels tested with best ORR (6/8 evaluable patients, 75%) in the highest dose cohort. In general responses start rapidly after treatment initiation and deepen with time. Among pom-refractory pts, 7 had progressed on a pom-containing regimen as the last prior therapy and 5 of these achieved OR, providing clinical proof of concept on published non-clinical data regarding the exquisite synergy of this combination (Welsh et al. 2024). Responses were also seen in patients exposed to anti-BCMA and/or TCE therapies; further recruitment is ongoing in this population. In the initial sample of pom-naïve pts (12), there is a trend for deeper response with 2 patients achieving CRs (17%) and 2 patients having MRD negativity 10^{-5} .

Summary. The first in class agent inobrodib in combination with pom-dex is tolerable and shows promising early efficacy in RRMM patients, justifying further clinical development.

B09

COMPARISON OF TOXICITIES AND OUTCOMES BETWEEN CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY (CAR-T THERAPY) AND BISPECIFIC ANTIBODIES IN RELAPSED REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background. Relapsed refractory multiple myeloma (RRMM) presents significant treatment challenges, with emerging therapies like CAR-T therapy and bispecific antibodies (BsAbs) offering promising options. This meta-analysis compares these therapies in RRMM, focusing on the reported toxicities and outcomes.

Methods. A systematic search of PubMed, Scopus, EMBASE, and Cochrane Library, supplemented by ASCO, ASH, and EHA conference abstracts, was performed using MeSH terms for studies on RRMM (aged ≥18 years) treated with CAR-T therapy or BsAbs therapies, yielding 1241 records. Of these, 51 articles were included. Studies without adverse events data or using these therapies as first/second-line treatments were excluded. Pooled absolute risks, confidence intervals, and heterogeneity metrics were calculated using R (v4.4.1), with subgroup analyses for CAR-T therapy and BsAbs. Study quality was evaluated using the Methodological Index for Non-Randomized Studies (MINORS).

Results. The results included 32 single-arm interventional studies on CAR-T therapy and 19 on BsAbs, with individual cohorts analysed separately, encompassing 2,982 patients in total. Grade (G) ≥3 treatment-emergent adverse events (TEAEs) were reported in all cases (100%) for CAR-T therapy (95% CI: 0.99-1.00) *vs* 60.88% for BsAbs (95% CI: 0.50-0.71). CRS was more frequent with CAR-T therapy (84.86%, 95% CI: 0.79-0.91) than BsAbs (62.92%, 95% CI: 0.55-0.71), though CRS Grade ≥3 was rare, in CAR-T therapy 0.01% (95% CI: 0.00-0.0002), in BsAbs 7.01% (95% CI: 0.02-0.16). Corticosteroids were used in 34.73% of CAR-T therapy and 33.48% of BsAbs patients, while tocilizumab was given in 55.62% and 44.32%, respectively. Neurotoxicity incidence was lower in CAR-T therapy (9.45%) compared to BsAbs (15.59%), with a lower risk of immune effector cell-associated neurotoxicity syndrome (ICANS) in CAR-T therapy 0.01% (95% CI: 0.0003-0.0005) vs BsAbs (4.83% (95% CI: 0.02-0.07). Hematologic toxicities were higher with CAR-T therapy, including G ≥3 neutropenia (86.87% *vs* 32.49%), anemia (49.83% *vs* 23.64%), thrombocytopenia (48.39% *vs* 23.27%), and lymphopenia (57.99% *vs* 32.50%). Overall infections were less frequent with CAR-T therapy 36.07% (95% CI: 0.26-0.46) *vs* BsAbs 51.27% (95% CI: 0.42-0.61). Grade ≥3 infections were also lower with CAR-T (9.78%, 95% CI: 0.06-0.14) *vs* BsAbs (23.10%, 95% CI: 0.17-0.29). CAR-T therapy showed higher fever (55.82%) and fatigue (31.42%), while BsAbs had higher diarrhea (29.07%) and TEAEs leading to discontinuation (3.94%). Hypogammaglobulinemia was slightly more common in CAR-T therapy (+4.21%). Fatal events were similar for CAR-T therapy 14.94% (95% CI: 0.09–0.21) and BsAbs 15.34% (95% CI: 0.03–0.27) with low treatment-related deaths of 0.01% in each group. The Overall Response Rate (ORR) was 81.48% (95% CI: 0.74–0.89) for CAR-T therapy and 54.00% (95% CI: 0.48–0.60) for BsAbs. The pooled absolute risk of individual outcomes is provided in Table 1.

Conclusion. In conclusion, CAR-T therapy shows higher rates of severe cytopenias and CRS, while BsAbs therapy is associated with increased infections and neurotoxicity. CRS is more common with CAR-T therapy, but severe cases are rare. These distinct toxicity profiles highlight the need for tailored approaches to optimize patient safety and treatment outcomes.

Table 1. Pooled Absolute Risks of Treatment-Related Outcomes: Comparison of Adverse Outcomes Between CAR-T Cell Therapy and Bispecific Antibody Therapy.

Outcome	Overall	CAR-T cell therapy	Bispecific-antibody therapy
Overall Response Rate (ORR)	53.81% (95% CI: 0.46–0.62)**	81.48% (95% CI: 0.74–0.89)**	54.00% (95% CI: 0.48–0.60)**
Grade ≥3 Treatment-Emergent Adverse Events (TEAE)	-	100% (95% CI: 0.99-1.00)**	60.88% (95% CI: 0.50-0.72)**
Cytokine Release Syndrome (CRS)	62.95% (95% CI: 0.55-0.71)**	84.86% (95% CI: 0.79-0.91)**	62.92% (95% CI: 0.55-0.71)**
CRS Grade ≥3	6.90% (95% CI: 0.04-0.13, p = 0.037)	0.01% (95% CI: 0.00-0.0002)*	7.01% (95% CI: -0.02-0.16, p = 0.115)
CRS patients treated with Corticosteroids	18.22% (95%CI: 0.01-0.35, p = 0.037)	25.82% (95% CI: 0.17–0.35)**	47.09% (95% CI: 0.32–0.62)**
CRS patients treated with Tocilizumab	47.09% (95% CI: 0.32-0.62)**	58.07% (95% CI: 0.48-0.69)**	47.30% (95% CI: 0.36-0.58)**
Neurotoxicity	15.49% (95% CI: 0.75-0.24)*	9.45% (95% CI: 0.05-0.14)**	15.59% (95% CI: 0.05-0.27, p = 0.005)
Neutropenia	39.08% (95% CI: 0.37-0.42)**	100% (95% CI: 0.99-1.00)**	41.10% (95% CI: 0.32-0.50)**
Neutropenia Grade ≥3	32.50% (95% CI: 0.24-0.41)**	86.87% (95% CI: 0.80-0.93)**	32.49% (95% CI: 0.24-0.41)**
Anemia	39.00% (95% CI: 0.30-0.48)**	80.36% (95% CI: 0.73-0.88)**	39.47% (95% CI: 0.34-0.45)**
Anemia Grade ≥3	24.23% (95% CI: 0.16-0.33)**	49.83% (95% CI: 0.42-0.58)**	23.64% (95% CI: 0.18-0.30)**
Thrombocytopenia	28.54% (95% CI: 0.17-0.41)**	71.78% (95% CI: 0.63-0.80)**	29.08% (95% CI: 0.24-0.34)**
Thrombocytopenia Grade ≥3	23.21% (95% CI: 0.12-0.35)**	48.39% (95% CI: 0.41-0.56)**	23.27% (95% CI: 0.11-0.36)*
Lymphopenia	38.16% (95% CI: 0.13-0.63, p = 0.003)	65.39% (95% CI: 0.49-0.82)**	37.58% (95% CI: 0.24-0.51)**
Lymphopenia Grade ≥3	33.13% (95% CI: 0.10%-0.57, p = 0.006)	57.99% (95% CI: 0.41-0.75)**	32.50% (95% CI: 0.22-0.43)**
Infections	51.09% (95% CI: 0.40-0.62)**	36.07% (95% CI: 0.26-0.46)**	51.27% (95% CI: 0.42-0.61)**
Infections Grade ≥3	23.01% (95% CI: 0.18-0 29)**	9.78% (95% CI: 0.06-0.14)**	23.10% (95% CI: 0.17-0.29)**
ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome)	0.01% (95% CI: -0.0001-0.0003, p = 0.253)	0.01% (95% CI: -0.0003-0.0005, p = 0.588)	4.83% (95% CI: 0.02-0.07)*
Diarrhea	28.48% (95% CI: 0.18-0 39)**	20.71% (95% CI: 0.14-0.28)**	29.07% (95% CI: 0.23-0.35)**
Fever	25.17% (95% CI: -0.006 to 0.51, p = 0.056)	55.82% (95% CI: 0.40-0.72)**	24.55% (95% CI: 0.18-0.32)**
Hypotension	-	14.16% (95% CI: 0.08-0.21)**	-
Hypoxia	-	0.01% (95% CI: -0.00-0.0002, p = 0.081)	-
Fatigue	25.63% (95% CI: 0 13–0 39)**	31.42% (95% CI: 0.20–0.43)**	25.39% (95% CI: 0.17–0.34)**
Death/Fatal Events	15.28% (95% CI: 0.05–0 26, p = 0.004)	14.94% (95% CI: 0.09–0.21)**	15.34% (95% CI: 0.03–0.27, p = 0.012)
Treatment-Related Death/Fatal Events	-	0.01% (95% CI: -0.0003–0.0006, p = 0.550)	0.01% (95% CI: 0.00–0.0002, p = 0.031)
TEAEs Leading to Drug Discontinuation	-	-	3.94% (95% CI: 0.02–0.06)**
Hypogammaglobulinemia (HG)	50.32% (95% CI: 0.04–0.97, p = 0.033)	50.35% (95% CI: 0.007–0.99, p = 0.047)	46.14% (95% CI: 0.20–0.72)*
Anti-Drug Antibodies (ADA)	0.01% (95% CI: -0.003–0.003, p = 0.999)	**26.57% (95% CI: 0.02–0.51, p = 0.031**	0.01% (95% CI: -0.00–0.0002, p = 0.157)

** p<0.0001, *p≤0.001

POSTERS

Biology and preclinical

P01

ABSTRACT NOT PUBLISHABLE

P02

TUNNELING NANOTUBES BETWEEN BONE MARROW STROMAL CELLS SUPPORT TRANSMITOPHAGY AND RESISTANCE TO APOPTOSIS IN MYELOMA

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Tunneling nanotubes (TNTs) are intercellular conduits containing F-actin fibers that facilitate cargo transfer between distant cells. Their formation is often triggered by cellular stress, such as oxygen and glucose deprivation (OGD), which is common in hypoxic environments. Multiple myeloma (MM), which proliferates in the bone marrow (BM), exists within a unique microenvironment characterized by steep oxygen-glucose gradients. The role of TNTs in the MM hypoxic niche remains unexplored. We established a novel co-culture model to simulate the MM niche by exposing a human MM cell line (JJN3) and BM stromal cells (BMSCs) to OGD. We analyzed mitochondrial membrane potential (ΔΨ), apoptosis, mitochondrial dynamics, and TNT formation to uncover mechanisms supporting MM cell survival. Under OGD, JJN3 cells exhibited a significant drop in ΔΨ, while BMSCs remained stable. Co-cultured BMSCs protected JJN3 cells from OGD-induced apoptosis. OGD stimulated homotypic TNT formation among BMSCs. Using MitoTracker staining and confocal microscopy, we observed increased mitochondrial transfer from JJN3 to BMSCs under OGD, with JJN3 mitochondria appearing in a post-fission state. Connexin 43 (CX43) was implicated in this transfer mechanism.

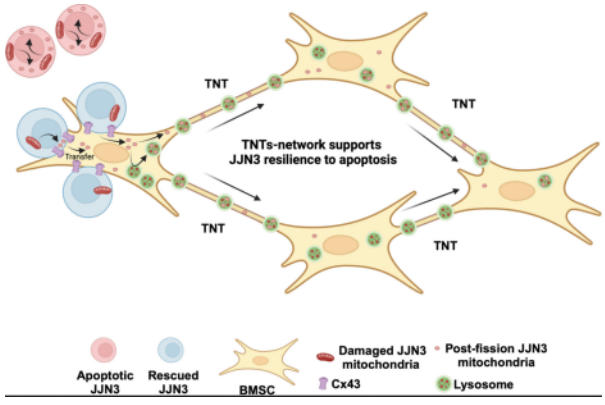

Figure 1.

Confocal imaging revealed JJN3 mitochondria within BMSCs interacting with Lamp1, particularly under OGD. JJN3 mitochondria were internalized by BMSCs in an actin cage, suggesting mitophagy. Notably, multiple JJN3 mitochondria exhibited fission points within BMSCs. Given the loss of ΔΨ in JJN3 mitochondria under OGD – a known mitophagy trigger – and the observed fission events, we propose that JJN3-to-BMSCs transmitophagy occurs under these conditions. We also analyzed TNTs between BMSCs for JJN3 mitochondrial presence and Lamp1 localization. The homotypic TNT network displayed punctate JJN3 mitochondria interacting with Lamp1, facilitating the transfer of post-fission JJN3 mitochondria. To evaluate the functional role of TNTs in protecting JJN3 from OGD-induced apoptosis, we disrupted the TNT network using Cytochalasin-D, which hindered the protective effect of BMSCs on JJN3. Our findings demonstrate that the TNT network among BMSCs supports the intercellular transfer of post-fission JJN3 mitochondria, promoting JJN3-to-BMSCs transmitophagy and enhancing JJN3 survival in the hypoxic MM niche. Targeting TNT-mediated mitochondrial exchange could offer a novel therapeutic strategy for addressing metabolic vulnerabilities in MM.

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P03

ROLE OF SIALYLATION OF MESENCHYMAL STROMAL CELLS IN MULTIPLE MYELOMA

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Context. In multiple myeloma (MM), the immune system is compromised at multiple levels. In this disease, the tumour microenvironment (TME) plays a key role in its development and its progression. In the TME, bone-marrow derived mesenchymal stromal cells (BM-MSCs) are characterized by several altered functions. Aberrant glycosylation occurs in most haematological malignancies, resulting in increased sialylation. In this context, recent studies identified some mechanisms of immune evasion based on sialoglycan interactions with the immunoregulatory Siglec receptors expressed by immune cells. Moreover, in the TME, immune cell functions such as macrophage polarization are often impaired.

Methods. BM-MSCs were plated in co-culture with two myeloma cell lines (RMPI 8226 and U266), and in the presence of a proinflammatory cocktail (IL-1β, IFN-γ, TNF-α and IFN-α). Four different FITC-lectins were used to detect glycans by flow cytometry. For Siglec ligand staining, recombinant human Siglec-hFC mixed with PE-anti IgG were used. The expression levels of different sialyltransferases were also evaluated via a qPCR screening of 84 key genes of glycosylation processes quantified on HD (healthy donors)-, MGUS (monoclonal gammopathy of undetermined significance)-, TMM (treated multiple myeloma)- and MM-BM-MSCs. The impact of BM-MSCs sialylation on primary macrophages polarization was studied by flow cytometry (HLA-DR/CD40 for M1 and CD206 for M2), qPCR and ELISA assays (CCL2/TNF-α for M1 and IL10/CCL22/ARG1 for M2) by inhibiting sialylation with neuraminidase A and P-3FAX-Neu5Ac, a sialyltransferase inhibitor.

Results. We first showed that MM-MSCs have a higher sialylation level than HD-, MMT , and MGUS-MSCs. An increase of sialylation level was observed on HD- and MM-MSCs when they were co-cultured in direct contact with myeloma cell lines compared to control conditions.

Siglec-9L was highly expressed in MM-MSCs compared to HD-MSCs. Interestingly, under inflammatory conditions, Siglec-7L expression increased and Siglec-9L expression decreased compared to control conditions. The qPCR screening revealed two differentially expressed genes implicated in the sialylation process in MM-MSCs compared to HD-MSCs: ST6GAL1 and NEU2. Finally, co-cultures of BM-MSCs with primary macrophages showed that M1 markers were increased and M2 markers were decreased (by flow cytometry and ELISA) when sialylation was inhibited.

Conclusion. Our results suggest that sialylation on BM-MSCs is increased after direct contact with myeloma cells. Moreover, Siglec-9L is more expressed by MM-MSCs than HD-MSCs with a particular role of inflammation. At the molecular level, we highlighted two differentially expressed genes: an increase of ST6GAL1 coding for a sialyltransferase enzyme and a decrease of NEU2 coding for a neuraminidase enzyme. Finally, we highlighted a link between hypersialylation and macrophage polarization, notably that an hypersialylation promotes the polarization of macrophages into an M2 state. Taken together, our work tends to show the importance of sialylation in the BM-TME of MM patients and could be an interesting therapeutic target to investigate.

P04

ROLE OF IGFBP6 AND THE IGF SYSTEM IN MULTIPLE MYELOMA: MECHANISMS OF CHEMORESISTANCE AND THERAPEUTIC IMPLICATIONS

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Multiple myeloma (MM) is a hematologic malignancy characterized by intricate genetic and metabolic alterations that drive disease progression and the development of chemoresistance. Despite significant research, the mechanisms underlying chemoresistance remain largely elusive. Emerging evidence indicates that the insulin-like growth factor (IGF) system and IGF-binding proteins, particularly IGFBP6, play pivotal roles in resistance mechanisms across various cancers. In this study, we analyzed the expression of IGFBP6, IGF2, and IGF1R in MM cell lines, patient-derived cell lines, and human biopsies using immunohistochemistry and quantitative real-time polymerase chain reaction (qRT-PCR). Moreover, we analyzed IGFBP6 expression and its relationship with patient outcomes using MM cell lines, patient-derived samples, and human biopsies. A Kaplan-Meier survival analysis revealed a striking inverse correlation between IGFBP6 expression and overall survival, with high IGFBP6 levels predicting significantly poorer outcomes ($p= 0.002559$). Patients with elevated IGFBP6 expression (≥ 0.3279) exhibited a pronounced reduction in survival probability compared to those with lower expression (<0.3279), underscoring its prognostic significance. Immunohistochemistry and qRT-PCR confirmed reduced IGFBP6 expression in bortezomib-sensitive cells compared to their resistant counterparts, which displayed elevated IGF2 and IGF1R levels, coupled with altered metabolic profiles. We further examined two MM cell lines (H929 and AMO), including variants sensitive and resistant to bortezomib (BTZ). BTZ-resistant cells demonstrated significantly reduced IGFBP6 expression alongside increased levels of IGF2 and IGF1R, coupled with a marked reduction in SHH expression compared to BTZ-sensitive cells. Consistently, CD138+ cells isolated from MM patients exhibited low IGFBP6 expression and elevated IGF2 and IGF1R levels. Additionally, metabolic reprogramming and adaptation to the tumor microenvironment were identified as hallmarks of MM, particularly in malignant plasma cells (PCs). BTZ-resistant cells displayed alterations in signaling pathways and energy metabolism. Notably, treatment with recombinant IGFBP6 protein reversed many of these metabolic and signaling changes, underscoring the critical role of the IGFBP6/SHH axis in the mechanisms of bortezomib resistance. These findings highlight the potential of IGFBP6 as both a prognostic biomarker and a therapeutic target. Modulating the IGFBP6/SHH axis could provide novel strategies to overcome resistance and improve outcomes in patients with MM. This study underscores the importance of exploring metabolic and molecular pathways in MM and their impact on treatment response, paving the way for more personalized therapeutic approaches.

P05

DEXAMETHASONE AND DARATUMUMAB IMPAIR T-CELL MEDIATED KILLING IN MULTIPLE MYELOMA: IMPLICATIONS FOR SEQUENTIAL THERAPIES

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For elderly patients the combination Daratumumab-lenalidomide-dexamethasone (Dara-Rd) is an emerging standard-of-care regimen, able to improve long-term outcomes in MM patients. Nevertheless, CD38 is ubiquitously expressed on both MM cells and immune cells, and the effect of daratumumab on MM microenvironment are still under investigation. Thus, we investigated the potential immunomodulatory effect of D-Rd on T-cells function in patients with newly diagnosed MM. PB samples were collected from newly diagnosed MM patients receiving Dara-Rd (n=7) at baseline, after 2,4 and 6 months of therapy. PBMCs were obtained using Ficoll-Paque (GE Healthcare, Piscataway Township, NJ) and then used for in vitro experiments and flow cytometry analysis (T lymphocytes populations were identified as $CD3^+$, $CD4^+/CD8^+$ cells). T-cells' activation was evaluated by flow cytometry (using a CD25, CD38, CD71, HLA-dr cocktail); mitochondrial mass was evaluated after cell staining with MitoTracker Green (Life Technologies); cell lysis was estimated by Annexin v FITC/7-ADD kit assay. Since our observation that T lymphocytes from MM patients receiving daratumumab-based therapies showed a redistribution of T cell subsets with decreased pool of terminal differentiated and highly differentiated end-stage $CD8^+$ cells after 2 months of administration ($p<0.05$) (n=4), we decided to conduct longitudinal monitoring of lymphocyte functionality in patients receiving exclusively Dara-Rd therapy (n=7). Our data showed that the mitochondrial mass of T lymphocytes significantly decreased after 6 months of therapy compared to baseline ($p<0.05$), associated to a trend of decreasing percentages of functional mitochondria and an increase in the dysfunctional ones. Additionally, there was a non-significant trend of increased expression of $HLA\text{-}DR^+$, a well-known marker of late activation and differentiation, in both unstimulated $CD4^+$ and $CD8^+$ cells compared to baseline, which might reflect a chronic activation state of T lymphocytes. Thus, we analyzed the expression of activation markers after 48h of stimulation with phytohemagglutinin. Although T lymphocytes exhibited an increased expression of activation markers, their activation capacity progressively decreased over time becoming statistically non-significant after 4 and 6 months of therapy compared to baseline meas-

urements, particularly in CD8+ cells. Next, to explore the impact of D-Rd therapy on T lymphocyte fitness, we treated PBMCs from healthy donors (n=2) and newly diagnosed MM patients (n=6) in vitro with single agent (daratumumab, lenalidomide, dexamethasone) and their combinations. Our results showed that mitochondrial functionality, activation capacity, proliferation rate and tumor cell lysis capacity of CD3+cells were negatively affected only in conditions with dexamethasone ($p<0.0001$). Interestingly, the impairment of T lymphocyte functionality induced by dexamethasone was reversed by using either Teclistamab ($p<0.0001$) or Elranatamab ($p<0.0001$), suggesting that T cell functionality is compromised during initial treatment, a factor that should be considered when designing new combinations and sequential treatments.

P06

ABSTRACT NOT PUBLISHABLE

P07

TIGIT AND NETOSIS: COULD THEY BE KEY PLAYERS IN MULTIPLE MYELOMA ?

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Multiple Myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of plasma cells (PCs) and immune evasion. The bone marrow (BM) microenvironment plays a central role in MM progression, promoting immune tolerance and chronic inflammation. Among the key processes involved are TIGIT, an immune checkpoint receptor that inhibits T cell and NK cell cytotoxicity, thus enhancing immune escape, and NETosis, a process where neutrophils release chromatin strands and pro-inflammatory factors that interact with PCs to sustain inflammation. We collected bone marrow blood samples from 25 newly diagnosed MM patients, between November 2022 and May 2024. Immunological analyses turned out that TIGIT was expressed in 86% (19/22) of newly diagnosed MM patients, predominantly on CD8+ T cells. TIGIT positivity correlated with markers of aggressive disease, including plasma cell infiltration >60%, free light chain ratio >100, International Staging System (ISS) scores II-III, Revised ISS scores, and elevated LDH (>220 mU/ml). Notably, all ultra-high-risk patients (100%, n=6) and 100% of ISS II-III patients were TIGIT-positive, while 66% of ISS I patients showed TIGIT expression ($p=0.01$). Diagnostic evaluation demonstrated 100% sensitivity, 100% specificity, and 95% overall accuracy in identifying TIGIT-positive cases. At once, we investigated the BM microenvironment of MM patients, distinguishing between TIGIT-positive (TIGITpos) and TIGIT-negative (TIGITneg) populations using morphological and immunological approaches. The morphological characterization revealed distinct differences between the two groups. In TIGITneg patients, the BM was predominantly characterized by plasma cell clusters, composed of large vacuolated cells with central nuclei. This cluster also contained T cells and macrophages without any morphological alterations. In contrast, TIGITpos patients exhibited isolated PCs with a polarized nucleus and no significant cytoplasmic changes, suggesting a more differentiated and immune-evading PC phenotype. Furthermore, neutrophilic infiltration was observed in TIGITpos patients, where neutrophils were predominantly in close contact with PCs and lymphocytes, highlighting a shift in the inflammatory microenvironment. Further analysis demonstrated that NETosis was more prominent in TIGITpos patients. Neutrophils in this group exhibited Neutrophil Elastase-positive strings, confirming active NET formation. Immunohistochemical analysis showed a significant increase in Ly6b and Neutrophil Elastase positive cells in TIGITpos patients. Additionally, IL-8 expression was also elevated in TIGITpos PCs, suggesting that PCs actively promote neutrophil chemotaxis. This interplay between PCs and neutrophils sustains inflammation, potentially driving disease progression and contributing to an autoimmune-like phenotype in MM. These findings highlight the complexity of the MM BM microenvironment, particularly the role of TIGIT in immune evasion and NETosis in inflammation-driven tumor progression. Our study suggests that targeting TIGIT could offer novel therapeutic strategies, potentially complementing current MM treatments and improving personalized disease management.

P08

PRECLINICAL EVALUATION OF ICASP9-TRANSDUCED ANTI-ROR1 CAR T-CELLS IN HEMATOLOGICAL MALIGNANCIES

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CAR T-cell therapies are successful therapeutic options for several B-cell malignancies and multiple myeloma. However, severe adverse events, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), may affect both efficacy and safety. Controlling these toxicities is critical for increasing the therapeutic potential of CAR T-cells in hematologic malignancies and expanding their clinical applications. Our research group investigated a novel anti-ROR1 CAR T-cell model targeting multiple myeloma and mantle cell lymphoma, evaluating its efficacy and safety profile through both *in vitro* and *in vivo* studies. To address treatment-associated toxicities, we incorporated the iCasp9 suicide gene system, a proven "safety switch" mechanism that triggers apoptosis. This approach has previously demonstrated efficacy in controlling Graft-versus-Host Disease (GvHD) during haploidentical stem cell transplantations. By combining two clinically validated technologies – iCasp9 and anti-ROR1 CAR T-cells – we developed a system to enhance safety without compromising therapeutic efficacy. Our *in vitro* experiments confirmed that the iCasp9-anti-ROR1 system successfully induced apoptosis, and in vivo studies showed no significant toxicities in murine models following the administration of the iCasp9-anti-ROR1 CAR T-cells. The activator drug of iCasp9, AP1903 (rimiducid), induced apoptosis of 80% of CAR T-cells in 30 minutes. The results have been confirmed *in vivo*, the number of CAR T-cells identified by flow cytometry decreasing significantly (12.9% *vs* 0.2%, $P<0.05$).

P09

CORRELATIVE RESEARCH ON PATIENTS WITH PLASMA CELL DYSCRASIAS: UPDATED ANALYSIS OF THE EMN36 INTERNATIONAL UNIFORM SAMPLE REPOSITORY

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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. A protocol to uniformly process and stock biological material in European Myeloma Network (EMN)-associated central laboratories was defined to collect peripheral blood (PB) and bone marrow (BM) aspirates of the enrolled pts. Samples were collected at baseline, at start of maintenance (transplant-eligible pts) or after 1 year on treatment (transplant-ineligible pts) and at the time of each subsequent progression. Additional samples of blood, marrow and biopsies of BM and EMD obtained according to clinical practice were collected as well. Local data about baseline disease characteristics, prognostic factors, treatment received, response and progression and survival status of pts were longitudinally collected.

Results. At the data cut-off (Dec 2, 2024), 262 of 301 screened pts were confirmed to be eligible and had baseline clinical data. The median age was 68 years (IQR 60-75). The majority of pts had IgG isotype (67%) and kappa light chain (59%). Among the 262 pts with baseline clinical data, 42 (16%) were diagnosed with MGUS, 47 (18%) with SMM, 169 (65%) with NDMM and 4 (2%) with pPCL. Among NDMM pts, 35% had International Staging System (ISS) stage I disease, 34% ISS II, 31% ISS III, 17% lactate dehydrogenase above the upper limit of normal and 17% ECOG performance status ≥2. Locally performed fluorescence *in situ* hybridization (FISH) was available in 109/169 (64%) NDMM pts. High-risk cytogenetics [t(4;14), t(14;16) or del(17p)] was present in 29% of evaluable pts, while ≥2 high-risk lesions [among t(4;14), t(14;16), del(17p) and 1q+] were present in 22% of evaluable pts. Treatment details were available for 156/167 NDMM pts: 50% received upfront regimens containing daratumumab (Dara): the most frequent regimen was Dara-VTd (18%), followed by Dara-Rd (13%), Dara-VRd (9%) and Dara-VMp (4%). Central laboratories received baseline samples from all screened pts. At the data cut-off, stock details were available for 230 pts. 2254 vials from BM aspirate samples, 2852 vials from PB samples and 93 slides/microsections from BM biopsies were stocked (Table 1). The median plasma cell purity of CD138+ fraction was 88% (IQR 72-96%).

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. 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	WBC (dry pellet)	230	1.0	7.5×10^6 cells
	WBC (viable)	49	1.9	24.1×10^6 cells
	BMMCs (viable)	174	1.7	18.1×10^6 cells
	CD138+ (RLT pellet)	147	1.2	0.9×10^6 cells
	CD138+ (viable)	82	1.4	2.5×10^6 cells
	CD138+ (dry pellet)	19	1	1.7×10^6 cells
	CD138+ (Carnoy-fixed)	33	1	0.5×10^6 cells
	CD138+ (cytospins)	47	2.2	0.2×10^6 cells
	CD138- (viable)	146	2.1	34.7×10^6 cells
	Plasma	222	3.9	0.8 ml
Peripheral blood material	PBMCs (viable)	84	2.0	22.2×10^6 cells
	Granulocytes (dry pellet)	214	1.0	11.3×10^6 cells
	Serum	230	3.6	0.5 ml
Bone marrow biopsy material	Slides	29	2	--
	Macrosections	29	1.2	--

Abbreviations. BMMC, bone marrow mononuclear cells; No., number; PBMCs, peripheral blood mononuclear cells; WBC, white blood cells.

P10

CLINICIANS' PERSPECTIVES AND METHODOLOGICAL APPLICATION OF FISH FOR THE DEFINITION OF CYTOGENETIC RISK IN PATIENTS WITH MULTIPLE MYELOMA: AN ITALIAN, REAL-WORLD, SURVEY-BASED REPORT FROM THE EUROPEAN MYELOMA NETWORK (EMN) ITALY

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Fluorescence *in situ* hybridization (FISH) is the standard technique currently used to detect cytogenetic abnormalities (CA) in multiple myeloma (MM). Its main aim is to better define patient prognosis. Although tailored treatment according to CA is not yet a standard procedure, initial evidence about the efficacy of specific treatments in some cytogenetic subgroups is emerging. Practical guidelines for FISH testing in clinical studies have been developed, but their application in the Italian real-world setting, the degree of standardization of laboratory techniques and the availability of the procedure are largely unknown. We developed a survey that was distributed from April to July 2023 among 70 Italian MM-treating centers associated with the European Myeloma Network (EMN) Italy, geographically well distributed across Italy. We aimed to record laboratory and clinicians' perspectives about the application of FISH in the Italian real-world setting, focusing on its availability, methodology and use in current clinical practice. Our survey results showed that FISH was widely available across the country, with 71% of the participating centers capable of performing it locally, while the remaining centers (predominantly centers with <30 newly diagnosed MM cases/year) sent the samples to external laboratories. We observed a lack of uniformity in terms of laboratory techniques, such as $CD138^+$ cell purification or the cut-off used to identify CA. Among the CA, 100% of laboratories at the participating centers routinely analyzed del(17p) and t(4;14), 98% analyzed t(14;16), 96% 1q+ (with 70% of laboratories distinguishing between gain *vs* amp(1q) according to copy number), 90% t(11;14), 88% del(1p32), 68% del(13q) and 52% hyperdiploidy. Prognostically, FISH emerged as a crucial technique, since 94% of centers used the Revised International Staging System (R-ISS) score at diagnosis, and 69% already implemented the newly described R2-ISS. Most of the centers performed FISH at diagnosis in all patients, while some centers did not routinely perform FISH in some categories of patients (e.g., patients aged >80 years). At relapse, 53% of centers routinely repeated FISH, only 9% never repeated FISH, while other centers repeated FISH in selected categories of patients. These data allowed us to obtain an updated overview of the use of FISH in Italy, serving as a benchmark to identify improvement strategies in the near future.

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Newly diagnosed multiple myeloma

P11

ABSTRACT NOT PUBLISHABLE

P12

DARATUMUMAB (DARA) + BORTEZOMIB, LENALIDOMIDE AND DEXAMETHASONE (VRD) *vs* VRD IN TRANSPLANT-INELIGIBLE (TIE) NEWLY DIAGNOSED MULTIPLE MYELOMA (MM) OR IF TRANSPLANT NOT PLANNED AS INITIAL THERAPY: MINIMAL RESIDUAL DISEASE ANALYSIS OF PHASE 3 CEPHEUS TRIAL

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Introduction. Minimal residual disease (MRD) negativity is associated with longer-term survival. In the phase 3 CEPHEUS study, DARA plus VRd (D-VRd) significantly increased depth of response, including rates of overall MRD negativity, complete response or better (≥CR), and sustained MRD negativity (*vs* VRd) in patients (pts) with TIE newly diagnosed MM (NDMM) or for whom transplant was not intended as initial therapy. These deep responses translated into significantly superior PFS for D-VRd *vs* VRd (HR 0.57; 95% CI 0.41-0.79; p=0.0005). We report an expanded analysis of MRD outcomes from CEPHEUS.

Methods. Eligible pts had NDMM with no intent for transplant based on age (≥70 yrs) or comorbid conditions, or deferred first-line transplant. Pts were stratified by ISS stage and age/transplant eligibility (<70 yrs ineligible, <70 yrs and transplant deferred, ≥70 yrs) and randomized 1:1 to D-VRd or VRd. All pts received 8 21-day cycles [C] of VRd (V: 1.3 mg/m^2 SC Days 1, 4, 8, 11; R: 25 mg PO Days 1-14; d: 20 mg PO/IV Days 1, 2, 4, 5, 8, 9, 11, 12), then 28-day cycles of Rd (R: 25 mg PO Days 1-21; d: 40 mg PO/IV Days 1, 8, 15, 22). The D-VRd group also received subcutaneous DARA (1800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; Halozyme]) weekly in C1-2, every 3 weeks in C3-8, and every 4 weeks in C9+. Treatment continued until progression or unacceptable toxicity. Primary endpoint was MRD-negativity rate (10^{-5}). MRD was evaluated in bone marrow aspirate samples at baseline, time of suspected CR, and 12, 18, 24, 30, and 36 months after first dose then annually in pts with CR.

Results. 395 pts (D-VRd, n=197; VRd, n=198) were randomized between Dec 11, 2018 and Oct 7, 2019. At median follow-up 58.7 months, overall MRD-negativity rates were significantly higher with D-VRd *vs* VRd at both 10^{-5} (60.9% *vs* 39.4%; OR 2.37; 95% CI 1.58-3.55; P<0.0001) and 10^{-6} (46.2% *vs* 27.3%; OR 2.24; 95% CI 1.48-3.40; p=0.0001). Prespecified subgroup analyses showed consistent MRD benefit with D-VRd in most subgroups, except for high cytogenetic risk. Sustained MRD negativity rates (≥12 months) were also higher with D-VRd *vs* VRd at both 10^{-5} (48.7% *vs* 26.3%; OR 2.63; 95% CI 1.73-4.00; P<0.0001) and 10^{-6} (32.0% *vs* 15.7%; OR 2.52; 95% CI 1.55-4.11; p=0.0001), with continued benefit of D-VRd for 2 yrs (10^{-5}: 38.6% *vs* 21.2%; 10^{-6}: 24.9% *vs* 12.6%) and 3 yrs (10^{-5}: 27.4% *vs* 13.6%) *vs* VRd. D-VRd improved landmark MRD-negativity rates and cumulative MRD negativity at all prespecified assessment timepoints (12/18/24/30/36/48/60 months) at both 10^{-5} and 10^{-6} *vs* VRd. PFS trended higher with D-VRd *vs* VRd in MRD-negative (10^{-5}: HR 0.61; 95% CI 0.35-1.06; 10^{-6}: HR 0.66; 95% CI 0.31-1.41) and MRD-positive (10^{-5}: HR 0.82; 95% CI 0.54-1.24; 10^{-6}: HR 0.74; 95% CI 0.51-1.06) pts. Estimated 54-mo PFS rates were 81.0% for D-VRd *vs* 69.5% for VRd in MRD-negative (10^{-5}) pts and 46% *vs* 33.7% for MRD-positive pts.

Conclusion. D-VRd led to significantly higher rates of overall and sustained MRD negativity (10^{-5} and 10^{-6}) *vs* VRd at all timepoints in TIE and transplant-deferred NDMM. This translated into significant improvements in overall PFS with D-VRd. Of pts who achieved MRD-negativity (10^{-5}) with D-VRd, >80% were alive and progression-free at 54 months. These data further support D-VRd as a new standard of care for TIE or transplant-deferred NDMM.

P13

PROSPECTIVE COMPARISON OF [18F]-FDG-PET/CT AND [68GA]-GA-PSMA-PET/CT FOR STAGING OF NEWLY DIAGNOSED MULTIPLE MYELOMA

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Background. [18F]-FDG-PET/CT is the most widely used imaging technique to detect bone disease in multiple myeloma (MM) and is recommended for response assessment by the International Myeloma Working Group. Prostate specific membrane antigen (PSMA) is expressed on the endothelium of neoangiogenic blood vessels. [68Ga]-Ga-PSMA-PET/CT currently represents a standard technique in staging of prostate cancer. However, PSMA is overexpressed in a variety of tumors characterized by neoangiogenesis, including MM.

Aims and Methods. We herein present a prospective single-center study aimed at evaluating the diagnostic performance of PSMA-PET in MM through comparison with FDG-PET. Patients (pts) with newly diagnosed (ND) MM underwent both scans within 14 days, before the start of any treatment. PSMA and FDG-PET were compared in terms of num-

ber of focal lesions (FLs), paraskeletal disease (PSD), diffuse bone marrow (BM) uptake and SUVmax.

Results. 51 NDMM pts were enrolled. In terms of positivity/negativity, 40 pts (78%) had concordant FDG and PSMA-PET: 23 (45%) were positive and 17 (33%) were negative at both tracers respectively. Conversely, 11 pts (22%) had discordant scans: 9 (18%) had positive FDG-PET and 2 (4%) had positive PSMA-PET (k = 0.57). FLs were detected in 27 pts (53%): FDG-PET detected FLs in 26 pts (51%) with 7 (14%) having a negative PSMA-PET; PSMA-PET detected FLs in 20 pts (39%) with 1 (2%) having a negative FDG-PET. Overall, 299 FLs were detected: FDG-PET detected 271/299 (91%) and PSMA-PET detected 90/299 (30%) FLs; 209 FLs (70%) were only FDG-positive, whereas 28 FLs (9%) were only PSMA-positive. In 8 pts (16%) FDG-PET and PSMA-PET detected the same number of FLs; in 13 (25%) and 6 pts (12%) FDG-PET and PSMA-PET revealed a higher number of FLs than the other tracer respectively (p=0.09). Median SUVmax of FLs was 5.7 (interquartile range, IQR: 4.1-7.5) for FDG and 5.2 (IQR: 3.4-6.1) for PSMA. 1 pt had PSMA uptake in FLs resulting higher than physiologic liver uptake (reference for radioligand therapy indication). PSD lesions were detected in 10 pts (20%) by FDG-PET and in 9 pts (18%) by PSMA-PET. Overall, 13 PSD lesions were detected: all (100%) were FDG-positive, 12 (92%) were PSMA-positive. Median SUVmax of PSD was 5.5 (IQR: 3.5-10.6) for FDG and 4.7 (IQR: 3.6-5.1) for PSMA. 2 pts had PSMA uptake in PSD lesions resulting higher than liver. Regarding BM diffuse uptake, 36 pts (71%) had concordant scans: 5 (10%) were positive and 31 (61%) were negative by both tracers. Among discordant pts, 12 (23%) had positive FDG-PET and 3 (6%) had positive PSMA (k = 0.24). Median SUVmax of BM was 4.8 (IQR: 4.3-5.2) for FDG and 3.3 (IQR: 2.6-4.9) for PSMA.

Conclusions. According to these preliminary results, in NDMM pts FDG-PET features a positivity rate resulting higher in detecting FLs and BM diffuse uptake and similar in detecting PSD lesions as compared to PSMA-PET. Furthermore, PSMA uptake of FLs and/or PSD lesions had higher values than physiologic liver uptake only in 2 pts. Due to these observations, lack of standardization in response assessment, short half-life requiring a local cyclotron for on-site production and elavated costs, PSMA does not seem optimal for imaging or theranostics in NDMM pts. However, it is not excluded that PSMA uptake may be higher in advanced phases of MM, characterized by further increase of neoangiogenesis.

P14

THE COMBINATION OF BELANTAMAB MAFODOTIN WITH LENALIDOMIDE AND DEXAMETHASONE IN INTERMEDIATE-FIT AND FRAIL NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA; FINAL RESULTS OF A PHASE 1/2 STUDY OF THE GREEK MYELOMA STUDY GROUP

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Belantamab mafodotin (belamaf) combinations showed superior efficacy over SoC regimens in relapsed/refractory multiple myeloma (MM) patients (pts) in the DREAMM-7/-8 clinical trials. In BelaRd we evaluated the safety & efficacy of a novel, extended dosing schedule of belamaf combined with lenalidomide & dexamethasone (Rd), in transplant-ineligible newly diagnosed MM pts. Part 1 of the phase 1/2 BelaRd trial (NCT04808037) evaluated the safety/tolerability of belamaf 2.5/1.9/1.4 mg/kg Q8W plus Rd & established a recommended phase 2 dose (RP2D) of 1.9 mg/kg Q8W. Dosing was guided by ophthalmologist-assessed Ocular Adverse Events (OAEs, Best Corrected Visual Acuity [BCVA] change from baseline & keratopathy). In Part 2 safety/efficacy of RP2D is assessed via 2 dose modification guidelines: Group A's one is same to Part 1; Group B uses Vision-Related Anamnestic (VRA, a pt-reported, 9-question tool capturing ocular symptoms & impact on ADL) & ≥Gr3 OAEs. We present safety/efficacy results from both parts of the trial. Of all Part 1 pts (n=36; median age: 72.5; male: 53%), 25 (69%) are ongoing & 11 (31%) discontinued (8 [22%] due to fatal events; 1 [3%] progressive disease (PD); 2 [6%] withdrew consent). 17%/75% of pts had stage I/II disease per R-ISS & 8% high-risk cytogenetics (HRC), while 89%/11% were intermediate-fit/frail as per IMWG frailty score. At a median FU of ~36 months, of 212/206/166 planned belamaf doses, 46%/32%/30% were skipped due to OAEs in the 2.5/1.9/1.4 mg/kg cohorts. Median time for re-administration after a dose hold was 6 weeks. Meaningful BCVA decline (Snellen <20/50) with ≥3 lines drop in the better seeing eye was recorded in 16%/11%/7% of ocular exams, with median time to resolution of 1.2/1.5/1.1 months for the 2.5/1.9/1.4 mg/kg cohorts, respectively. Of Part 2 pts (n=30; median age: 76; male: 67%), 22 (73%) are ongoing & 8 (27%) discontinued (6 [20%] due to fatal events; 1 [3%] PD; 1 [3%] withdrew consent). 27%/63% of pts had stage I/II disease per R-ISS & 17% had HRC. 97%/3% of pts were intermediate-fit/frail as per IMWG frailty score. At a median FU of ~20 months, of 138/122 planned belamaf doses, 28%/16% were skipped due to OAEs in Group A & due to VRA results in Group B, while the median time for belamaf re-administration was 4.1/4.7 weeks for Groups A & B, respectively. Meaningful BCVA decline with ≥3 lines drop in the better seeing eye was recorded in 10%/6 % of ocular exams in Groups A & B, with median time to resolution of ~1 month for both Groups. VRA recorded ocular symptoms & reduction in ADL for substantial (≥50%) time in 39% (7/18) of ocular exams with Gr≥3 OAEs. The ORR were 100% & 96.7% in Parts 1 & 2 and median time to 1st response was ~ 1 month. The 12/24/36-months PFS rates for all pts were 87.7%/78.7%/70.3%. The respective PFS rates for the 42 pts who received 1.9 mg/kg Q8W were 87.8%/74.9%/67.4% (Figure 1). The BelaRd regimen demonstrated substantial clinical activity, with rapid, deep & durable responses in an unfit population, with only 1 PD observed in each part after a prolonged FU period. The prolonged dosing schedule for belamaf successfully mitigated the risk for OAEs, as a low frequency of ≥Gr3 OAEs/meaningful BCVA decline was observed, that resolved rapidly. These results fully justify the performance of a phase 3 clinical trial evaluating BelaRd combination against SoC in this setting.

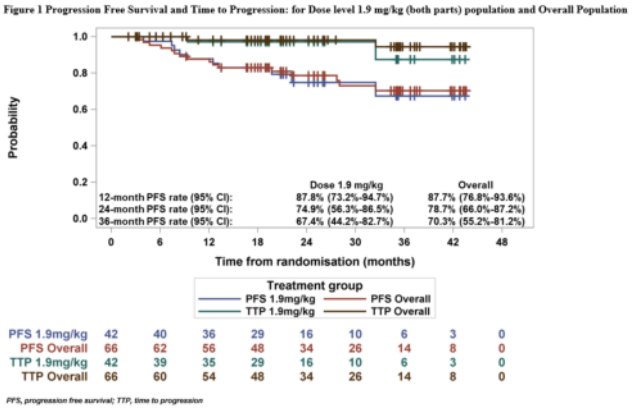

Figure 1.

P15

STEM-CELL MOBILIZATION AND TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE WITH OR WITHOUT ISATUXIMAB (EMN24 ISKIA TRIAL)

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Introduction. In the phase 3, randomized EMN24/IsKia trial, the addition of isatuximab to carfilzomib-lenalidomide-dexamethasone (Isa-KRd) as induction and consolidation in transplant-eligible NDMM patients (pts) significantly improved the measurable residual disease negativity (10^{-5}) rate at the end of consolidation (Isa-KRd 77% *vs* KRd 67%, p=0.049). Here we present a preplanned analysis on stem-cell (SC) mobilization and collection and transplantation outcomes.

Methods. Pts received 4 28-day induction cycles with Isa-KRd *vs* KRd and subsequently started SC mobilization 4-6 weeks after day 21 of cycle 4 with either cyclophosphamide (Cy; 2-3 g/m²) plus granulocyte colony-stimulating factor (G-CSF; 10 µg/kg) from day 5 until SC collection was completed or G-CSF alone ±plerixafor (PLX) according to its label. Pts received autologous SC transplantation (ASCT) conditioned with melphalan at 200 mg/m².

Results. 302 pts were randomized to Isa-KRd (151) or KRd (151) induction. 140 (93%) *vs* 141 (93%) pts in the Isa-KRd *vs* KRd arms started SC mobilization at a median time of 25 days from the end of induction, with more patients receiving cyclophosphamide in the Isa-KRd arm than in the KRd arm (75% *vs* 62%). A similar percentage of pts in the Isa-KRd (97%) *vs* KRd (99%) arms completed SC mobilization (p=0.4). PLX use was similar in the two arms (39% *vs* 29%, p=0.1). The median number of $CD34^+$ SCs collected was 5.0×10^6 cells/kg (IQR 3.7×10^6-6.6×10^6) in the Isa-KRd *vs* 5.5×10^6 (IQR 3.8×10^6-7.8×10^6) in the KRd arm (p=0.14). The median number of apheresis days was 2 (IQR 1–2) in the Isa-KRd *vs* 1 (IQR 1-2) in the KRd arm (p=0.08). The successful mobilization rate ($\geq2\times10^6$ $CD34^+$ cells/kg) was similar in pts mobilized with Cy+G-CSF *vs* G-CSF (99% *vs* 96%, p=0.2), although a higher SC yield was obtained with Cy+G-CSF *vs* G-CSF (6.37×10^6 *vs* 3.74×10^6 cells/kg; p<0.001). A second mobilization, mostly with G-CSF±PLX (73% of pts) was performed in 19 pts (14%) in the Isa-KRd and 7 pts (5%) in the KRd arm, mainly due to $<2.0\times10^6$ cells/kg collected with the first attempt (15 *vs* 6 pts); of these, 15 *vs* 7 pts in the Isa-KRd *vs* KRd arms successfully completed SC collection. Among pts who underwent mobilization, 134 (95%) in the Isa-KRd *vs* 137 (97%) in the KRd arm underwent ASCT. The median number of $CD34^+$ transplanted cells was 3.1×10^6 cells/kg (IQR 2.4×10^6-4.0×10^6) in the Isa-KRd *vs* 3.3×10^6 (IQR 2.7×10^6-4.4×10^6) in the KRd arm (p=0.10). The median time to neutrophil recovery ($\geq0.5\times10^9$/L) was 15 days (IQR 13-27) in the Isa-KRd *vs* 14 (IQR 12-27) in the KRd arm (p=0.33); the median time to platelet recovery ($\geq20\times10^9$/L) was 18 days (IQR 14-25 in the Isa-KRd *vs* 16 (IQR 13-24) in the KRd arm (p=0.1).

Conclusions. SC mobilization and collection with either Cy+G-CSF or G-CSF was feasible and successful after KRd ±isatuximab induction therapy in the majority of pts and allowed for comparable hematopoietic reconstitution in all transplanted pts. The upfront use of PLX could be considered to optimize SC collection.

P16

FEASIBILITY OF MINIMAL RESIDUAL DISEASE ASSESSMENT BY NEXT GENERATION SEQUENCING IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS TREATED IN A REAL-LIFE SETTING. A 7-YEAR SINGLE-CENTER EXPERIENCE

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The relevance of Minimal Residual Disease (MRD) in the management of Newly Diagnosed Multiple Myeloma (NDMM) mainly stemmed from clinical trials (CTs) data, and evidence of its application in a real-life setting is yet to be robustly built. Herein, we provide insights on our experience with Next generation Sequencing (NGS) monitored MRD in NDMM treated in clinical practice, with the purpose of showing its feasibility. We therefore retrospectively analyzed patients (pts) with NDMM tested consecutively for MRD from March 2016 to December 2023 at our Institution. Hence, we focused on MRD dynamics in pts treated with standard of care regimens with at least one MRD measurement. MRD was measured by NGS (LymphoTrack® assay, Invivoscribe). Overall, 282 pts were evaluated: 263 (93%) had a trackable clonotype, whereas 19 (7%) were not evaluable due to lack of clonal rearrangement(s). Among the trackable pts, 99 (38%) were not monitored further, 60 due to early progression/poor response (61%) and 39 to physician discretion (39%). Of the 164 pts with at least one evaluation, 43 were treated in a CT and discarded from the current analysis. The 121 analyzed pts were treated as follows: 44 with bortezomib, thalidomide, dexamethasone (VTd) and 47 with daratumumab-VTd (D-VTd) in an autologous stem cells transplantation (ASCT) + lenalidomide maintenance setting; 30 with daratumumab-based regimens in a non-transplant eligible (NTE)

setting. Collectively, a total of 187 tests were performed: 144 (77%) evaluations reached 10^{-5} sensitivity with a minimal confidence of 90%; 33 (18%) samples were hemodiluted, as per the ALLgorithMM criteria (Vigliotta *et al*., 2022). Median follow up (FU) of VTd pts was 62 months (mos). Thirty pts (68%) had not yet relapsed, 27 (90%) being MRD negative (MRD-) and 3 (10%) MRD positive (MRD^+). Twenty-four pts were tested for MRD before maintenance and 14 (58%) were MRD-. Twenty pts underwent first MRD evaluation during maintenance and 13 (65%) were MRD^-. Of the 17 MRD^+ pts at first time point, 8 (47%) became MRD-, while of the 35 pts who eventually reached MRD negativity, 4 (11%) showed MRD resurgence. Sustained MRD negativity was observed in 30 pts: maintenance was discontinued in 13 of them, and with a median of FU 8.5 mos, one pt relapsed to date. Overall, 5 (14%) MRD- and 7 (41%) MRD^+ pts eventually relapsed. Two pts were lost to FU. The median FU of D-VTd pts was 22.2 mos; all were tested before maintenance. Of the 30 pts with available results, 24 (80%) were MRD. The median FU of daratumumab-treated NTE pts was 24 mos; all were tested being in VGPR/CR after 12 mos of treatment. Of the 19 pts with available results, 11 (58%) were MRD^-. To sum up, our data support the feasibility of NGS-based MRD assessment in NDMM. The amount of pts with evaluable clonotypes approximates the percentages reported in CTs, with the main hamper being the quality of samples. Major pitfalls, not fully addressed by CTs, are a) number of pts not undergoing further MRD monitoring due to lack of clinical utility; b) frequency of evaluations with unacceptable sensitivity ($<10^{-5}$); and c) reduced reliability caused by hemodiluted samples. In addition, our data further suggest the association between MRD negativity and prolonged disease control, thus supporting the relevance of MRD implementation in the management of MM pts. The updated FU will be presented at the meeting.
Acknowledgments: AIRC 22059, BolognAIL.

P17

PHASE 3 RANDOMIZED STUDY OF DARATUMUMAB (DARA) MONOTHERAPY VERSUS ACTIVE MONITORING IN PATIENTS (PTS) WITH HIGH-RISK SMOLDERING MULTIPLE MYELOMA (SMM): PRIMARY RESULTS OF THE AQUILA STUDY

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Introduction. High-risk SMM is a precursor to active MM without approved treatment. However, recent data suggest pts at high risk of progression to MM may benefit from early treatment. DARA is approved as monotherapy for RRMM and in combination with standard-of-care regimens for RRMM and NDMM. Based on the phase 2 CENTAURUS study with DARA monotherapy in intermediate- or high-risk SMM, the phase 3 AQUILA study sought to determine if DARA could delay progression to MM *vs* active monitoring. We report the primary analysis from AQUILA.

Methods. Eligible pts had a confirmed diagnosis of high-risk SMM for ≤5 years, defined as clonal BMPCs ≥10% and ≥1 risk factor (serum M protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved Ig isotypes, serum involved:uninvolved free light chain ratio ≥8 and <100, and/or clonal BMPCs >50% to <60%). Focal and lytic lesion assessment was performed by CT and MRI and centrally reviewed prior to enrollment. Pts were randomized 1:1 to DARA SC *vs* active monitoring. DARA (QW in Cycles 1-2, Q2W in C3-6, and Q4W thereafter) was given in 28-day cycles until cycle 39, 36 months, or progression, whichever came first. The primary endpoint was PFS, defined as progression to active MM as assessed by an independent review committee and according to IMWG diagnostic criteria for MM (SLiM-CRAB) or death. Major secondary endpoints included ORR, PFS on first-line (FL) MM treatment (PFS2), and OS.

Results. 390 pts (DARA, n=194; active monitoring, n=196) were randomized. Median (range) age (64 [31-86] years) and time from SMM diagnosis to randomization (0.72 [0-5.0] years) were balanced between groups. Median treatment duration with DARA was 38 cycles (35.0 months). At median (range) follow-up 65.2 (0-76.6) months, PFS was significantly improved with DARA *vs* active monitoring (HR, 0.49; 95% CI, 0.36-0.67; p<0.0001). Median PFS was not reached with DARA *vs* 41.5 months for active monitoring; estimated 60-month PFS rates were 63.1% *vs* 40.8%, respectively. There was generally consistent PFS improvement with DARA *vs* active monitoring across subgroups. ORR was 63.4% with DARA *vs* 2.0% with active monitoring (p<0.0001). At clinical cutoff, 64 (33.0%) pts in the DARA group and 102 (52.0%) in the active monitoring group had started FL MM treatment. Median time from randomization to FL treatment was not reached with DARA *vs* 50.2 months with active monitoring (HR, 0.46; 95% CI, 0.33-0.62; nominal p<0.0001). There was a positive trend in favor of DARA for PFS2 (HR, 0.58; 95% CI, 0.35-0.96) and OS (60-month rates: DARA, 93.0%; active monitoring, 86.9%; HR, 0.52; 95% CI, 0.27-0.98). 41 deaths were observed (DARA, 15; active monitoring, 26). Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 40.4% and 30.1% with DARA and active monitoring, respectively. The most common (≥5%) grade 3/4 TEAE was hypertension (DARA, 5.7%; active monitoring, 4.6%). Frequency of TEAEs leading to DARA discontinuation was low (5.7%), as was fatal TEAE incidence in both groups (DARA, 1.0%; active monitoring, 2.0%).

Conclusions. DARA monotherapy was well tolerated and showed a clinically meaningful and significant benefit in preventing or delaying progression to active MM *vs* active monitoring in high-risk SMM. ORR was significantly higher and time to FL MM treatment was prolonged with DARA *vs* active monitoring. These results strongly support early DARA monotherapy *vs* active monitoring, the current standard of care in high-risk SMM.

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DARATUMUMAB (DARA)/BORTEZOMIB/LENALIDOMIDE/DEXAMETHASONE (D-VRD) WITH D-R MAINTENANCE (MAINT) IN TRANSPLANT-ELIGIBLE (TE) NEWLY DIAGNOSED MYELOMA (NDMM): ANALYSIS OF PERSEUS BASED ON CYTOGENETIC RISK

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Introduction. In the primary analysis of the phase 3 PERSEUS study, subcutaneous DARA (DARA SC) + VRd induction/consolidation (ind/consol) and D-R maint improved progression-free survival (PFS) and increased rates of deep and durable responses, including minimal residual disease (MRD) negativity and sustained MRD negativity, *vs* VRd ind/consol and R maint in TE NDMM, regardless of cytogenetic risk status. We report an expanded analysis of PERSEUS (PFS, overall MRD negativity, and sustained MRD negativity) based on the presence of high-risk cytogenetic abnormalities (HRCAs), including gain(1q21) and amp(1q21).

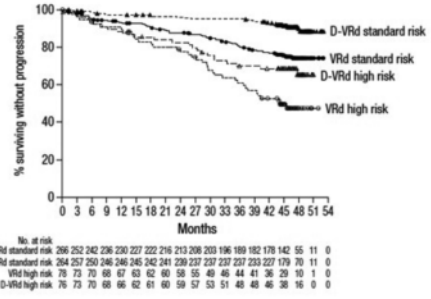
Methods. TE patients (pts) with NDMM were randomly assigned 1:1 to D-VRd or VRd. Pts in both arms received up to six 28-day cycles (4 pre-ASCT ind, 2 post-ASCT consol) of VRd (V 1.3 mg/m^2 SC on Days [D] 1, 4, 8, 11; R 25 mg PO on D 1-21; d 40 mg PO/IV on D 1-4, 9-12) and R maint (10 mg PO on D 1-28 until progressive disease [PD]). In the D-VRd arm, pts also received DARA SC (DARA 1,800 mg + recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; Halozyme]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W during maint until PD. Cytogenetic risk was assessed by FISH. High risk was defined per protocol as the presence of ≥1 of the following HRCAs: del(17p), t(4;14), t(14;16). Revised high risk was defined as the presence of ≥1 of the following HRCAs: del(17p), t(4;14), t(14;16), gain(1q21), amp(1q21). Cytogenetic subgroups included standard risk (0 HRCAs per protocol); high risk (per protocol); revised standard risk (0 HRCAs per the revised definition); revised high risk; gain(1q21) and amp(1q21) (3 copies and ≥4 copies, respectively, of chromosome 1q21 ± other HRCAs); and (only) 1 HRCA and ≥2 HRCAs (per the revised definition). MRD-negativity rate (clonoSEQ®) was defined as the percentage of pts in the intent-to-treat population who achieved both complete response or better and MRD negativity.

Results. 709 pts were randomized (D-VRd, n=355; VRd, n=354). At a median follow-up of 47.5 months, PFS favored D-VRd *vs* VRd across all cytogenetic risk subgroups (Figure 1). Overall MRD-negativity rates (10^{-5}) were higher with D-VRd *vs* VRd: standard risk (77.3% *vs* 48.1%; p<0.0001), high risk (68.4% *vs* 47.4%; p=0.0086), revised standard risk (75.3% *vs* 47.3%; P<0.0001), revised high risk (73.1% *vs* 49.3%; p<0.0001), gain(1q21) (69.5% *vs* 46.5%; p=0.0086), amp(1q21) (85.7% *vs* 55.6%; p=0.0104), 1 HRCA (75.3% *vs* 50.0%; p=0.0002), and ≥2 HRCAs (66.7% *vs* 47.4%; p=0.1044). Rates of sustained MRD negativity (10^{-5}) for ≥12 months were higher with D-VRd *vs* VRd across subgroups: standard risk (69.3% *vs* 31.2%; P<0.0001), high risk (48.7% *vs* 25.6%; p=0.0032), revised standard risk (66.1% *vs* 31.7%; P<0.0001), revised high risk (59.2% *vs* 27.7%; p<0.0001), gain(1q21) (62.7% *vs* 29.6%; p=0.0002), amp(1q21) (71.4% *vs* 27.8%; p=0.0006), 1 HRCA (61.9% *vs* 28.2%; p<0.0001), and ≥2 HRCAs (51.5% *vs* 26.3%; p=0.0303). Rates of overall MRD negativity and sustained MRD negativity for ≥12 months at 10^{-6} were higher with D-VRd *vs* VRd across subgroups and will be presented.

Conclusions. The addition of DARA SC to VRd ind/consol and to R maint provided clinical benefit in terms of PFS and induced higher rates of deep and sustained responses *vs* VRd ind/consol and R maint across all cytogenetic risk subgroups. These results support D-VRd ind/consol and D-R maint as a new standard of care for TE NDMM, regardless of cytogenetic risk status.

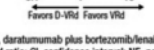
Figure. (A) Subgroup analysis of PFS based on protocol-defined cytogenetic risk status and (B) cytogenetic risk subgroup analysis of PFS in the ITT population.

A.



B.

	D-VRd n/N	D-VRd Median PFS (mo)	VRd n/N	VRd Median PFS (mo)	HR (95% CI)	*P* value
Standard risk	25/264	NE	62/266	NE	0.35 (0.22-0.56)	<0.0001
High risk	24/76	NE	38/78	44.1	0.59 (0.36-0.99)	0.0439
Revised standard risk	12/174	NE	35/167	NE	0.29 (0.15-0.56)	0.0001
Revised high risk	33/130	NE	62/148	NE	0.53 (0.35-0.81)	0.0027
Gain(1q21)	15/59	NE	26/71	NE	0.62 (0.33-1.18)	0.1400
Amp(1q21)	6/28	NE	17/36	46.7	0.37 (0.15-0.94)	0.0306
1 HRCA	21/97	NE	43/110	NE	0.47 (0.28-0.79)	0.0035
≥2 HRCAs	12/33	NE	19/38	44.1	0.73 (0.35-1.50)	0.3878



PFS, progression-free survival; ITT, intent-to-treat; D-VRd, daratumumab plus bortezomib/lenalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NE, not estimable; HRCA, high-risk cytogenetic abnormality.

Figure 1.

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A DETAILED IMAGING ANALYSIS ON BONE DISEASE BURDEN IN 119 NEWLY DIAGNOSED PTS WITH MULTIPLE MYELOMA

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Introduction. Whole body low dose computed tomography (WBLDCT) is the cornerstone of detecting myeloma bone disease (MBD) and establishing the diagnosis of symptomatic multiple myeloma (MM). Herein, we evaluated the bone disease burden in patients (pts) with newly diagnosed MM using WBLDCT and we explored possible correlations with survival outcomes.

Methods. We consecutively enrolled pts with NDMM who performed baseline WBLDCT assessed at a single referral center according to standard clinical practice. A detailed analysis of bone-related parameters was performed independently by two radiologists with expertise in MM. More specifically, each patient was evaluated for the presence of any osteolytic lesions, the total number and the largest diameter of the lesions, the presence of cortical destruction, the presence of fractures and vertebral compound fractures (VCFs) and the presence of appendicular skeleton medullary cavities (ASMC). Each bone was assessed separately.

Results. 119 pts (57.5% females) were included, with a median age of 67 years (range 37-81). Pts were assessed per ISS and R-ISS stage as follows: 31 (26.3%) and 20 (16.9%) stage 1, 30 (25.4%) and 71 (60.2%) stage 2, 57 (48.3%) and 27 (22.9) stage 3, respectively. As per R2-ISS they were distributed as follows: 48 (40.7%) low risk, 24 (20.3%) low-intermediate risk, 33 (28.0%) intermediate-high risk and 13 (11.0%) high risk. 73 pts (61.3%) had performance status 0-1, whereas 19 (16.1%) had at least one high-risk cytogenetic abnormality. The pts received induction treatment as follows: 80 (67%) based on proteasome inhibitors, 14 (12%) based on immunomodulatory drugs, 22 (19%) based on both a PI and an IMiD and 3 (2%) based on anti-CD38 monoclonal antibodies. 31 (26.3%) of the pts underwent autologous stem-cell transplantation. During a median follow-up of 4.2 years (range 0.1-5.4), 79 pts (67.0%) showed disease progression and 63 (54.2%) died. The median progression-free survival (PFS) was 2.19 years (95% CI: 1.61-3.31) and median overall survival (OS) was 6.24 years (95% CI: 4.06-not reached). Regarding osteolysis assessment, the median (range) number of osteolyses in each bone group were as follows: 2 (0-96) for the spine, 0 (0-30) for the skull, 0 (0-41) for the shoulder, 0 (0-28) for the appendices and 0 (0-42) for the ribs. Regarding the ASMC assessment in the bilateral femurs and humerus, 47 pts (39.5%) showed fatty ASMCs, 39 pts (32.8%) had diffuse ASMCs, 30 pts (25.2%) had nodular ASMCs, whereas 38 pts (31.9%) had mixed ASMCs subtypes. The 119 pts were stratified according to the presence (n=52) or absence (n=67) of VCFs. The presence of VCFs was a single adverse predictor for PFS and OS. More specifically, the median PFS was 42.7 months for pts without VCFs compared to 19.8 months for pts with at least one VCF (HR 1.69, 95%CI: 1.09 -2.62). Similarly, pts with at least one VCF had a twofold increase for risk of death (HR 1.99, 95%CI: 1.21-3.25), compared to those without. However, among all the examined imaging variables, no factor or combination factors had independent significance for patient prognosis.

Conclusions. Although the presence of VCFs at WBCT at diagnosis of MM was correlated with survival outcomes in the univariate analysis, none of the imaging parameters retained statistical significance in the multivariate analysis. Therefore, it seems that the extend of the MBD burden at diagnosis does not impact OS in the era of modern anti-myeloma treatment regimens.

P20

SEQUENTIAL WHOLE BODY MAGNETIC RESONANCE IMAGING FOR EVALUATING TREATMENT RESPONSE IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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Introduction. Whole-body magnetic resonance imaging (WBMRI) is often being used to evaluate newly diagnosed multiple myeloma (NDMM) patients (pts) at first presentation, in order to differentiate symptomatic from asymptomatic disease. The role of imaging re-evaluation at fixed timepoints for all symptomatic pts under treatment is rather unclear.

Methods. In this prospective cohort study, consecutive pts with NDMM who underwent WBMRI at the time of diagnosis and two months after treatment initiation were included. All pts provided written informed consent and the study was approved by the IRB.

Results. 78 pts with NDMM were included, with a median age of 68 years (range 32-89), whereas 32.1% were females. All pts underwent WBMRI at baseline with the following distribution of imaging patterns: 38 (48.7%) focal, 19 (24.4%) normal, 9 (11.5%) variegated, 8 (10.3%) diffuse and 4 (5.1%) distinct foci of both diffuse and focal. Baseline WMBRI revealed paramedullary disease (PMD) in 17 (21.8%) pts and fractures in 21 (26.9%). 43 pts (55.1%) received anti-CD38-based upfront treatment, 17 (21.8%) received bortezomib-lenalidomide-dexamethasone (VRd), and 18 (23.1%) received other regimens. Two months after treatment initiation, 73 pts (93.6%) had achieved at least partial remission (PR). Median time to best response was 2.7 months (range 0.8-17.8); 7 CR or better (9.0%), 44 VGPR (56.4%), 22 PR (28.2%), 1 MR (1.3%) and 1 SD (1.3%). Imaging responses assessed according to the second WBMRI were as follows: 13 (16.7%) CR, 31 (39.7%) nearCR (nCR), 11 (14.1%) PR and 3 (3.8%) SD. Out of the 17 pts with PMD at baseline, all but one responded (94.1%). During a median follow-up of 16.5 months (range 3-27), 3 pts (3.8%) progressed and 2 (2.6%) died. One disease progression was identified at the second WBMRI, before documented hematological progression or clinical deterioration. Median survival times were not reached. Interestingly, nCR WBMRI responses were associated with VGPR serum responses (OR 2.72, 95%CI: 1.05-7.49). There was no association between type of first line of therapy and WBMRI response. Although ISS stage at baseline was associated with serum response (Fisher's, p=0.025), it was not associated with WBMRI response (p=0.646). Imaging pattern at baseline was significantly associated with imaging PR or better on WBMRI (p=0.022) but not with hematologic response (p=0.697). Overall, 21 (26.9%) pts presented with fractures at baseline. Importantly, 12 pts (15.4%) were diagnosed with new fractures at the time of the second WBMRI; seven (8.9%) were recurrent events. These new fractures were not evaluated as progressive disease, since there were no new osteolyses or plasmacytomas and the disease was in hematologic response. Inter-

estingly, the presence of fractures identified by WBMRI at baseline were associated with new occurrences of fractures at the second WBMRI (p=0.021). Specifically, pts with a fracture at baseline had 5.02 (95% CI: 1.37, 19.99) times the odds to present with a new one at the second WBMRI. Imaging pattern at baseline was not associated with the occurrence of a new fracture at the time of the second MRI.

Conclusion. Sequential imaging assessment with WBMRI at baseline and after two months of treatment may complement hematological evaluation of disease response in pts with NDMM while re-evaluation may identify early signs of disease refractoriness. Longer follow-up will reveal the potential prognostic value of sequential WBMRI.

P21

DELETION 17P, AND IGH HIGH-RISK TRANSLOCATIONS CONCURRING WITH CHROMOSOME 1 ARM ABNORMALITIES ARE THE STRONGEST PROGNOSTICATORS FOR OVERALL SURVIVAL IN THE REAL-WORLD SETTING: A VALIDATION ANALYSIS BY THE GREEK MYELOMA STUDY GROUP

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Chromosome 1 (Chr1) abnormalities, including 1q21 gain/amplification (1q21+) and 1p32 deletion (del1p32), are associated with poor prognosis in Multiple Myeloma (MM). A novel IMS/IMWG definition of high-risk MM (HRMM) was recently published and includes: a) del17p and/or TP53 mutations; b) IgH-related high-risk translocations (IgH-HRT) -i.e. t(4;14), t(14;16), and t(14;20)- concurring with 1q21+ and/or del1p32; c) monoallelic del1p32 with 1q21+ or biallelic del1p32; and d) β2-microglobulin (β2M) >5.5 mg/dL with serum creatinine (sCr) <1.2 mg/dL. Our objective was to validate the proposed prognostic factors for HRMM in a large cohort of newly diagnosed MM (NDMM) patients treated in real-world (RW). We analyzed 1478 NDMM patients (pts) [M/F: 736/742; median age: 66 (33-91); IgG: 880, IgA: 388, light chain: 181, IgD: 11, non-secretory: 15, IgM: 2, IgE:1)] diagnosed from 2003-2023, and included In the Greek Myeloma Study Group registry. All pts had complete RISS/R2ISS data, while data for 1p were available in 522 pts (35%). Cytogenetics were distributed as follows: low risk (including pts with unknown 1p status): 925 pts (62.5%), 1q21+ and/or del1p32 only: 283 (19%), IgH-HRT combined with 1q21+ and/or del1p32: 65 (4.5%), IgH-HRT: 61 (4%), del17p (alone or combined with other aberrations): 144 (10%); β2M >5.5mg/dL with normal sCr occurred in 60 pts (5.5%). Of total, 88% pts were treated with novel agents; 544 (37%) received lenalidomide plus PI-based or daratumumab-based regimens; 466 (31.5%) underwent autologous transplantation. After a median follow up of 60 months (95% CI: 56-64), 651 (44%) pts died. Median PFS and OS was 31 months (95% CI: 29-33) and 78 months (95% CI: 71-85), respectively and differed significantly among risk groups (p<0.001). Patients with IgH-HRT plus1q21+ and/or del1p32 and pts with del17p had significantly shorter PFS and OS compared to low risk pts, to pts with sole IgH-HRT or single 1q21+and/or del1p32 (PFS: 18 and 20 months, *vs* 35, 31 and 29 months, respectively and OS: 36 and 41 months, *vs* 92, 93 and 79 months, respectively; p<0.05). In the univariate analysis, 1q21+and/or del1p32 with additional IgH-HRT, del17p, ISS, RISS and R2ISS were significant prognosticators for OS (p<0.05); β2m >5.5 mg/dL with normal sCr was marginally significant (p=0.1). In the multivariate analysis, IgH-HRT plus 1q21+ and/or del1p32 and del17p were the only significant prognostic factors for OS when adjusted for staging systems (HR: 2.6, 95% CI:1.6-4.1, p< 0.001 and HR: 2.3, 95% CI: 1.6-3.2, p<0.001, respectively); C-index for del17p and IgH-HRT plus 1q21+ and/or del1p32 were 0.73 and 0.70, respectively and outperformed the C-index of ISS, RISS and R2ISS that was 0.60, 0.60 and 0.61, respectively; IgH-HRT plus 1q21+ and/or del1p32 and del17p retained their significance across both transplant eligible and ineligible groups, regardless of modern therapies. In conclusion, we confirmed that, in RW, del17p and IgH-HRT combined with chr1 aberrations are the most significant prognostic factors for OS outperforming the predictive value of staging systems. In contrast, single IgH-HRT or isolated chr1 abnormalities did not show a negative impact on OS, suggesting that, the combination of primary and secondary genetic "hits" plays a critical role in MM outcomes. Notably, del17p, either alone or in concurrence with other high-risk abnormalities, retained its prognostic significance confirming its pivotal prognostic role in OS of MM patients.

P22

SIGNIFICANCE OF DIFFUSION-WEIGHTED WHOLE-BODY MRI (DW-MRI) IN STAGING AND RESPONSE ASSESSMENT IN MULTIPLE MYELOMA PATIENTS: A RETROSPECTIVE STUDY

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Diffusion-weighted whole-body MRI (DW-MRI) is increasingly used in the management of multiple myeloma (MM) patients in staging and in response evaluation. However, comparison data with other functional imaging methods and on the combination with other laboratory-based response assessment methods are lacking in the literature. The purpose of this retrospective single-centre study is to describe the use of DW-MRI in staging of MM and at evaluation of response after therapy in a real-world contest. We enrolled all MM patients with at least one DW-MRI for staging or response assessment in this study. A total of 24 patients with MM were staged with DW-MRI. DW-MRI showed bone lesions in 83% of cases; 12,5% of cases didn't have therapeutic criterion other than DW-MRI lesions. A comparison with PET-CT scan was possible in 13 cases. PET-CT scan was positive for disease localization in only 6 cases. In 3 cases, both PET and DW-MRI were negative, while 4 patients had a negative PET-CT scan despite the positivity of DW-MRI. 3 patients had extramedullary lesion: both methods identify these lesions. Considering the disease re-evalution setting after therapy, as per clinical practice, we performed DW-MRI only in patients with a serologic response to at least very good partial response (VGPR): a total of 24 patients was included in the analysis. For all cases a comparison with detection of minimal residual disease (MRD) in bone marrow samples by next-generation flow cytometry (NGF) was possible. Of these, 15 patients had negative MRD on bone marrow aspirate but 7 of them still showed positive DW-MRI for myeloma localizations; in the group of patients with positive MRD on bone marrow aspirate (9 patients), only 2 had a negative DW-MRI.

Conclusions. This small retrospective study confirms that DW-MRI is a valid option for staging myeloma patients and appears to have greater accuracy than PET-CT in identifying disease localizations. Recently, in

multiple myeloma patients MRD negativity on bone marrow aspirate has been approved by the FDA as an endpoint for therapy, and new clinical trials are exploring an MRD-based therapeutic approach. The discordance between DW-MRI and bone marrow analysis by NGF showed in our study, suggest that MRD assessment needs to be multiparametric and not just based on a single technique.

P23

DARATUMUMAB PLUS BORTEZOMIB, LENALIDOMIDE, AND DEXAMETHASONE IN TRANSPLANT-ELIGIBLE PATIENTS WITH MULTIPLE MYELOMA: A POOLED ANALYSIS OF PATIENTS AGED ≥65 YEARS FROM BOTH PERSEUS AND GRIFFIN STUDIES

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Introduction. In the PERSEUS and GRIFFIN studies, adding daratumumab (DARA) to bortezomib/lenalidomide/dexamethasone (D-VRd) induction/consolidation (ind/consol) and R (D-R) maintenance (maint) resulted in deep responses and improved PFS *vs* VRd/R in transplant-eligible (TE) patients (pts) with newly diagnosed multiple myeloma (NDMM). Pts ≥65 yrs of age constitute a group whose outcome is of particular interest. In PERSEUS among pts aged ≥65 yrs, PFS hazard ratios (HRs) were 0.97 (computerized algorithm [comp alg]) and 0.87 (Independent Committee Review [IRC]), potentially due to small numbers of events, cytogenetic risk imbalances (high risk: D-VRd 25.5%; VRd 19.5%), and censoring of pts for PFS after ≥2 missing consecutive disease evaluations (events censored: D-VRd, 0; VRd, 3). However, other randomized studies have shown the benefit of DARA in older pts, including GRIFFIN with D-VRd. To better understand the effect of DARA in combination with VRd in older pts with TE NDMM we performed a post hoc, pooled analysis of PERSEUS and GRIFFIN in pts aged ≥65 yrs.

Materials and Methods. In both studies, TE pts with NDMM aged 18-70 yrs were randomized 1:1 to D-VRd or VRd. Pts received 4 ind cycles (PERSEUS 28-day cycles/GRIFFIN 21-day cycles) and 2 post-ASCT consol cycles of VRd, then R maint. Pts randomized to D-VRd also received DARA during ind/consol and maint. In this post hoc analysis, PFS data was used from comp alg in GRIFFIN and IRC in PERSEUS, and HRs and 95% CIs were estimated using a Cox regression model stratified by ISS disease stage and cytogenetic risk, with no censoring of PFS events after ≥2 missing disease evaluations. Pooled analyses were conducted in pts aged ≥65 yrs.

Results. Pts aged ≥65 yrs represented 25.5% of pts in PERSEUS (D-VRd, 94/355; VRd, 87/354) and 27.1% of pts in GRIFFIN (D-VRd, 28/104; VRd, 28/103). Among pts aged ≥65 yrs, 9.0% in D-VRd and 13.0% in VRd had ISS stage III disease and 22.7% and 19.3% had high-risk cytogenetics. Median PFS was not reached in either treatment group or study. Stratified by ISS and cytogenetic risk and not censoring pts on basis of 2 consecutive missing disease assessments, PFS HRs favored D-VRd in PERSEUS (HR 0.61 [95% CI 0.32-1.14]), GRIFFIN (HR 0.33 [95% CI 0.06-1.76]), and the pooled dataset (HR 0.56 [95% CI 0.31-1.01]). Rates of MRD neg (10^{-5}) were also higher with D-VRd *vs* VRd in PERSEUS (67.0% *vs* 49.4%; OR 2.08 [95% CI 1.14-3.79]), GRIFFIN (64.3% *vs* 17.9%; OR 6.40 [95% CI 1.80-22.75]), and the pooled dataset (66.4% *vs* 41.7%; OR 2.75 [95% CI 1.61-4.71]). Data on sustained (≥12 mo) MRD and overall response (IMWG), including complete response or better, will be presented. No new safety concerns were identified in pts aged ≥65 yrs.

Conclusion. D-VRd ind/consol and D-R maint led to improved PFS and MRD neg *vs* VRd/R in TE NDMM pts aged ≥65 yrs. These data support D-VRd/D-R as a standard of care and highlight the benefit of DARA during ind/consol and maint for all TE pts with NDMM, regardless of age.

P24

REAL-LIFE ANALYSIS OF MINIMAL RESIDUAL DISEASE IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS ELIGIBLE FOR TRANSPLANT

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Background. Minimal Residual Disease (MRD) in multiple myeloma (MM) is currently considered a surrogate marker for progression-free survival (PFS) and has recently been proposed as a potential endpoint for clinical trials. MRD negativity has been associated with significantly improved survival outcomes, regardless of disease setting (newly diagnosed or relapsed/refractory), assessment methods, cytogenetic risk, timing, or MRD sensitivity thresholds.

Methods. We conducted a real-life, single-center retrospective analysis of 185 newly diagnosed MM patients (pts) eligible for ASCT, consecutively treated at AOU Careggi Hospital between February 2013 and December 2023. Patients received VTD (4-6 cycles) as induction treatment until December 2021, when the treatment was replaced with Dara-VTD according to CASSIOPEIA schedule. From November 2018 onward, all pts received lenalidomide maintenance after ASCT. MRD analysis on bone marrow samples was conducted using conventional 2nd generation 8-color flow cytometry, with a sensitivity of 10^{-5}. Bone marrow assessments were performed in all pts at two time points: after induction and pre-maintenance.

Results. The median age was 58 years (range 32-69), M/F: 97/88. High-risk (HiR) cytogenetic abnormalities (CA) [del(17p), t(4;14), t(14;16), and/or gain/amp(1q)] were observed in 61 pts (33%), while 15 (8%) had ≥2 HiR CA. A total of 141 pts (76%) received VTD induction regimen, whereas 44 (24%) were treated with Dara-VTD. Most pts (80%) underwent a single ASCT with melphalan 200 mg/m² conditioning, while 37 (20%) received tandem ASCT due to HiR CA. Among all cohort, 109 pts (59%) received lenalidomide maintenance. At the first time point-post-induction- the overall response rate was 99.4%; 82% of

pts achieved ≥VGPR and 27% a CR or better. MRD negativity (MRD-) was obtained in 75 pts (40.5%); the MRD- rate increased from 37% of the VTD group to 52% when daratumumab was added to the induction regimen. At the second time point pre-maintenance, 102 pts (55%) achieved CR or better, consistent with an increased MRD negativity rate of 70.8% in the entire population. The MRD- rate was 67% in the triplet regimen cohort and increased to 81% for those who received Dara-VTD. After a median follow-up of 62 months (range 9-128), the median PFS (mPFS) for the entire cohort was 66 months (mo), while the median overall survival was not reached (NR, 80% at 60 mo). Achieving at least a VGPR after induction (84 mo *vs* 39 mo, p<0.001) and obtaining ≥CR pre-maintenance (100 mo *vs* 48.4 mo, p=0.011) were significantly correlated with better PFS. According to MRD status, the achievement of MRD negativity was associated with increased mPFS, both when assessed post-induction (92.3 mo in MRD- pts *vs* 56.6 mo in MRD+, p=0,01) and pre-maintenance (99 mo MRD- *vs* 45 mo in MRD+, p<0,001). Based on cytogenetic risk, achieving MRD negativity in pts with HiR CA provided a significant PFS benefit, aligning their outcomes with those of standard-risk pts, (NR *vs* 57 mo in HiR CA pts with MRD+, p=0,04). In 45 pts (24%) MRD was also assessed at ≥12 mo after the start of maintenance. Among these, 37 showed a sustained MRD, while 9 pts lost their MRD-. The mPFS of pts who lost MRD- was significantly shorter and comparable to MRD+ pts (NR in MRD- *vs* 51 mo in MRD loss *vs* 45 in MRD+,p<0,001).

Conclusion. This real-life study confirms MRD's role as an early PFS marker, highlighting the value of sustained MRD and its positive impact on HiR CA pts.

P25

SECONDARY PRIMARY MALIGNANCIES IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH AUTOLOGOUS STEM-CELL TRANSPLANTATION WITH OR WITHOUT MAINTENANCE WITH IMMUNOMODULATORY AGENTS: A REAL-LIFE EXPERIENCE

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Background. Secondary primary malignancies (SPMs) in patients affected by multiple myeloma (MM) have recently been of interest due to survival improvement granted by new treatments. An oncogenic effect has been suspected particularly for alkylating agents and immunomodulatory drugs (iMIDs) administered in first-line therapy.

Aims. To analize the incidence and risk factors of SPMs in MM patients treated with doublets or triplets and single or double stem-cell transplantation (ASCT) followed or not by maintenance with immunomodulatory drugs in real-life clinical practice at Ospedale Santa Maria della Misericordia in Udine, Italy.

Methods. We retrospectively collected clinical and survival data of all newly diagnosed MM patients that underwent at least a single ASCT from January 2010 to December 2020, with a follow-up extended to August 2024. The following data were collected: patient features (sex, age, autoimmune disease and treatment, previous neoplasms and treatment), MM characteristics (monoclonal component, stage, cytogenetics, bone involvement) first-line treatment (induction scheme, mobilization, number of ASCTs, consolidation and maintenance) and they were compared in patients with and without SPM development.

Results.189 patients were treated, 101 males and 88 females, with a median age at diagnosis of 59 years (range 35-74). 33 patients were diagnosed with an high-risk FISH cytogenetics. 13 patients requested more than 1 mobilization cycle to reach an adequate CD34+ harvest, 136 underwent a single and 53 a double ASCT. 107 patients started an iMIDs maintenance (80 with lenalidomide, 27 with thalidomide). Of 189 patients, 33 developed a SPM (17%; the most common typologies were: 46% cutaneous non melanoma, 15% hematological and 9% breast cancers), with a median time of onset of 70 months (range 13-277) from the diagnosis of MM, 59 months (range 5-148) from the first ASCT and 64 months (range 24-118) after maintenance start. The cumulative incidence of SPMs was 6% at 5 years and 15% at 10 years from the diagnosis of MM. Overall survival (OS) of the groups without and with SPMs was respectively of 73% and 99% at 5 years, 59% and 95% at 10 years. There were no significative differences regarding patients characteristics at diagnosis. We found that the dose of cyclophosphamide (CP) in thalidomide-treated patients correlated with higher incidence of SPMs (p=0.02). Moreover, the duration of lenalidomide maintenance beyond two years in patients treated with iMID-induction before ASCT correlated with higher incidence of SPMs (p=0.02).

Conclusions. In this real-life study the development of invasive solid cancers as well as haematological neoplastic diseases after ASCT was rare and did not have a detrimental impact on the outcome. The high dose of CP of the mobilization and the duration of lenalidomide maintenance beyond 2 years in patients who had already received iMIDs during the induction may increase SPMs incidence.

P26

FEASIBILITY AND EFFECTIVENESS OF DEXAMETHASONE-SPARING AND DOSE-REDUCTION STRATEGIES IN DARATUMUMAB-BASED REGIMENS FOR FRAIL AND SARCOPENIC NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: A SINGLE CENTER, REAL LIFE EXPERIENCE

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Introduction. Daratumumab-containing regimens are the standard of care for older multiple myeloma (MM) patients (pts), but frail individuals face poorer outcome in part due to reduced treatment tolerance. Dose-reduction strategies, currently being tested in clinical trials, are recommended to balance efficacy and toxicity. Sarcopenia, a loss of skeletal muscle mass, is an objective frailty marker linked to worse outcome. It can be assessed using low-dose CT at the L3 vertebral level, complementing geriatric scores. We implemented steroid-sparing and dose-adjusted strategies for non-transplant eligible (NTE) newly diagnosed MM (NDMM) pts treated with daratumumab-based regimens and analyzed outcomes by IMWG frailty score and sarcopenia to evaluate the effectiveness of dose-adjusted strategies in frail pts.

Patients and Methods. We retrospectively analyzed 94 NTE NDMM pts (median age 77) diagnosed at our institution from April 2021 to January 2024 and treated with daratumumab-lenalidomide-dexamethasone (DRD) or daratumumab-bortezomib-melphalan-prednisone (DVMP). To reduce toxicity and improve tolerance, DRD included reduced dexamethasone doses (20 mg weekly during the first two cycles and subsequently maintained only as premedication for daratumumab at a dose of 10 mg in responsive pts). Dose reductions of the remaining drugs were applied according to EHA-ESMO guidelines per clinical judgment. Sarcopenia was assessed with skeletal muscle area measured at the L3 vertebral level to calculate the skeletal muscle index. Gender-specific cutoffs classified sarcopenia (Fearon K *et al.*, Lancet Oncol 2011). Pts were categorized by IMWG frailty score, merging fit and

intermediate-fit into "non-frail" due to the small number of fit pts. Response rates, progression-free survival (PFS), overall survival (OS), and safety were analyzed and compared by frailty and sarcopenia.

Results. Among 94 pts, 26% were ISS stage 3, and 38% had high-risk cytogenetics. By IMWG frailty score, 2% were fit, 40% intermediate-fit, and 58% frail. Sarcopenia was observed in 69 (73%) pts, more frequent in frail than non-frail pts (63% *vs* 36%, p=0.05). DRD was administered to 82% of pts, DVMP to 18%. Dose reduction was applied in 79% overall and 100% of frail pts. ORR was 83% (≥VGPR 65%, CR 17%, sCR 1%). After a median follow-up of 25 months, 2-year PFS was 78%, and 2-year OS was 89%. Two-year PFS was 80% and 70% in DRD and DVMP-treated pts, respectively, with no significant difference (p=0.67). No significant difference in PFS and OS was observed between non-frail and frail pts (2-year PFS 84% *vs* 73%, p=0.26; 2-year OS 94% *vs* 85%, p=0.16), or between sarcopenic and non-sarcopenic pts (2-year PFS 80% *vs* 72%, p=0.86; 2-year OS 90% *vs* 86%, p=0.83). Grade ≥3 AEs included neutropenia (49%), thrombocytopenia (14%), and pneumonia (10%). Temporary drug discontinuation due to AEs occurred in 81% of pts, with no significant differences between frail *vs* non-frail or sarcopenic *vs* non-sarcopenic pts. AE rates were comparable except for higher grade ≥3 thrombocytopenia in frail pts (12% *vs* 2%, p=0.038).

Conclusion. We confirmed the efficacy and safety of DRD and DVMP in a real-life NTE NDMM population. A dexamethasone-sparing regimen and upfront dose reduction strategies enhance treatment tolerability and achieve long-term outcomes even in frail and sarcopenic pts. These observations underline the importance of a tailored treatment strategy according to geriatric assessment.

P27

DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS AGED ≥80 YEARS: A MULTICENTER RETROSPECTIVE ANALYSIS OF EFFICACY AND TOLERABILITY

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Introduction. Daratumumab plus Lenalidomide and Dexamethasone (DRD) is the therapy of first choice in newly diagnosed Multiple Myeloma (MM) patients who are considered not eligible for autologous transplantation. A huge amount of data regarding this regimen has been published, both coming from prospective trials and real-life evaluations. Nevertheless, considering in particular the subgroup of patients aged ≥80 years, less is known due to the fact that these patients are underrepresented in registration trials. Due to the intrinsic frailness of this population, a balance between efficacy and toxicity needs to be carefully done and that is why there is often a concern in offering them such therapy. In this abstract, we present a retrospective analysis from a group of 49 NDMM patients aged ≥80 years from 6 different Institutions from Campania region in southern Italy treated with DRD.

Materials and Methods. In our study there were 33 males and 16 females, median age 82 years (range 80-90). In 7 patients age was ≥85 years. Myeloma subtype was IgG=34, IgA=12, micromolecular=3. Median Hemoglobin was 10.6 g/dl (range 8.5-12.8), median creatinine clearance 61 ml/min (range 9-92), median serum calcium 9.6 mg/dl (range 8.6-11.9). FISH is available only in 24 cases (standard=18, unfavourable=6). All patients had symptomatic disease, and in particular number of positive SLiM CRAB criteria were 1=14, 2=20, ≥3=15. Comorbidities were present in 41 patients (1=10, 2=15, ≥3=16), while 8 patients had no significant concomitant diseases apart from MM symptoms. All patients were given thrombosis prophylaxis, more in detail with Cardioaspirin (23), LMWH (14), and NAO (14). RESULTS. Initial dose of Lenalidomide in mg per day was 25=13, 15=16, 10=15, 7.5=1, 5=4. Initial week dose of Dexamethasone in mg was 40=7, 20=23, 10=14, 4=5. Overall response rate is 96% (44/46), while 3 patients has just started treatment. In particular, Complete Remission (CR) and Very Good Partial Remission (VGPR) rate are 33% and 39%, respectively. Median number of cycles to CR obtainment is 6. Significant toxicity included documented infections or FUO, present at least once in 35 patients (71%) and thrombosis in 5 cases (10%). Four patients needed transfusional support. Use of Epoietin and GCSF was necessary in 30 (61%) and 25 (51%) cases, respectively. Support with intravenous IgG was needed in 10 patients (20%). Reduction from initial dose of Lenalidomide and Dexamethasone was necessary in 19 (39%) and 21 (43%) patients, respectively. Lenalidomide was definitely stopped in 14 patients (29%). After a median follow up of 16 months (range 1-46), median number of cycles administered is 12 (1-49). At the moment of writing 8 patients (16%) have died, none directly from MM (4 deaths due to cardiovascular events, 1 to Covid infection, 3 related to surgery). Two patients relapsed and started second line treatment. Overall survival (OS) and Progression free survival (PFS) are projected at 16 months to the rate of 87% (77-98.4) and 81.9% (70.4-95.2), respectively. Median OS and PFS are both 44 months. Of note, Italian National Statistics Institute (ISTAT) report for year 2023 states that death probability of general population from Campania region aged 80-89 years is 346 per mille.

Conclusion. DRD is a feasible combination even in very elderly patients aged 80 years or more, and there is no indication to exclude them from this therapy aprioristically. Toxicity is acceptable, but there is a significant rate of patients who need reduction of drugs dose. Results are satisfying, but given the nature of the population a long term plateau of survival curves cannot be reached.

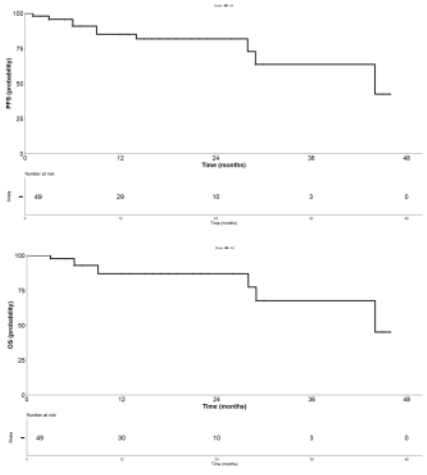

Figure 1.

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MRD-DRIVEN DISCONTINUATION OF LENALIDOMIDE MAINTENANCE POST TRANSPLANT IN PATIENTS WITH NEWLY-DIAGNOSED MULTIPLE MYELOMA: A PROSPECTIVE STUDY

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Background. The optimal duration of maintenance after transplant in multiple myeloma (MM) is yet to be defined.

Methods. In this prospective study, we included patients with newly diagnosed MM from January 1st, 2016 to December 31st, 2021, who underwent ASCT followed by lenalidomide maintenance. MRD status was assessed in patients who had achieved stringent complete remission (sCR) and then at 6, 12, 24, and 36 months after the initiation of lenalidomide maintenance. MRD samples were evaluated according to the EuroFlow protocol. Patients, who had at least 3 consecutive MRD negative results and had received at least 36 months of maintenance, underwent a PET/CT scan. If patients had achieved imaging MRD negativity, they discontinued lenalidomide maintenance and MRD was performed every 6 months thereafter. If a patient converted from MRD negative to positive or if the patient relapsed from sCR, lenalidomide maintenance was restarted.

Results. Overall, 194 patients received induction with proteasome inhibitor-based regimens (VCD, VRD or VTD) and underwent ASCT. During a median follow-up of 63.5 months (range 6-104 months) from diagnosis, 49 (25.2%) patients had disease progression and 20 (10.3%) patients died. During the follow-up period, 51 (26.3%) patients achieved sustained bone marrow MRD negativity and imaging MRD negativity at 3 years after maintenance initiation. Thus, they discontinued lenalidomide maintenance, according to study schedule. Their median age at MM diagnosis was 56 years (range 39-66). Twenty-seven (53%) patients were males, whereas 53% had IgG, 25.5% had IgA and 21.5% had light chain MM. The patient distribution per ISS was ISS 1 66.6%, ISS 2 19.6% and ISS 3 13,8%, whereas per R-ISS was RISS-1 60,8%, RISS-2 33.3% and RISS-3 5.9%. In this subgroup of the patients, 31% had at least 1 high risk cytogenetic risk factor (1q21 addition or amplification, t(4;14), t(14;16) and p53 loss). The median follow-up time from maintenance discontinuation for these patients was 32 months (range 4-52). Six months after discontinuation of lenalidomide maintenance, 48 out of 50 patients were found to be MRD negative. At 12 months post-lenalidomide discontinuation, 39 out of 41 patients continued to be MRD negative. At 18 months, 37 out of 38 evaluable patients remained MRD negative. At 24 months, 34 out of 36 patients were MRD negative and at 30 months 23 out of 25 evaluable patients were MRD negative. Three years after discontinuation 12 out of 14 patients were MRD negative, whereas at 42 months and 48 months post lenalidomide discontinuation all evaluable patients (N=8) and (N=4), respectively, were MRD negative. Overall, 11 patients restarted treatment with lenalidomide monotherapy after converting from MRD negative to MRD positive following the initial completion of maintenance, 4 of whom progressed and received second-line treatment. For these patients, the median follow-up from the re-initiation of lenalidomide is 7 months (0-35 months), and the median time to progression for those who progressed is 9.5 months (range 1-26 months). The median PFS is 74 months (CI:38-104). Only one patient who discontinued maintenance died for reasons not related to MM less than 6 months after lenalidomide discontinuation.

Conclusions. Sustained MRD negativity after ASCT and a completion of 3 years lenalidomide maintenance may guide the safe discontinuation of maintenance, although this has to be proven in prospective randomized clinical trials.

P29

PFS2 IN THE SETTING OF PATIENTS WITH FIRST-LINE MULTIPLE MYELOMA, NOT ELIGIBLE FOR TRANSPLANT PROCEDURE AND FRAIL, ACCORDING TO BORTEZOMIB, LENALIDOMIDE AND DEXAMETASONE (VRD) SCHEDULE: EFFICACY AND SAFETY

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The Multiple Myeloma is a disabling and unfortunate pathology with an unpredictable clinical-laboratorystic course. Despite advances in treatment options over the last decade, patients with multiple myeloma (MM) typically have recurrent relapses. Although there are several treatments available for relapsed patients, they have limited efficacy. In particular, patients who have had subsequent relapses or who are refractory to treatment have poor survival. PFS2, time from randomization to second disease progression or death, is recommended by the EMA as a surrogate for OS, and to assess effect of maintenance therapy or the impact of treatment on the efficacy of a subsequent line of therapy. This retrospective study investigates the real-world efficacy and safety of Bortezomib/Velcade, Lenalidomide/Revlimid and Dexametasone (VRD) as a therapy for not eligible multiple myeloma (NEMM) patients treated outside of controlled clinical trials according to marketing approval. A cohort of 54 NEMM patients from 1 italian center received at least for cycle of VRD as a first line of treatment between September 2016 and October 2020. To qualify as responsive, patients were required to achieve at least a partial remission (PR). Patients received Bortezomib s.c. at the recommended dosing schedule, 1.3 mg/m² (subcutaneous) on days 1, 4, 8, and 11 of each cycle; lenalidomide 25 mg/d on days 1 to 21; and dexamethasone 40 mg on days 1 to 4 and 9 to 12 at 4-week intervals for 6 cycles.

At the initiation of VRD therapy, 25 patients were males, with 18,5% classified as stage III according to the Revisioned International Staging System (R-ISS). Cytogenetic data from FISH analysis data were available for 47 patients (87%), with 69.7% showing favorable cytogenetic profiles, while 30.3% were categorized as high-risk due to aberrations such as t(4;14), t(14;16), gain(1q21), t(11;14), and del(17p). As of September 2020, all patients were evaluable for response. The median number of VRD cycles administered was 6 (range 4–6). ORR was 94% and was generally consistent across subgroups with PFS of 15 months. The safety profile of VRD was similar to that of Len-dex alone and a higher incidence of hematological adverse events (neutropenia and trombocitopenia), but of low grade (65% grade 1-3), although without an increase in infection or thrombosis rate. In conclusion, this comprehensive real-world study confirms the safety and efficacy of VRD as a valid first therapy for NEMM, in conditions of severe frailty and unfitness, more advantageous from a pharmaco-economic point of view and increases the therapeutic opportunities of the patient subsequently treated with antiCD38-based immunotherapy.

P30

RENAL RESPONSE IN MULTIPLE MYELOMA TRANSPLANT ELIGIBLE PATIENTS PRESENTING WITH RENAL FAILURE IN THE ERA OF D-VTD: A REAL LIFE EXPERIENCE

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Background. Renal impairment (RI) in multiple myeloma (MM) is defined by IMWG as creatinine >2mg/dL (177umol/L) or creatinine clearance (CrCl) <40ml/min due to MM. Criteria for renal response have been recently well defined by IMWG with the strong recommendation to use it in clinical practice. It has been demonstrated that RI in MM is related to poor outcome, indeed in the international staging system (ISS) the value of serum β2-microglobulin reflects in part the grade of RI. It is well established that bortezomib-based treatment improves renal overall remission, but specific data in the quadruplet therapy era in transplant eligible new diagnosed MM (TENDMM) patients are not available, primarily due to the exclusion of these patients from clinical trials. From Dec 2021 D-VTd has been approved by AIFA as the standard of care in TENDMM patients. Interestingly, in the registrative phase 3 Cassiopeia study, that compared D-VTd *vs* VTd, although none of the drugs are considered nephrotoxic, patients with creatinine clearance <40 ml/min were excluded. The aim of this study was to assess the renal response in patients with TENDMM, who underwent D-VTd treatment, in the real life setting.

Patients and Methods. From Jan 2022 to Aug 2024 a total of 401 patients were diagnosed with TENDMM. Among these patients, 24 presented with acute kidney injury (CrCl <40 ml/min) and were included in the study. Evaluation of renal failure and renal response was done according to IMWG criteria. Patients with concomitant AL amyloidosis were excluded.

Results. Median follow-up was 20.5 months. The median age was 63 years. At diagnosis, 7 patients (30%) presented with ECOG score >1, 10 (42%) had hypertension and none of them had type II diabetes. In 7 patients LDH value was above the upper normal limit and in almost all of them the value of β2-microglobulin was increased, with more than 70% of patients with a value above 5.4 mg/L. 15 patients (63%) had a Hb value <100 g/L, 16 (67%) had a serum free light chain ratio >100; 24-h urine protein was >2 g in 11 patients (46%), with a Bence Jones positivity in all cases. Median CrCl was 22.7 ml/min (range 5-39). All patients received the D-VTd regimen as first line of therapy. 6 of them received a lower dose of thalidomide and 2 did not receive it at all. No other dose adjustment was needed in the induction phase. Up to now, 18 patients (75%) underwent at least one autologous stem cell transplantation with a reduced dose of Melphalan (Mel140) in 3 patients. ORR was 96%, with sCR/CR in 63% of patients, VGPR in 21% and PR in 13%. Median time to best response was 3.35 months. 75% of patients achieved a complete renal response, while a partial response (PR) was observed in 12.5% and minor response (MR) in 12.5%. Median time to renal response was 83 days. Almost all patients underwent high dose steroids for 1-2 cycles. Finally, we observed that even if 20 patients achieved a good quality response (≥VGPR), not in all of them complete renal recovery was observed (3 MR, 2 PR).

Conclusions. Renal response is a crucial endpoint of treatment, especially in TENDMM. If relapse occurs, it is relevant to have recovered from RI in order to be considered for clinical trials or new approved therapies, as CAR-T, which in Italy is feasible only in patients with CrCL >45 ml/min. Finally, in the near future D-VRd will become the standard of care for TENDMM but, due to renal toxicity of lenalidomide, D-VTd might still remain a valid option.

P31

SOLUBLE SERUM IL8 (SIL8) LEVELS IN MULTIPLE MYELOMA PATIENTS

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BSoluble IL8 (sIL8), also known as CXCL8, is a pro-inflammatory CXC chemokine generated by both normal and malignant cells. Overexpression of IL-8 has been reported in breast cancer cells, and elevated serum IL-8 concentrations are associated with osteolytic lesions and bone metastases in these individuals. Limited data on sIL8 in myeloma patients have revealed elevated mean serum values, showing that this molecule may contribute to disease progression.

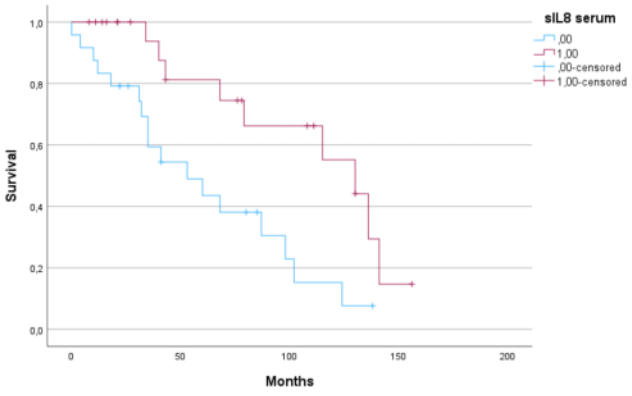

Figure 1. Overall survival of symptomatic MM patients based on sIL8 serum levels.

Aim. To evaluate sIL8 possible prognostic contribution in newly diagnosed MM patients.

Patients and Methods. 101 patients MM patients were included in the study out of which fifty newly diagnosed patients with symptomatic MM and 51 smoldering MM patients. Medical records were reviewed and clinical characteristics were collected after patient's informed consent. Serum sIL8 levels were determined in patients' frozen sera by ELISA (Duoset R&Dsystem) according to the manufacturer's instructions. Sera of 24 healthy individuals were also measured. Median age of patients was 67 years (31-87) with 50% women. Immunoglobulin type was IgG in 69% patients, IgA in 12%, Light-Chain in 16% and other types in 3 %. ISS 1, 2 and 3 were 22 %, 25 % and 53 % patients, respectively. For the overall survival study, sIL8 serum levels were assessed at the time of diagnosis in symptomatic MM patients. Median value was used as a cut off point for the survival analysis. High sIL8 levels were defined as above median value. Median Overall Survival was 41 months (range: 1-156). Statistical analysis was performed using SPSS software v.29.

Results. sIL8 mean serum levels of symptomatic MM patients were significantly higher 142 pg/ml (range; 0-1557) than the levels of sIL8 in healthy individuals 91 pg/ml (range; 0-1795,8) (p=0.001). Mean sIL8 levels in SMM patients were similar to those in symptomatic MM [143 pg/ml (0-579,55)]. Separate analysis was performed to SMM and symptomatic MM patients. Overall survival was improved in patients with serum values of sIL8 above median (p=0.006). (Figure 1) sIL8 serum levels did not appear to impact TTT (p=0.252).

Conclusion. sIL8 serum levels in newly diagnosed symptomatic MM patients were strongly linked with OS. These first findings showed the prognostic potential of sIL8. Further research and correlation analysis with disease characteristics is indeed needed.

P32

SOLUBLE SERUM FAS LIGAND (SFASL) LEVELS IN MULTIPLE MYELOMA PATIENTS

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Background. FasL is a transmembrane protein that interacts with the Fas receptor (also known as CD95). It can act directly on nearby cells or be secreted in the extracellular environment as a soluble form after being cleaved by matrix metaloproteinases. The binding of FasL to FasR causes the recruitment of cytoplasmic signaling proteins, which leads to apoptosis. Fas is primarily a tumor suppressor, but it may also have growth-promoting activity because malignant cells rely on constitutive Fas activity, which is boosted by their own Fas-L. FasL has been associated with Interleukin 6 expression in myeloma. There are conflicting results about FasL's prognostic relevance in myeloma, as well as very limited data on its value in SMM progression.

Aim. To determine the correlation of sFasL levels and disease activity in Multiple Myeloma patients

Patients and methods. 101 patients MM patients were included in the study out of which fifty newly diagnosed patients with symptomatic MM. Median age of symptomatic MM patients was 67 years (31-87) with 50% women. Immunoglobulin type was IgG in 69% patients, IgA in 12%, Light-Chain in 16% and other types in 3 %. ISS 1, 2 and 3 were 22 %, 25 % and 53 % respectively. We also focused on 51 individuals with smoldering multiple myeloma who were included in our research. Median age of asymptomatic MM patients was 68 years (34-85) with 65% men. Immunoglobulin type was IgG in 83% patients, IgA in 12%, Light-Chain in 5%. ISS 1, 2 and 3 were 66 %, 17 % and 17 %, respectively. Notably, of asymptomatic MM patients, seven were advanced from SMM to MM. sFasL serum levels were measured at diagnosis of SMM. Medical records were reviewed and clinical characteristics were collected after patient's informed consent. sFas Ligand serum levels were determined in patients' frozen sera by ELISA (Duoset R&Dsystem) according to the manufacturer's instructions. Sera of 24 healthy individuals and 50 newly diagnosed symptomatic MM, were also measured. Median value was used as a cut off point for the survival analysis. High sFas Ligand levels were defined as above median value. Median Overall Survival (OS) was 105 months (range: 9-266) and median Time to Treatment (TTT) was 54 months (1-266). Statistical analysis was performed using SPSS software v.29.

Results. Median serum sFasL in smoldering MM patients were 33,45 pg/ml (0-1901), in healthy individuals 54,74 (1,88-1889) and significantly lower in symptomatic MM patients 17,23 pg/ml (0-1890) compared to the above groups. (p=0.001). In the survival study, lower levels of sFasL were associated with a shorter TTT (p=0.037). (Figure 1) Separate analysis in symptomatic MM patients did not show impact of sFasL in overall survival (p=0.435).

Conclusion. sFasL serum levels in SMM patients were correlated with TTT. These preliminary results suggest a correlation with TTT. The finding is very interesting indeed and should be validated in larger patients' series.

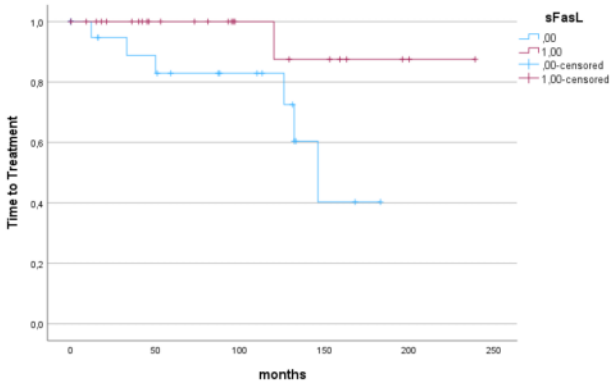

Figure 1. TTT of SMM patients based on sFasL.

P33

LOW VACCINATION RATES AGAINST SEASONAL INFLUENZA AND PNEUMONIA IN MGUS AND MM PATIENTS AFTER COVID-19 PANDEMICS: A REAL-LIFE SURVEY

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Background. Infection prevention is part of supportive care in Multiple Myeloma patients. Despite in Italy all recommended vaccines are available for free through structured vaccination campaigns, and patients can receive vaccines during their routine visits for day hospital therapy without requiring additional visits to primary care providers, many patients continue to refuse vaccination. To understand the barriers limiting vaccination success in MM population we designed a retrospective study to compare the adherence to vaccination campaign during and after COVID-19 pandemics, namely 2019 and 2024.

Methods. In this single center survey we included all consecutive MGUS/MM patients referring to our center between September and October 2019 (N=202) compared to those referred between October and December 2024 (N=410). Seasonal vaccination against flu (FV) and S. pneumoniae (PV) was recommended to all patients, independently from age, disease status (including both newly diagnosed, relapsed and refractory patients) or treatment (continuous versus fixed therapy, MGUS *vs* active MM), associated to VRS, H. Zoster and COVID-19 in the 2024 cohort. All vaccinations were given by general practitioner according to Italian law for prevention activities. Patients were monitored for any-grade infection rate and hospitalization rate for infections.

Results. In the 2019 cohort, the adherence to FV and pneumococcus vaccination were respectively 72 and 48%; the most frequent infections were bacterial bronchitis, pneumonia and genito-urinary infections due to K.pneumoniae (N=9%) and E.coli (N=6%). The rates of hospitalization for infections at 12 months in were higher in newly diagnosed patients compared to those in remission and continuous treatment (18% *vs* 4%, p<0.001). In the 2024 cohort, including 330 MGUS patients, 66 MGUS patients who progressed to MM, and 14 newly-diagnosed MM

patients, vaccination coverage was consistently low across all groups. Pneumococcal, meningococcal, and herpes zoster vaccines showed limited uptake (lower than 10%), while flu vaccination reached only 29%.

Conclusions. Vaccination rates among MM and MGUS patients remain insufficient, underscoring the need for targeted educational campaigns and stronger public health strategies to reduce infection-related morbidity and mortality.

P34

LONG SURVIVAL WITH DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE IN NTE-NDMM PATIENTS. A SURVEY OF TWO HEMATOLOGICAL CENTERS

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The approval of novel agents in the treatment of multiple myeloma, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) and the introduction of daratumumab in the front-line setting has dramatically improved patient survival outcomes. The combination of daratumumab, lenalidomide and dexamethasone (D-Rd) was approved by the EMA for the first-line treatment, based on the results of MAIA trial. In this survey we collected data from 96 consecutive non-transplant eligible newly diagnosed multiple myeloma (NTE-NDMM) patients, aged ≥70 or <70 with comorbidities that contraindicated high dose chemotherapy for bone marrow transplantation, treated in two hematological centers of Catania city with D-Rd combination. We evaluated all patients who received at least one administration of each drug. Daratumumab was given subcutaneously in all patients.

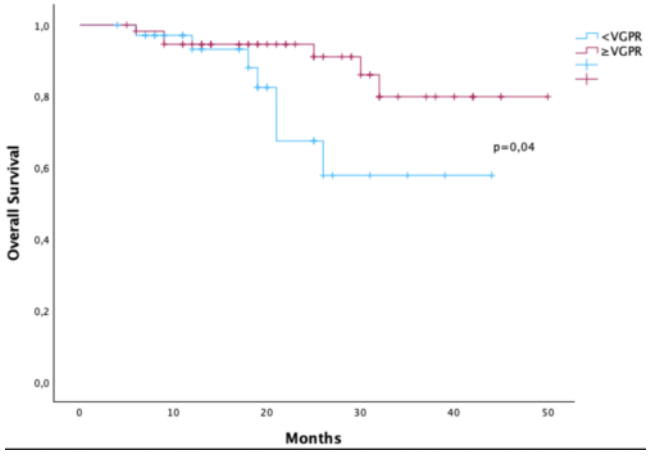

Figure 1.

The median age was 73 years, with 32 patients aged ≥75 and 23 ≤70. Although number of patients (75 pts, 78%) were deemed frail according to the Fancon frailty score, that includes ECOG and Charlson scales, treament was well tolerated. After a median follow-up of 20 months, the mPFS and mOS were not reached. There was no significant difference in PFS between patients <75 *vs* ≥75 years old (p=0,19). Most patients (47%) were ISS III stage, but there was no difference in PFS based on ISS staging system (p=0,07). The overall response rate (ORR), defined as patients who obtained at least a very good partial response (VGPR) was 59,4%. Taking in account patients who reached ≥VGPR *vs* <VGPR there was a significant difference both for PFS (mPFS not reached *vs* 19 months, respectively, p<0,001) and OS (mOS both NR, but with a significant difference and an expected 24-month OS of 80% *vs* 58%, respectively, p=0,04). 55 patients (57%) reduced the initial dose of lenalidomide, often due to gastrointestinal toxicity (18 patients, 18,8%). Dexamethasone was given orally at a dosage of 20 mg weekly and reduced in case of related toxicity or intolerance. 18 patients had disease progression: all received a II line of treatment. There were 15 deaths of which 8 due to relapse/progression of the disease during a subsequent line of therapy and 7 during D-Rd due to worsening of clinical conditions without disease progression. The most relevant grade 3-4 adverse events (AE) were anaemia (13 patients, 13,5%), neutropenia (17 patients, 17,7%) and infections (14 patients, 14,6%). This study confirms the efficacy of the D-Rd in first line for Multiple Myeloma even in frail patients, further demonstrating that the achievement of at least a VGPR is a very good predictor for response and long-term survival.

P35

ADDITION OF DARATUMUMAB TO FIRST-LINE THERAPY OF NEWLY DIAGNOSED MULTIPLE MYELOMA IN PATIENTS ELIGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION: A SINGLE-CENTER EXPERIENCE

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The results of the CASSIOPEIA trial have led to the approval of Daratumumab (Dara) in addition to Bortezomib, Thalidomide and Dexamethasone (VTD) as the standard of care induction and consolidation treatment in transplant-eligible newly diagnosed multiple myeloma (TENDMM) patients (pts) in Italy. We, therefore, retrospectively analyzed the data of 66 TENDMM pts who were consecutively treated with Dara-VTD in ASST Papa Giovanni XXIII, Bergamo, Italy, between January 2022 and December 2023. The aims were to describe their treatment response, toxicity, progression-free survival (PFS), overall survival (OS) and to compare these data with those of a group of 76 pts consecutively treated with VTD between January 2019 and December 2021. The clinical and disease features were similar in the Dara-VTD and VTD groups, the only exception being a higher rate of extramedullary disease in the Dara-VTD group (N=6 *vs* N=1; p=.0497). The rate of optimal response (defined as ≥ Very Good Partial Response) in the Dara-VTD group was not significantly higher than in the VTD group (77.3% and 76.3% respectively). Dara had a negative impact on the collection of hematopoietic stem cells (HSC): we reported a higher incidence of poor mobilizers in the Dara-VTD group (43.5% *vs* 9.2%, p<.0001), causing an increased use of Plerixafor (51.6% *vs* 7.7%, p <.0001) and a lower number of harvested HSC (median $4.2x10^6$/kg *vs* $6.5x10^6$/kg, p < .0001); nevertheless, the number of pts who underwent autologous stem cell transplantation (ASCT) was similar in the Dara-VTD and VTD groups (89.4% and 80.3% respectively; p=.13); although a second ASCT was planned for 15 pts treated with Dara-VTD, it was performed in only 3 pts, mainly because of insufficient HSC harvest. Even though the overall incidence of grade 3 or 4 adverse events was similar in the two groups, the addition of Dara to the induction regimen was associated with a higher incidence of grade ≥ 3 neutropenia (21.2% *vs* 6.6%, p=.0106) and grade ≥ 3 hepatic toxicity (16.7% *vs* 3.9%). Furthermore, Dara-VTD pts developed more

often hypogammaglobulinemia (defined as gammaglobulins < 400 mg/dL), requiring IgG supplementation (15.2% *vs* 5.3%, p=.049). After a median follow-up of 2.1 years in the Dara-VTD and 4.1 years in the VTD group, the 2-years PFS was higher in the Dara-VTD group (78% *vs* 64%), even if not significantly (p=.07); the 2-years OS was 87% in both groups. Twenty-nine of our 66 Dara-VTD pts (43.9%) had clinical or disease features which would have made them ineligible for the CASSIOPEIA trial (age >65 years, Eastern Cooperative Oncology Group performance status >2, hemoglobin <7.5 g/dL, serum creatinine ≥2 mg/dL and/or corrected serum calcium >14 mg/dL): these pts had a rate of optimal responses similar to that of the other Dara-VTD pts (76.9% and 78.4% respectively). In conclusion, our results confirmed the efficacy and manageable toxicity of the Dara-VTD combination, even in pts with features of increased frailty or aggressive disease. Our experience confirms a higher incidence of poor mobilizers and a lower number of harvested HSC in pts treated with Dara-VTD; only a minority of high-risk pts could receive a double ASCT, whose role in a modern first-line therapy based on quadruplets should be further investigated.

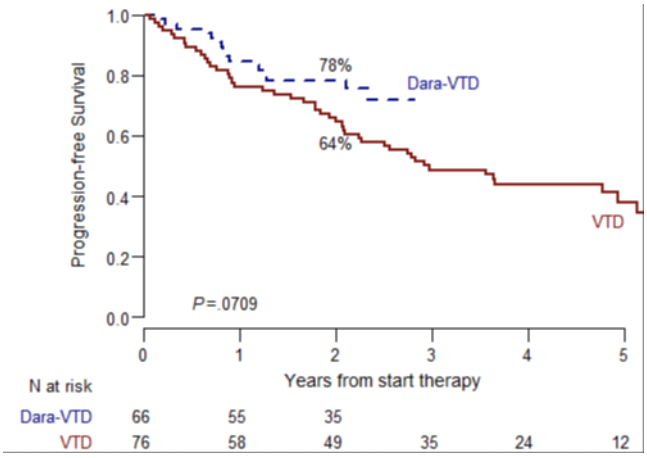

Figure 1.

P36

REAL-LIFE EXPERIENCE WITH FIRST-LINE TREATMENT WITH DARATUMUMAB-BASED THERAPY IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA INELIGIBLE FOR AUTOLOGOUS STEM-CELL TRANSPLANTATION

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Daratumumab, lenalidomide, and dexamethasone (DRd) and daratumumab, bortezomib, lenalidomide, and dexamethasone (D-VMp) are the preferred treatment regimens for patients (pts) with transplant-ineligible (TIE) newly diagnosed multiple myeloma (NDMM), due to the results of MAIA and ALCYONE trial. However, there are no randomized head-to-head studies of DRd versus D-VMp and data regarding real-life outcomes with these regimens are limited. The aim of our study is to evaluate the real-life effectiveness and safety of DRd and D-VMp. We retrospectively analyzed data of 51 NDMM pts managed at the Hematology Center of the Sapienza University of Rome from 2021 to 2024 treated with DRD and D-VMp. The most of pts were treated with DRd (71%) and 46% of pts were treated with D-VMp. Median age of the entire cohort was 75 years (57-83), 33 pts (65%) were male. A history of MGUS was present in 22 pts; 24/49 pts (49%) were ISS III. The majority of pts showed IgG-κ (31%) and IgG-λ (33%) isotype. Eighty percent (80%) of pts were considered fit, 18% unfit and 4% frail, according to the IMWG frailty score. About half of pts (47%) had a Charlson Comorbidity Index of 3, and the most common reported comorbidity was cardiac (61%). Forty-one pts (80%) had an ECOG performance status of 0 at diagnosis; 44 (86%) pts had bone lesions, 27 (53%) pts had anemia, 11 (22%) pts had acute renal insufficiency (IRA). Four pts (57%) in the D-VMp required in-hospital dialysis. The characteristics of the pts at diagnosis in the two groups of treatment were well balanced (Table 1), except for a significantly higher rate of anemia (p=0.02) and IRA (p=0.004) in the D-VMp group compared to DRd group. At a median follow-up of 14.3 months, the median number of cycles received was 10 (IQR 1-41).

Table 1. Baseline clinical characteristics of the entire cohort and for each group of treatment. MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; ISS: International Staging System; ECOG PS: ECOG Performance Status Scale.

		Type of therapy		
Baseline clinical characteristics	**Overall, N = 51**	**DRD, N = 38**	**DVMP, N = 13**	**p-value[1]**
Male, n (%)	33 (65%)	27 (71%)	6 (46%)	0.20
Age at diagnosis, median (range)	75.0 (57.0, 83.0)	74.0 (57.0, 83.0)	76.0 (71.0, 81.0)	0.16
Previously MGUS, n (%)	22 (43%)	18 (47%)	4 (31%)	0.47
Previously SMM, n (%)	6 (12%)	6 (16%)	0 (0%)	0.30
ISS, n (%)				0.20
1	9 (18%)	5 (14%)	4 (33%)	
2	16 (33%)	14 (38%)	2 (17%)	
3	24 (49%)	18 (49%)	6 (50%)	
Not available	2	1	1	
Isotype monoclonal component, n (%)				0.22
IgG-k	16 (31%)	12 (32%)	4 (31%)	
IgG-k; IgG-λ	2 (3.9%)	2 (5.3%)	0 (0%)	
IgA-k	6 (12%)	5 (13%)	1 (7.7%)	
IgA-λ	3 (5.9%)	3 (7.9%)	0 (0%)	
IgG-λ	17 (33%)	13 (34%)	4 (31%)	
FLC-k	4 (7.8%)	2 (5.3%)	2 (15%)	
FLC-λ	2 (3.9%)	0 (0%)	2 (15%)	
IgM-λ	1 (2.0%)	1 (2.6%)	0 (0%)	
Anemia, n (%)	27 (53%)	16 (42%)	11 (85%)	**0.020**
Renal acute injury, n (%)	11 (22%)	4 (11%)	7 (54%)	**0.004**
Bone lesions, n (%)	44 (86%)	33 (87%)	11 (85%)	>0.99
Hypercalcemia, n (%)	5 (9.8%)	2 (5.3%)	3 (23%)	0.19
ECOG PS, n (%)				0.22
0	41 (80%)	31 (82%)	10 (77%)	
1	9 (18%)	7 (18%)	2 (15%)	
2	1 (2.0%)	0 (0%)	1 (7.7%)	
Comorbidities, n (%)	48 (94%)	35 (92%)	13 (100%)	0.72
Cardiovascular comorbidities, n (%)	31 (61%)	24 (63%)	7 (54%)	0.79
Metabolic comorbidities, n (%)	17 (33%)	12 (32%)	5 (38%)	0.91
Previous other tumors, n (%)	13 (25%)	7 (18%)	6 (46%)	0.11
Gastrointestinal comorbidities, n (%)	4 (7.8%)	4 (11%)	0 (0%)	0.53
Respiratory comorbidities, n (%)	3 (5.9%)	3 (7.9%)	0 (0%)	0.72
Infectious comorbidities, n (%)	3 (5.9%)	2 (5.3%)	1 (7.7%)	>0.99
Renal comorbidities, n (%)	3 (5.9%)	2 (5.3%)	1 (7.7%)	>0.99
Endocrinological comorbidites, n (%)	10 (20%)	5 (13%)	5 (38%)	0.11

Specifically, the median number of DRd cycles was 11 (IQR 1,41) and the median number of D-VMp cycles was 7 (IQR 2-18). Considering the entire cohort, the best response was reached after a median of 72 days (IQR 25-910), without significantly difference in the two group of treatment (p=0.07). The ORR of the entire cohort was 98%, with 58% of pts reached ≥VGPR. No statistically difference in terms of ORR was reported according to the two therapy regimens (95% in the DRd group versus 92% in the D-VMp group, p=0.19). The median PFS of the entire cohort was 77% at 12 months and 73% at 24 months, respectively. No difference was reported according to the two group of treatment (p=0.9). Despite the limit of the short follow-up of our study, the

median OS for the entire cohort was 81% at 12 and 24 months. Considering the safety profile, 55% of pts in DRd group started lenalidomide at the maximum dosage of 25 mg; neutropenia (90%) and infections (74%) were the main treatment-related adverse events (AV) reported. Furthermore, 66% of pts had to reduce lenalidomide dosage. In the D-VMp group, 92% of pts started bortezomib at standard dose and 69% of pts had to postpone alkeran due to IRA. Infections were the most important treatment-related AV (46%) reported in the D-VMp group. Despite the limit of a retrospective study and a limited cohort, our analysis demonstrated that, in the real-life setting of TIE-NDMM pts, the D-based therapies showed clinical and rapid efficacy, with no new reported concerns regarding safety.

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FIRST-LINE DARATUMUMAB-BASED REGIMENS WITH OR WITHOUT AUTOLOGOUS STEM-CELL TRANSPLANTATION IN MULTIPLE MYELOMA PATIENTS AGED 65-70: A REAL-WORLD STUDY ON EFFICACY AND SAFETY

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Introduction. Daratumumab is approved for first line treatment in patients with Multiple Myeloma (MM) both eligible or ineligible for ASCT, with three different combinations available, namely DVTD (plus Bortezomib + Thalidomide + Dexamethasone) which is part of a program that includes also autologous stem cell transplantation (ASCT), and DRD (plus Lenalidomide + Dexamethasone) and DVMP (plus Bortezomib + Melphalan + Prednisone) which are given continuously until progression. For patients aged 65 to 70 years there are still no standardized criteria to select the appropriate regimen. To compare results and toxicity, we retrospectively analyzed data from a cohort of 91 consecutive newly diagnosed MM patients from 9 Institutions, aged 65-70 years, and treated outside clinical trials with different Dara-based combinations according to clinical characteristics and to physician's choice.

Materials and Methods. In our study there were 54 males and 37 females, median age 67 years (range 65-70) distributed as follows: 55 DVTD (median 66, range 65-70), 31 DRD (median 69, range 65-70), and 5 DVMP (median 69, range 67-70). All patients had symptomatic MM requiring therapy. Clinical and disease characteristics of the patients are detailed in the Table 1. Overall response rate of the whole population was 93% (85 out of 91). More in detail, rate of complete + very good partial remission (CR + VGPR) was 81% for DVTD patients and 69% for DRD/DVMP patients. One DVTD and 2 DRD patients were refractory and proceeded to second line treatment, while there were 3 early deaths in DRD group due to cardiovascular events. Toxicity and supportive therapy were recorded and main results are reported here. Documented infections or FUO were present in 10/55 (18%) and 17/36 (47%) in DVTD and DRD/DVMP group, respectively. There were 5 cases of thrombosis (all in DRD patients), and 12 cases of grade ≥2 peripheral neuropathy (all in DVTD patients). Use of Epoietin was necessary in 21/55 (38%) and 20/36 (56%) in DVTD and DRD/DVMP group, respectively, and red blood cell transfusions were needed in 8 patients (1 DVTD and 7 DRD/DVMP). Finally, during therapy and/or follow up use of intravenous IgG was needed in 11/91 patients (12%): 5 DVTD and 6 DRD/DVMP. Of note, 9/43 DVTD patients evaluable for mobilization (21%) did not proceed to ASCT for refusal (2), subsequent frailness (4), no mobilization (1), and early relapse after mobilization (2). After a median follow up of 16 months (range 1-45), Progression Free Survival (PFS) and Overall Survival (OS) are not reached in the whole population and in both subgroups (p=0.78 and 0.051, respectively). Estimated PFS at 16 months are 90% (whole population), 88.5% (DVTD) and 92.2% (DRD/DVMP). Relapse was observed in 7 patients in DVTD group, and 7 in DRD/DVMP group (13% and 22% of responding patients, respectively). At the moment of writing, 14 patients have died (in 4 case for MM), four being from DVTD and 8 from DRD/DVMP group. DISCUSSION. In our cohort, younger or older age and frailness are the major factors determining the choice of using ASCT as part of the first line therapeutic program in 65-70 years old MM patients (see table for p values). Significant toxicity is more present in the DRD/DVMP, but this may be primarily affected by the unfavorable clinical characteristics of patients more than by the type of regimen. A significant rate of DVTD patients actually did not undergo ASCT, and this is not observed in younger patients. OS and particularly PFS do not show significant differences in the two groups. Although these results need to be confirmed with longer follow up, we can speculate that less fit patients do not need to be included in a transplant program to achieve and maintain remission.

Table 1. Patients characteristics.

	Total	DVTD	DRD	DVMP	p value (DVTD vs DRD/DVMP)
Number of patients	91	55	31	5	
Sex: M/F	54/37	34/21	15/16	5/0	0.55
Median age at diagnosis, years (range)	67 (65-70)	66 (65-70)	69 (65-70)	69 (67-70)	0.00016
Myeloma subtype					
IgG	62	36	23	3	0.49
IgA	19	12	5	2	0.78
Micromolecular	9	6	6	-	0.42
Non secretory	1	1	-	-	0.41
Laboratory					
Median WBC (x10E3/ul) (range)	5,7 (2.2-15.2)	5.5 (2.8-15.2)	6.6 (2.4-12.6)	7.0 (4.2-9.9)	0.17
Median Hb (g/dl)(range)	11.3 (7.4-13.5)	11.8 (7.4-15.6)	10.6 (7.6-13.5)	10.1 (9-12.6)	0.002
Median Plt (x10E3/ul) (range)	210 (89-426)	212 (103-351)	209 (89-426)	167 (141-287)	0.98
Median Creatinine Clearance (ml/min)(range)	78 (5.7-136)	80 (6-136)	63.9 (21-135)	65.7 (5.7-96)	0.34
Median LDH (IU/L)(range)	174 (78-620)	167 (78-620)	190 (98-517)	169 (98-379)	0.22
Median serum Calcium (mg/dl)(range)	9.8 (7.2-14.5)	9.4 (7.2-14.5)	9.2 (8.3-13.3)	10.3 (8.6-10.5)	0.78
FISH					
Standard	46	27	14	5	0.73
Unfavourable	18	11	7	-	0.94
Not done/Failed	27	17	10	-	0.75
R-ISS:					
I	16	14	2	-	0.015
II	34	20	12	2	0.81
III	13	4	7	2	0.02
Not available	28	17	10	1	0.97
Fitness					
Fit	50	43	7	-	<0.0001
Intermediate	26	8	15	3	0.0003
Frail	15	4	9	2	0.0034
Comorbidity					
0	17	15	2	-	0.009
1	21	14	5	2	0.50
2	21	16	5	-	0.09
≥3	32	10	19	3	<0.0001
Slim-CRAB Criteria					
1	36	28	7	1	0.006
2	42	23	16	3	0.30
≥3	13	4	8	1	0.02

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NEGATIVE IMPACT OF HIGH SERUM CREATININE AND LACTATE DEHYDROGENASE AT DIAGNOSIS CAN BE OVERCOME BY AUTOLOGOUS STEM CELL TRANSPLANTATION

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Background. Multiple myeloma (MM) is a hematological neoplasm that develops due to the malignant proliferation of plasma cells. High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is part of the standard treatment for eligible patients. Elevated creatinine levels along with elevated lactate dehydrogenase (LDH) levels are important parameters in the treatment and follow-up processes of MM. This study is designed to evaluate the early outcomes after ASCT in MM patients with elevated creatinine and LDH levels at the time of diagnosis.

Methods. Between January 2012 and December 2023, patients who underwent ASCT with a diagnosis of MM were evaluated retrospectively at the Hematology Department of Ankara University Medical School. Patients with a creatinine level of ≥2 mg/dL at the time of diagnosis and those with a creatinine level of <2 mg/dL were identified, and the outcomes of the two groups were compared. Additionally, patients with an LDH level at or above the upper limit of normal at diagnosis and those with normal LDH levels were identified, and the outcomes of these two groups were also compared.

Results. Since elevated LDH is one of the Revised International Staging System (R-ISS) staging criteria, there were no patients in R-ISS stage 1 in the group with elevated LDH. The high levels of beta-2 microglobulin observed in all patients with creatinine ≥2 mg/dL also resulted in no patients in R-ISS stage 1 in this group. There was no significant difference in the response rates between the groups at the 100-day mark after ASCT, which was the primary endpoint. The median overall survival for patients with elevated LDH was found to be 71 months, while for patients with normal LDH, it was 130 months, and this difference was statistically significant (p=0.008).

Conclusion. The results of our study indicate that elevated creatinine and LDH levels in newly diagnosed MM patients do not have a significant impact on ASCT outcomes. Given that ASCT remains the standard treatment for eligible patients, relying solely on these parameters when making treatment decisions may be problematic. The shorter median overall survival for patients with elevated LDH compared to those without suggests that different treatment modalities may be needed for these patients in the post-ASCT period. However, since these treatment options were not evaluated in this study, further research is necessary to draw definitive conclusions.

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CIRCULATING TUMOR CELLS - NEW PROGNOSTIC BIOMARKER IN MULTIPLE MYELOMA

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Background. Circulating tumor cells (CTC) as non-invasive biomarker provides good insight into tumor burden and disease dynamics. Determination of the CTC cut-off with prognostic value could enhance risk stratification and guided treatment approach in multiple myeloma (MM). The aim of this study was to assess the prognostic significance of CTC levels in newly diagnosed MM patients and their association with clinical and biological parameters.

Patients and Method. The CTC presence was analyzed in 63 newly diagnosed patients during period March 2023 - November 2024. (male/female, 26/37pts, median age 68yrs, range 32-85yrs). According to the M protein and MM clinical stage (CS, Durie&Salmon) respectively, the distribution was as follows: IgG 40pts (63.5%), IgA 14pts (22.2%), BJ 9pts (14.3%), and CS I was present in 8pts (12.7%), II 5pts (7.9%) III in 50pts (79.4%). Renal impairment was noticed in 17pts (27%). Median extent of the monoclonal plasma cell (PC) bone marrow infiltration was 50%, range 10-90%. According to the R-ISS: R-ISS1 was found in 18 pts (28.6%), R-ISS2 in 38 (60.3%), R-ISS3 in 7 (11.1%). The distribution according to the R2-ISS was: R2-ISS 1 15pts (23.8%), R2-ISS 2 16pts (25.4%), R2-ISS 3 28pts (44.4%), R2-ISS 4 1pt (1.6%). Treatment with bortezomib based triplets were applied in 49 pts (77.8%), and antiCD38 monoclonal antibodies in 8pts (12.7%). More than half of the group (40pts, 63%), represented transplant ineligible patients.

Results. The median CTC concentration was 0.3CTC/µl (range 0-389.3 CTC/µl), and median CTC percentage was 0.004% (range 0-18%). Treatment response (≥PR) was achieved in 42pts (66.7%). The median progression-free survival (PFS) was 20.2 months (95% CI: 18.5-21.9m), and the estimated mean overall survival (OS) was 18.06m (95% CI: 15.1-20.9m). The CTC count correlated with clinical stage (CTC *vs* CS, rho=0.389; p=0.002), and PC bone marrow infiltration (CTC *vs* PC, rho=0.356; p=0.004). Furthermore, R-ISS (rho=0.389; p=0.002) and R2-ISS (rho=0.366; p=0.004) scores were associated with increased CTC levels, as well.

Conclusion. The correlation of CTC concentrations with advanced disease stage, higher bone marrow infiltration, and worse prognostic scores (R-ISS and R2-ISS) indicates aggressive character of disease. These findings underlines the utility of CTC as an important prognostic biomarker in MM, especially in disease stratification and management.

Relapsed/refractory multiple myeloma

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OVERALL SURVIVAL (OS) WITH CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) VERSUS STANDARD OF CARE (SOC) IN LENALIDOMIDE (LEN)-REFRACTORY MULTIPLE MYELOMA (MM): PHASE 3 CARTITUDE-4 STUDY UPDATE

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Introduction. A single cilta-cel infusion significantly improved progression-free survival (PFS; hazard ratio [HR], 0.26 [protocol-specified weighted analysis]; P<0.0001) *vs* SoC in patients (pts) with len-refractory MM after 1-3 prior lines of therapy at 16-month (mo) median follow-up in CARTITUDE-4. We report longer-term data, including updated prespecified OS analysis at 34-mo median follow-up.

Methods. Pts were randomized to cilta-cel or SoC (pomalidomide, bortezomib, and dexamethasone [PVd] or daratumumab, pomalidomide, and dexamethasone [DPd]). Pts assigned to cilta-cel underwent apheresis, bridging therapy (PVd or DPd), lymphodepletion, and cilta-cel infusion (target dose, 0.75×10^6 CAR+ viable T cells/kg). The primary endpoint was PFS. Key secondary endpoints, tested hierarchically, were complete response (CR) or better, overall response, overall minimal residual disease (MRD) negativity (10^{-5}), OS, and time to worsening on the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q) total symptom score.

Results. 419 pts were randomized (cilta-cel, n=208; SoC, n=211). Median OS was not reached (NR, 95% CI, not estimable [NE]-NE) with cilta-cel or SoC (95% CI, 37.75 mo-NE) (HR, 0.55; 95% CI, 0.39-0.79; p=0.0009); 30-mo OS rates were 76% and 64%, respectively. OS benefit across prespecified subgroups was generally maintained. Median PFS was NR with cilta-cel (95% CI, 34.50 mo-NE) and 11.79 mo (95% CI, 9.66-14.00) with SoC; 30-mo PFS rates were 59% and 26%, respectively. The ≥CR rate was 77% *vs* 24%, the overall response rate was 85% *vs* 67%, and the overall MRD-negativity rate was 62% *vs* 18% with cilta-cel *vs* SoC, respectively. Median duration of response was NR (95% CI, NE-NE) with cilta-cel and 18.69 mo (95% CI, 12.91-23.72) with SoC. Median time to symptom worsening based on MySIm-Q was NR (95% CI, NE-NE) with cilta-cel and 34.33 mo (95% CI, 32.20-NE) with SoC (HR, 0.38; 95% CI, 0.24-0.61; P<0.0001). In the safety set (cilta-cel, n=208; SoC, n=208), 97% of pts in each arm had grade (gr) 3/4 treatment-emergent adverse events (TEAEs); cytopenia was the most common. Treatment-emergent infections occurred in 63% and 76% of pts in the cilta-cel and SoC arms, respectively (gr 3/4, 28% *vs* 30%). Hematologic second primary malignancies occurred in 7 pts (3%) in the cilta-cel arm (myelodysplastic syndrome, n=4 [2 progressed to acute myeloid leukemia (AML)]; AML, n=1; peripheral T-cell lymphoma, n=2) and 1 pt (<1%) in the SoC arm (Epstein-Barr virus-associated lymphoma). There were 50 and 82 deaths in the cilta-cel and SoC arms, respectively, of which 21 and 51 were due to progressive disease.

Conclusion. At ~3 years of follow-up, cilta-cel significantly extended OS, reducing the risk of death *vs* SoC by 45%, and significantly improved quality-of-life measures *vs* SoC. Collectively, these data continue to support the overall benefit-risk profile of cilta-cel *vs* SoC in pts with len-refractory MM as early as after first relapse.

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CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) VS STANDARD OF CARE (SOC) IN PATIENTS WITH LENALIDOMIDE (LEN)-REFRACTORY MULTIPLE MYELOMA (MM) AFTER 1-3 LINES OF THERAPY: MINIMAL RESIDUAL DISEASE NEGATIVITY (MRD-NEG) IN THE PHASE 3 CARTITUDE-4 TRIAL

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Introduction. Cilta-cel is approved for len-refractory MM after ≥1 line based on the CARTITUDE-4 trial (NCT04181827). At the first interim analysis (15.9-month [mo] median follow-up), cilta-cel improved progression-free survival (PFS) *vs* SoC (hazard ratio [HR] 0.26; P<0.0001). At the second interim analysis, overall survival (OS) was significantly improved with cilta-cel *vs* SoC (HR 0.55; p=0.0009). We report overall and sustained MRD-neg, overall MRD-neg complete response or better (≥CR), and MRD-neg ≥CR at mo 12, from the prespecified second interim analysis of CARTITUDE-4.

Methods. Pts were assigned 1:1 to cilta-cel or SoC (PVd/DPd). PFS was the primary endpoint; ≥CR rate, overall response rate, overall MRD-neg rate, and OS were key secondary endpoints. MRD was assessed centrally via next-generation sequencing (clonoSEQ v2.0; Adaptive Biotechnologies). MRD was evaluated at d 56 post infusion in the cilta-cel arm; and in both arms at suspected ≥CR and at 6, 12, 18, and 24 mo post infusion (cilta-cel arm) or cycle 1 d 1 (SoC arm), and yearly until

progression/start of subsequent therapy in pts in ≥CR. Sustained MRD-neg (10^{-5}) was defined as confirmed MRD-neg ≥12 mo apart without MRD positivity in between. Pts were evaluable for sustained MRD-neg if they achieved MRD-neg and had ≥1 evaluable MRD sample ≥12 mo after the first neg result or progressed/died/started subsequent treatment <12 mo after first neg result.

Results. 419 pts were randomized (intent-to-treat [ITT] set; cilta-cel, n=208; SoC, n=211). At median follow-up 33.6 mo, 145 pts (cilta-cel) and 103 (SoC) were evaluable for MRD (10^{-5}). MRD-neg rates (10^{-5}) in the ITT set and MRD-evaluable subset were higher with cilta-cel *vs* SoC (ITT, 62% *vs* 18%; MRD evaluable, 89% *vs* 38%; both P<0.0001). Across subgroups, cilta-cel *vs* SoC consistently increased overall MRD-neg rates (10^{-5}). In the ITT set, 48% of the cilta-cel arm achieved MRD-neg (10^{-5}) by d 56, with the MRD-neg rate rising to 60% by 6 mo. Overall MRD-neg rates (10^{-6}; ITT) were higher with cilta-cel *vs* SoC (57% *vs* 9%; P<0.0001). In the cilta-cel arm, 119 (57%) pts *vs* 26 (12%) in the SoC arm achieved overall MRD-neg (10^{-5}) ≥CR (P<0.0001). At the 12-mo MRD assessment, 92 (44%) pts in the cilta-cel arm *vs* 17 (8%) in the SoC arm (P<0.0001) had MRD-neg (10^{-5}) ≥CR. In pts with MRD-neg (10^{-5}) ≥CR at mo 12, median PFS was not reached (NR; 95% CI not estimable [NE]-NE) with cilta-cel and 37.8 mo (95% CI 25.0-NE) with SoC; median OS was NR (95% CI NE-NE) and NR (95% CI 37.8 mo-NE), respectively. Sustained MRD-neg rates (10^{-5}; ITT) were 40% in the cilta-cel arm *vs* 6% in the SoC arm (P<0.0001); among 110 and 26 evaluable pts for sustained MRD, sustained MRD-neg rates were 75% *vs* 50% (p=0.0159). Among the 176 pts who received cilta-cel as study treatment, overall MRD-neg (10^{-5}) was achieved by 129 (73%) pts (89% of 145 evaluable pts).

Conclusions. At 33.6-mo median follow-up in CARTITUDE-4, cilta-cel *vs* SoC significantly increased overall MRD-neg rates >3-fold in the ITT set, with pts achieving MRD-neg rapidly post cilta-cel. These data further underscore the benefit of cilta-cel, which led to significant >3-fold increases *vs* SoC in MRD-neg ≥CR rates at any time and at mo 12, and sustained MRD-neg. Our data demonstrate higher rates of deep and sustained MRD-neg achieved with cilta-cel *vs* SoC in len-refractory MM as early as first relapse.

P42

BELANTAMAB MAFODOTIN+BORTEZOMIB+DEXAMETHASONE (BVD) *VS* DARATUMUMAB+VD (DVD) IN RRMM: UPDATES ON OVERALL SURVIVAL (OS) AND EFFICACY IN DREAMM-7

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Background. Most patients with multiple myeloma (MM) progress after treatment with first-line combination regimens, and need efficacious subsequent-line combinations with new drug classes. Belantamab mafodotin, a B-cell maturation antigen–targeting antibody-drug conjugate, has demonstrated deep and durable responses in patients with relapsed/refractory MM (RRMM). Here, we report updated secondary efficacy endpoints, including a prespecified overall survival (OS) analysis of DREAMM-7.

Methods. DREAMM-7 is a global, 1:1 randomised, open-label, phase 3 trial comparing the efficacy and safety of belantamab mafodotin+bortezomib+dexamethasone (BVd) *vs* daratumumab+Vd (DVd) in patients with RRMM who have received ≥1 prior line of therapy. The primary endpoint was progression-free survival (PFS); secondary endpoints included OS, duration of response (DOR), minimal residual disease (MRD) negativity, and time from randomisation to disease progression after subsequent antimyeloma therapy or death from any cause (PFS2).

Results. A total of 494 patients were randomised 1:1 to BVd (n=243) or DVd (n=251). Median (m) follow-up was 39.4 months (mo). While mOS was not reached (NR) in either arm, BVd showed a statistically significant OS benefit over DVd (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.43-0.79; p=.00023). BVd *vs* DVd resulted in higher rates of complete response or better and MRD negativity (25% *vs* 10%), longer mDOR (95% CI) (40.8 mo [30.5 mo-NR] *vs* 17.8 mo [13.8-23.6 mo]) and longer mPFS2 (95% CI) (NR [45.6 mo-NR] *vs* 33.4 mo [26.7-44.9 mo]; HR 0.59; 95% CI 0.45-0.77).

Conclusion. BVd significantly prolonged OS in patients with RRMM who have received ≥1 prior line of therapy. These results support BVd as a potential new standard of care in MM at first relapse or later.

P43

EFFECTIVENESS OF BRIDGING THERAPY CORRESPONDS TO IMPROVED OUTCOMES AFTER RECEIVING CAR-T THERAPY: PHASE 3 CARTITUDE-4 STUDY OF PATIENTS WITH RELAPSED, LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA

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Introduction. In the phase 3 CARTITUDE-4 trial, ciltacabtagene autoleucel (cilta-cel) *vs* standard care significantly improved progression-free survival (PFS; hazard ratio [HR] 0.26, P<0.0001) and rates of overall response (85% *vs* 67%) and complete response or better (73% *vs* 22%) in patients with relapsed, lenalidomide-refractory MM after 1-3 prior lines of therapy. Patients who received cilta-cel as study treatment (ie, did not have disease progression before cilta-cel infusion) had high rates of overall response (99.4%), complete response or better (86.4%), and 12-month PFS (89.7% from randomization). Bridging therapy controls disease while CAR-T cell therapy is being manufactured and potentially reduces the risk of toxicities by debulking. The impact of disease control prior to CAR-T infusion on postinfusion clinical outcomes is not well established. We present post hoc analyses describing cilta-cel efficacy by response to bridging therapy in patients who received cilta-cel as study treatment in CARTITUDE-4.

Methods. Patients in the cilta-cel arm underwent apheresis, received bridging therapy with either pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd), and then a single cilta-cel infusion 5-7 days after the start of lymphodepletion. PFS (measured from randomization) was analyzed in patients who had a ≥25% reduction in paraprotein from baseline (prior to apheresis) to the start of lymphodepletion *vs* others (paraprotein either increased, no change, or <25% reduction). CAR+ T cells in peripheral blood were assessed by flow cytometry. A ligand-binding assay was used to quantify serum soluble BCMA (sBCMA). In vivo effector-to-target (E:T) ratio was derived by peak CAR-T cell expansion normalized to pre-infusion sBCMA levels.

Results. Among 176 patients who received cilta-cel as study treatment (DPd, n=158; PVd, n=18), 148 had a ≥25% reduction in paraprotein during the bridging period. At 15.9-month median follow-up, median PFS was not reached (95% CI, not estimable [NE]-NE) in patients with ≥25% reduction *vs* 19.2 months (95% CI, 15.8-NE) in the others (HR, 0.32; 95% CI, 0.16-0.66). Estimated 12-month PFS rates were 91.8% and 78.1%, respectively. In patients with available biomarker data (n=171), a significantly higher in vivo E:T ratio was observed in those with a ≥25% reduction in paraprotein *vs* the others (median [IQR], 62.6 [139.2] *vs* 5.4 [62.3]).

Conclusion. Greater response to bridging therapy (≥25% paraprotein reduction) correlated with longer PFS. This may be explained mechanistically by a higher in vivo E:T ratio, previously shown to be associated with longer PFS (Montes de la Oca, ASH 2023). These data emphasize the importance of optimized bridging therapy for disease control prior to receiving cilta-cel.

P44

EFFICACY AND SAFETY OF WEEKLY SELINEXOR, IN COMBINATION WITH POMALIDOMIDE, AND DEXAMETHASONE (SPD) FOR TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM): UPDATES FROM THE STOMP TRIAL

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Introduction. Despite the promise of T-cell engaging therapies, there is still no standard of care for patients with RRMM after treatment with immunomodulatory agents (IMiDs), proteasome inhibitors (PI), or anti-CD38 monoclonal antibodies (αCD38). Selinexor is an oral exportin 1 (XPO1) inhibitor approved with dexamethasone (d) in penta-refractory MM, and with d and bortezomib in RRMM after ≥1 prior therapy. Median progression-free survival (mPFS) reported in observational studies was ~4.6 months in triple-class-exposed (TCE) RRMM with common anti-MM agents, but selinexor was rarely administered in this subgroup of patients. In the phase 1b/2 STOMP trial (NCT02343042), selinexor is being evaluated with pomalidomide (P) and d (SPd) for treatment of RRMM. Here, we present updated efficacy and safety for the cohorts that received SPd with selinexor at a dose of 40 mg or 60 mg once weekly (QW).

Methods. Selinexor was assessed at various doses and schedules in combination with Pd (P doses were 2 mg, 3 mg, or 4 mg QD) in the STOMP trial. Study objectives included the maximum tolerated dose determination and the recommended phase 2 dose to assess safety and efficacy of SPd. International Myeloma Working Group criteria were used for investigator-determined response evaluations.

Results. Of 81 patients enrolled in the SPd arm as of October 1, 2024, 53.1% were male, median age (range) was 65 years (37-85), and patients had a median (range) of 3 (1-10) prior lines of therapy; 20 patients received selinexor 60 mg QW (SPd60) and 16 received selinexor 40 mg QW (SPd40). In the SPd arm, prior exposure/refractory status was: IMiDs 100%/86.4%, PI 100%/80.2%, αCD38 33.3%/30.9%, and triple class 33.3%/25.9%. Median follow-up was 17.5 months in SPd60 and 33.8 months in SPd40. Overall response rate (ORR) was 55.0% (95% CI 31.5, 76.9) for SPd60 and 43.8% (95% CI 19.8, 70.1) for SPd40. The rate of ≥ very good partial response was 30.0% (95% CI 11.9, 54.3) in SPd60 and 31.3% (95% CI 11.0, 58.7) in SPd40, with 2 stringent TCE complete responses (CRs; 1 in SPd60 and 1 in SPd40) and 1 CR (SPd40). In SPd60, median PFS was 9.1 months with a median duration of response (DOR) of 10 months. The median PFS and median DOR were not reached in SPd40. The most common treatment-emergent adverse events (TEAEs) were neutropenia (SPd60: any grade/grade 3/4 75.0%/60.0%; SPd40: 75%/68.8%), fatigue (75.0%/15.0%; 68.8%/6.3%), nausea (70.0%/0; 50.0%/0), anemia (65.0%/25.0%; 31.3%/18.8%), and thrombocytopenia (45.0%/25.0%; 25.0%/18.8%). Median duration of exposure in weeks was 22.0 (range 7,114) in SPd60 and 28.0 (4, 201) in SPd40, with a median relative selinexor dose intensity of 77.5% (46.5 mg/week) and 91.3% (36.5 mg/week), respectively.

Conclusions. SPd, an all-oral combination with weekly selinexor,

showed signs of preliminary efficacy and was generally tolerable in patients with RRMM. Although the ORR was greater in the SPd60 cohort, patients in the SPd40 cohort experienced less frequent TEAEs, a longer duration of exposure, and a higher selinexor dose intensity was achieved. Further evaluation of low-dose weekly selinexor, which is supported by these data, is ongoing in the EMN29 trial (NCT05028348) of SPd40 *vs* elotuzumab-Pd in TCE RRMM progressing immediately after a αCD38-containing line of therapy.

P45

THE TREATMENT OF PATIENTS PROGRESSING AFTER LENALIDOMIDE MAINTENANCE: AN ITALIAN REAL-LIFE STUDY OF 284 CASES

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The extensive use of lenalidomide (Len) in the first line treatment of Multiple Myeloma (MM) often results in first relapsed patients who have been exposed or refractory to Len. In all the randomized clinical trials that evaluated the regimens used in MM patients relapsed after Len, the proportion of Len refractory (Len-R) cases is highly variable and never encompasses the whole cohort. Moreover, most patients were treated at second relapse without specifying whether they received Len in combination or as maintenance after autologous stem cell transplant (ASCT). Consequently, the outcome of Len-R patients after ASCT and maintenance is unclear. The aim of this real-life study is to evaluate the efficacy of the current on-label regimens approved and used in a cohort of patients who relapsed after Len maintenance. Starting from 1st January 2017, 284 consecutive patients followed in 30 Italian centers were included in this preliminary analysis. Considering the induction regimens, almost all patients (98.6%) received at least a bortezomib or carfilzomib-based triplet combination, while few cases (16/284, 5.6%) received an anti-CD38 monoclonal antibody-based quadruplet. All patients received at least one ASCT (tandem ASCT in 37.7% of cases) and Len maintenance until progression with a median number of 20 cycles of Len (2-108) administered. The treatments received at relapse were as follows: Isa-KD in 125 cases (44.1%), D-PD in 57 cases (20.1%), D-VD in 36 cases (12.7%), P-VD in 24 cases (8.5%), KD in 17 cases (6%) while 21 cases (7.4%) were treated with a Len based triplet (mostly D-RD). Chemo-based combinations were used only in 4 cases. With a median follow up of 17 months, the median progression free survival (PFS) and overall survival were 22 months and not reached respectively. Patients treated at biochemical relapse showed improved PFS compared to patients treated at clinical relapse (24 *vs* 17 months, p=0.0049). Clinical and biological high-risk disease consistently demonstrated poorer outcomes compared to low-risk disease.

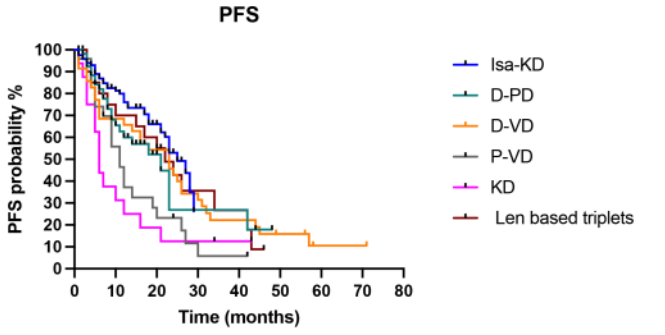

Figure 1.

Specifically, cytogenetic high-risk cases and patients with elevated LDH levels or β2 microglobulin levels >3.5 mg/L at relapse showed significantly inferior PFS compared to other cases (cytogenetic high-risk: 17 *vs* 27 months, p=0.0444; high LDH: 12 *vs* 23 months, p=0.0067; β2 microglobulin >3.5 mg/L: 10 *vs* 24 months, p=0.002). Furthermore, patients who experienced early relapse (<18 months form starting maintenance) showed a significantly reduced PFS (17 *vs* 25 months, p=0.0035) compared to those with late relapse. Considering the type of treatment, anti-CD38 based combinations showed improved PFS with respect to anti-CD38 sparing combinations (23 *vs* 11 months, p=0.0044) while no significant differences were found between PI+anti-CD38 or IMIDs+antiCD38 treated cases (24 *vs* 21 months, p=0.1906). Focusing on specific regimens, the median PFS was 25 months for Isa-KD, 23 months for D-VD, 22 months for Len based triplets, 21 months for D-PD, 11 months for P-VD and 6 months for KD. To our knowledge, this is the largest study evaluating the outcome of patients progressing after Len maintenance. In a cohort of selected patients (all Len-R at first relapse and mostly anti-CD38 naive) we highlighted that anti CD38-based combinations granted superior outcomes, with the Isa-KD regimen showing the longer PFS. However, clinical and biological high-risk disease still provided a dismal outcome.

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EFFICACY OUTCOMES BY MINIMAL RESIDUAL DISEASE NEGATIVITY IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA TREATED WITH BELANTAMAB MAFODOTIN+BORTEZOMIB+DEXAMETHASONE VS DARATUMUMAB+BORTEZOMIB+DEXAMETHASONE: ANALYSIS FROM THE DREAMM-7 TRIAL

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Background. In DREAMM-7 (NCT04246047), belantamab mafodotin plus bortezomib and dexamethasone (BVd) demonstrated a statistically significant and clinically meaningful progression-free survival (PFS) benefit *vs* the standard-of-care triplet daratumumab, bortezomib, and dexamethasone (DVd) in patients with relapsed or refractory multiple myeloma who had received ≥1 prior line of treatment. MRD negativity has been shown to be a predictor of PFS and overall survival (OS) in multiple myeloma. We aimed to understand if minimal residual disease (MRD) negativity translated to improvements in PFS and OS in the DREAMM-7 trial.

Methods. In DREAMM-7, patients with ≥1 prior line of treatment were randomised (1:1) to BVd or DVd. The primary endpoint was independent review committee (IRC)–assessed PFS with OS and MRD negativity as secondary endpoints. Patients achieving complete response or better (≥CR) were tested for MRD negative by next-generation sequencing with 10^{-5} sensitivity with follow-up every 6 months until disease progression. An exploratory MRD analysis was also performed in patients who achieved a very good partial response or better (≥VGPR). Post hoc subgroup analyses of PFS (IRC assessed) and OS were performed based on IRC-assessed response (≥CR or ≥ VGPR) and MRD-negative status and evaluated using the Kaplan-Meier method; CIs were estimated using the Brookmeyer-Crowley method.

Results. In total, 494 patients (BVd, n=243; DVd, n=251) were randomised in the intention-to-treat population. As previously reported, at the first interim analysis (data cutoff: October 2, 2023; median follow-up, 28.2 months), a higher proportion of patients in the BVd arm had CR-based MRD-negative status *vs* the DVd arm (60 of 243 [25%] *vs* 24 of 251 [10%] patients). A higher proportion of patients achieved sustained MRD negativity for ≥12 months (≥CR) with BVd (10%) *vs* DVd (2%) by the data cutoff. Rates of CR-based MRD negativity favoured BVd *vs* DVd in prespecified subgroups of patients with disease refractory to lenalidomide (25% *vs* 6%) and patients with ≥1 high-risk cytogenetic abnormality (31% *vs* 7%); this is consistent with findings from the intention-to-treat analysis. A similar trend was observed in an exploratory analysis of patients with ≥VGPR, with 94 of 243 (39%) patients achieving VGPR-based MRD negativity in the BVd arm *vs* 43 of 251 (17%) patients in the DVd arm. Inability to achieve MRD-negative status was associated with lower PFS and OS outcomes compared with the intention-to-treat population. Among patients who did not achieve CR-based MRD negativity, median PFS was 15.3 months (95% CI, 12.7-18.0 months; BVd, 25.0 months; DVd, 11.8 months), with an 18-month PFS rate of 45% (95% CI, 40%-50%; BVd, 57%; DVd, 36%); median OS was not reached at the data cutoff, and the 18-month OS rate was 74% (95% CI, 69%-78%; BVd, 79%; DVd, 70%). In patients who achieved CR-based MRD-negative status, median PFS and OS were not reached; by the data cutoff, 13% (BVd, 10%; DVd, 21%) of patients had PFS events, and 5% (BVd, 5%; DVd, 4%) had OS events.

Conclusions. In the DREAMM-7 trial, patients in the BVd arm achieved MRD-negative status at more than double the rate observed in the DVd arm, and more patients achieved sustained MRD-negative status for ≥12 months with BVd. MRD negativity was associated with durable PFS and OS benefits, which is consistent with previous reports; this highlights the importance of the greater response depth that is achieved with BVd.

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EFFICACY OF IDECABTAGENE VICLEUCEL (IDE-CEL) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND PRIOR CENTRAL NERVOUS SYSTEM MANIFESTATION: A MULTICENTER REAL-WORLD ANALYSIS

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Background. Central nervous system (CNS) involvement in multiple myeloma (MM) is a rare complication associated with poor prognosis. CNS involvement is characterized by plasma cell infiltration of the CNS parenchyma, meninges or cerebrospinal fluid (CSF). B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR)-T cell therapies have become a standard of care for relapsed/refractory (r/r) MM. For r/r MM pts with a history of CNS disease (MM-CNS), real-world evidence regarding the efficacy and safety profiles of CAR-T cells remains limited, as these pts were excluded from the pivotal studies. To address this gap, we sought to evaluate the efficacy of idecabtagene vicleucel (ide-cel) in MM-CNS pts in a real-world context.

Methods. We conducted a multicenter retrospective study including

r/r MM pts undergoing ide-cel treatment between March 2022 and May 2024 at seven German/Swiss tertiary care centers. Pts were grouped by the presence of CNS disease prior to ide-cel infusion. Only pts with intradural and/or intraparenchymal lesions or detection of myeloma cells in the CSF were regarded as MM-CNS pts. Descriptive and survival analyses, including propensity score matching between MM-CNS and non-MM-CNS pts (optimal matching with 1:3 ratio; age at ide-cel, number of prior therapy lines and IMWG response at ide-cel as co-variates) were performed.

Results. In total, 158 r/r MM patients underwent ide-cel therapy during the study period. Ten (6.3%) pts from five centers met the criteria for CNS disease prior to CAR-T treatment. The median age of MM-CNS pts at CAR-T infusion and the median number of therapy lines prior to ide-cel were 61 years (range: 47-71 years) and 5 (range: 2-8), respectively. One month post-CAR-T, best serologic responses were as follows: 4/10 CR, 5/10 pts with VGPR/PR, and 1/10 in PD. Regarding CNS disease, 3/10 pts maintained response until last FU (CR: 2, PR: 1), while 5/10 pts improved response to CR (4/10) and PR (1/10), respectively. In two remaining pts, SD (1/10) or PD (1/10) as best response was documented post-ide-cel (Figure 1A). Information on CAR-T cell persistence and CSF plasma cell clearance was available in one patient. With a median follow-up of survivors of 11 months, a median OS of 12.9 months and a median PFS of 10.5 months were observed (Figure 1B). To compare outcomes between pts with and without CNS manifestations, we applied propensity score matching identifying a matched cohort of 24 pts without CNS myeloma. After matching, survival outcomes and serologic response rates were comparable for the MM-CNS cohort and non-CNS cohort (median OS: 13 months (MM-CNS) *vs* not reached (non-CNS myeloma), p= 0.52; median PFS: 10.5 *vs* 11.3 months, p= 0.76) (Figure 1C). Overall response rates (CR/VGPR/PR) were 75% for both MM-CNS and non-MM-CNS pts (p=1.00). All four deaths occurred due to r/r disease (Figure 1A).

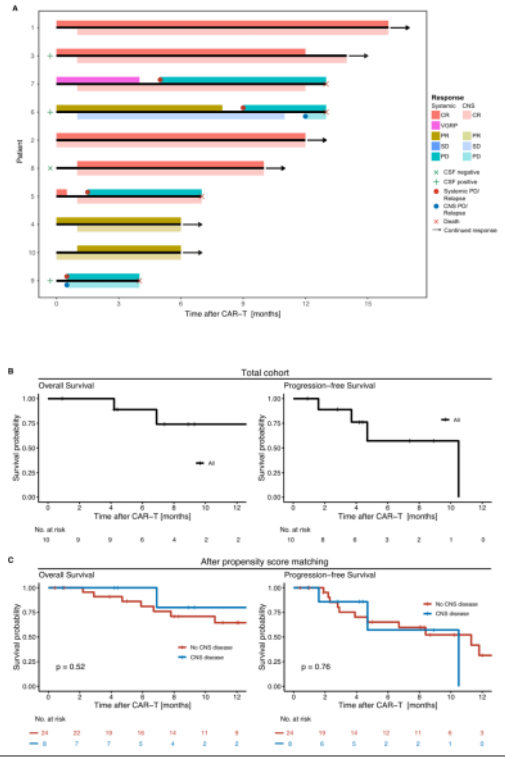

Figure 1.

Conclusions. We observed that CAR-T cell therapy achieves encouraging response rates in MM-CNS pts. Besides, we demonstrated that outcomes of CAR-T cell therapy in a MM-CNS patient cohort appear to be comparable to a matched cohort of classical non-CNS myeloma pts after ide-cel treatment. Finally, BCMA-directed T-cell lymphocytes measurement in the CSF was performed in one patient confirming their ability to penetrate the blood brain barrier. Our findings indicate that CAR-T cell therapy can be effective in MM pts with CNS involvement.

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LONG-TERM BENEFITS IN PATIENT (PT)-REPORTED OUTCOMES AND TIME TO NEXT THERAPY (TTNT) OF CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) VS STANDARD OF CARE (SOC) FOR PTS WITH LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA (MM): RESULTS FROM THE PHASE 3 CARTITUDE-4 TRIAL

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Background. Cilta-cel demonstrated superior progression-free survival (PFS) and overall survival compared to SOC in lenalidomide-refractory MM after 1-3 prior lines of therapy (LOT) in the phase 3 CARTITUDE-4 trial. A single cilta-cel infusion showed clinically meaningful PFS *vs* SOC (hazard ratio [HR] 0.26; p<0.0001) at median follow-up 15.9 months (mo). A second interim analysis demonstrated reduction in risk of death by 45% (HR 0.55; p=0.0009) *vs* SOC, with an estimated 30-mo survival rate of 76.4%. We report the pt reported outcomes (PROs) and TTNT at ~3-year median follow-up.

Methods. 419 pts were randomized; cilta-cel (N=208) or SOC (N=211). The Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q), including symptom (pain, fatigue, digestion, cognition) and impact (activity limitations, social functioning, emotional impact) domains, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), were used in pts until disease progression. Time to worsening (TTW) of symptoms and impact were defined as time from randomization to a decrease in score of at least 0.5 standard deviation from baseline without observed superior subsequent improvement, and TTW of global health status/quality of life (GHS/QoL) was defined using an anchor-based approach with CARTITUDE-4 data. TTNT was defined as time from randomization to the start of subsequent anti-myeloma therapy or death due to progression. Outcomes were assessed by Kaplan-Meier method. Cox proportional hazard models were used to estimate HRs and 95% confidence intervals (CIs). Clinical data cut-off was May 1, 2024 (median follow-up 34 mo).

Results. MySIm-Q symptom and impact domain scores showed cilta-cel was associated with significantly longer TTW of symptoms (HR 0.38; 95% CI 0.24-0.61; p<0.0001) and impact (HR 0.42; 95% CI 0.26-0.70; p=0.0007) *vs* SOC. By 30 mo, 77% of cilta-cel pts had not experi-

enced worsening of symptoms, *vs* 63% of pts on SOC. Similarly, 83% of cilta-cel pts had not experienced worsening of functional impacts, *vs* 69% on SOC at 30 mo. Median time until symptom worsening was not reached (NR) for cilta-cel, and was 34.33 (95% CI 32.20-NR) mo for SOC. A median time to impact worsening of 39.16 (95% CI 38.70-NR) mo was estimated for the cilta-cel arm, *vs* 35.88 (95% CI 32.20-NR) mo for SOC. MySIm-Q results are further supported by those observed on the EORTC QLQ-C30 GHS/QoL scale, with time to worsening significantly delayed (HR 0.40; 95% CI 0.25-0.64; p<0.0001) *vs* SOC. 79% of cilta-cel pts had not experienced a worsening of GHS/QoL by 30 mo, *vs* 66% of pts on SOC. The median time to GHS/QoL worsening for cilta-cel was 39.92 (95% CI 39.92-NR) mo, *vs* 34.33 (95% CI 32.03-NR) mo for SOC. Treatment with cilta-cel significantly delayed, by 66%, time to subsequent anti-myeloma treatment or death due to progression (HR 0.34; 95% CI 0.26-0.46; p<0.0001) *vs* SOC. Median TTNT was NR for cilta-cel and was 13.37 (95% CI 11.99-17.08) mo for SOC.

Conclusion. The increase in the TTNT and sustained benefits in PROs, along with prolonged survival, support cilta-cel as a new SOC treatment for MM pts who are refractory to lenalidomide and have received 1-3 prior LOTs. With ~3 years of follow-up, a single infusion of cilta-cel provided pts with a longer delay in worsening of MM related symptoms, functional impacts, and GHS/QoL. The totality of clinical and patient-reported evidence demonstrates the significant benefit of cilta-cel.

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CLINICAL EFFICACY OF ISATUXIMAB PLUS CARFILZOMIB - DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS: UPDATE OF A REAL-LIFE MULTI-CENTER RETROSPECTIVE EXPERIENCE

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Introduction. Isatuximab, a novel anti-CD38 monoclonal antibody, has shown efficacy in combination with carfilzomib and dexamethasone (isa-KD) in relapsed/refractory multiple myeloma (RRMM) patients in the phase III IKEMA trial (NCT03275285). Due to its novel introduction in clinical practice, its real-world efficacy is still unexplored. In this multi-center retrospective study, we reported results of isa-KD in RRMM patients in a real-life setting.

Methods. A total of 103 RRMM patients from 16 Hematology Units in Italy who started Isa-KD outside clinical trials (previous lines 1-3) were enrolled from March 2022 to March 2024. High genetic risk MM and lenalidomide refractoriness were assessed using IMWG criteria, including chromosome 1 abnormalities.

Table 1.

Characteristics	Overall cohort N = 103	2nd line cohort N = 69
Median age, years (range)	64 (45-84)	63 (45-77)
Male, n (%)	53 (51)	37 (54)
ECOG scale, n (%)		
0-1	88 (86)	61 (88)
≥ 2	15 (14)	8 (12)
M-protein type, n (%)		
IgG	64 (63)	40 (58)
IgA	21 (20)	15 (22)
Light chain only	17 (16)	12 (17)
Not secernent	1 (1)	1 (1)
Light chain type, n (%)		
Kappa	49 (48)	32 (46)
Lambda	53 (52)	37 (54)
High genetic risk MM, n (%)	39 (38)	27 (39)
Extramedullary disease, n (%)	17 (16)	10 (15)
Glomerular filtration rate < 40 ml/min, n (%)	15 (14)	8 (12)
Revised international staging system, n (%)		
I	23 (22)	19 (27)
II	38 (37)	27 (39)
III	20 (19)	13 (19)
Not available	22 (21)	10 (15)
Previous therapy lines, n (%)		
1	69 (67)	-
2-3	34 (33)	
Previous autologous stem cell transplantation, n (%)	78 (76)	58 (84)
Previous bortezomib treatment, n (%)	96 (93)	64 (93)
Previous anti-CD38 treatment, n (%)	15 (15)	4 (6)
Previous thalidomide treatment, n (%)	80 (78)	55 (80)
Previous lenalidomide maintenance, n (%)	63 (61)	54 (78)
Median duration of lenalidomide maintenance, months (range)	23 (2-62)	26 (2-62)
Lenalidomide exposed, n (%)	20 (19)	14 (20)
Lenalidomide refractory, n (%)	73 (71)	47 (68)
< 12 months of lenalidomide maintenance, n (%)	21 (20)	18 (26)
< 24 months of lenalidomide maintenance, n (%)	32 (31)	25 (36)
Overall response rate (ORR), n (%)	87 (85)	61 (88)
Complete response	19 (18)	14 (20)
Very good partial response	40 (39)	32 (46)
Partial response	28 (27)	15 (22)
Time to best response, months, median (range)	3 (1-20)	2 (1-20)
Total isa-KD administrations, median (range)	6 (1-24)	7 (1-24)
Consolidation with ASCT, *n* (%)	13 (12)	10 (15)
Number of MM progressions, n (%)	30 (29)	14 (20)
Progression free survival, median, months (95%CI)	NR	NR
One-year PFS, %	72	92
Number of deaths, n (%)	23 (22)	14 (20)
Overall survival, median, months (95%CI)	NR	NR
One-year OS, %	77	95
-Hypertension, n (%)	15 (14)	10 (15)
Grade I-II	12 (11)	9 (14)
Grade III-IV	3 (2)	1 (1)
- Cardiac tachyarrhythmias, n (%)	4 (3)	2 (3)
- Hematological toxicity, n (%)	43 (42)	32 (46)
Grade I-II	23 (22)	18 (26)
Grade III-IV	20 (19)	14 (20)
-Pneumonia, n (%)	14 (13)	10 (20)

Results. Baseline characteristics are summarized in Table 1. High genetic risk (39%), extramedullary disease (EMD; 16%) and severe renal dysfunction (glomerular filtration rate <40 ml/min; 14%) were highly represented. Median follow-up time was 12 months (95%CI: 10.3-13.6). Most subjects (76%) had received autologous stem cell transplantation (ASCT) and 61% of them received lenalidomide maintenance with a rate of lenalidomide-exposure and refractoriness of 19% and 71% respectively. Median Progression-Free Survival (PFS) was not reached [95% CI, not estimable (NE)], with 1-year PFS of 72%, as well as median Overall Survival (OS) was not reached (95% CI, NE), with 1-year OS of 77%. Median PFS was significantly shorter in high genetic risk (13 months, 95% CI, 7.2-18.7) compared with standard genetic risk patients

(not reached; 95% CI, NE; HR: 3.1; 95% CI, 1.3–7.1; p<0.005), as well as in subjects with EMD (14 months [95% CI, 8.5–19.4] *vs* not reached [95% CI, NE]; HR, 2.5; 95% CI, 1.1–5.8; p=0.02), or those treated with Isa-Kd after ≥2 lines of therapy versus one prior line (13 months [95% CI, 6.2–21.9] *vs* not reached [95% CI, NE]; HR, 2.1; 95% CI, 1.1-4.5; p=0.04). Previous exposure to anti-CD38 agents was significantly associated with worse outcomes (8 months [95% CI, 5.4-10.7] *vs* not reached [95% CI, NE]; HR, 3.2; 95% CI, 1.3–7.7; p<0.005). Moreover, we conducted a subanalysis on patients (N=69; Table 1) treated with Isa-Kd after one prior line of therapy, showing a not reached median PFS and OS, with 1-year PFS and OS of 92% and 95%, respectively. PFS was shorter for patients with early MM progression within 12 months (median PFS, 14 months [95% CI, 0.1–28.92] *vs* not reached [95% CI, NE]; HR, 5.5; 95% CI, 1.4-21.5; p=0.005) or 2 years (median PFS, 14 months [95% CI, NE] *vs* not reached [95% CI, NE]; HR, 11.5; 95% CI, 1.4-91; p<0.005) after initiating lenalidomide maintenance. Isa-KD was well tolerated with cardiac toxicity and pneumonia as the most frequent severe adverse events.

Conclusion. In conclusion, our real-life experience showed that Isa-KD is a feasible treatment option even in a real-life setting in a much more difficult population compared to the IKEMA study (higher rates of high genetic risk, EMD, refractoriness to lenalidomide, pre-treatment with anti-CD38 monoclonal antibodies). In the second-line setting, PFS was significantly higher, although patients with early MM relapse and short lenalidomide maintenance showed a worse prognosis. This type of patients continues to represent an unmet clinical need, where perhaps only the introduction of first-line T-cell reconditioning therapies can improve prognosis. However, larger prospective clinical studies are needed.

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LINVOSELTAMAB IN PATIENTS IDENTIFYING AS BLACK OR AFRICAN AMERICAN WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS FROM LINKER-MM1

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Linvoseltamab demonstrated high efficacy and generally manageable safety in patients (pts) with RRMM (Bumma et al. JCO 2024). Black or African Americans have higher incidence of MM, and distinct MM characteristics and outcomes, *vs* White Americans. Here, we assess efficacy and safety of linvoseltamab in Black *vs* non-Black pts from the Ph 1/2 LINKER-MM1 trial (NCT03761108). Eligible pts had MM that either progressed on/after ≥3 lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody; or was ≥triple-class (PI/IMiD/anti-CD38) refractory. Pts received IV linvoseltamab weekly through week (wk) 14, then once every two weeks (Q2W) from wk 16. Pts in the 200 mg Ph 2 cohort who reached ≥VGPR and received treatment for ≥24 wks transitioned to Q4W dosing. Primary endpoints: safety (Ph 1) and objective response rate (ORR) by independent review committee (IRC) (Ph 2). Secondary endpoints (in Ph 1 and 2) included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). As of Jan 6, 2024, 117 pts had received linvoseltamab 200 mg: 20 were Black (19 American) and 97 non-Black (83 White, 10 Asian, 1 other, 3 no race reported). Median age in Black *vs* non-Black pts: 67 yrs (35% ≥75 yrs) *vs* 70 yrs (25% ≥75 yrs). Both groups had received a median 5 prior lines of therapy. ORR by IRC: 85% (86% in pts ≥75 yrs) in Black pts *vs* 68% (67% in pts ≥75 yrs) in non-Black pts. Higher ORR in Black *vs* non-Black pts was seen across prespecified subgroups: ISS III, ORR 75% (3/4) *vs* 59% (10/17); baseline extramedullary plasmacytomas, ORR 100% (2/2) *vs* 47% (8/17); high-risk cytogenetics, ORR 100% (8/8) *vs* 73% (43/59). In Black pts, median DOR was not reached (NR) (95% CI 8.3 months [mos]–non-evaluable [NE]) and estimated 12-mo probability of response was 68% (95% CI 38.8–85.2); in non-Black pts, median DOR was 29.4 mos (95% CI 19.2–NE) and 12-mo probability of response was 84% (95% CI 72.5–91.2). In Black pts, median PFS was NR (95% CI 7.3–NE), and 12-mo PFS was 67% (95% CI 40.1–83.5); in non-Black pts, median PFS was NR (95% CI 16.2–NE) and 12-mo PFS was 71% (95% CI 59.8–79.3). In Black pts, median OS was NR (95% CI 7.3–NE), and 12-mo OS was 74% (95% CI 47.9–88.1); in non-Black pts, median OS was 31.4 mos (95% CI 21.6–NE) and 12-mo OS was 76% (95% CI 65.3–83.2). Median linvoseltamab exposure was 54 wks (Black pts) *vs* 53 wks (non-Black pts). The most common TEAEs in Black pts were neutropenia (Black pts: any grade [Gr] 65%, Gr≥3 65%; non-Black pts: any Gr 38%, Gr≥3 37%), anemia (Black pts: any Gr 45%, Gr≥3 40%; non-Black pts: any Gr 37%, Gr≥3 29%), diarrhea (Black pts: any Gr 40%, Gr≥3 5%; non-Black pts: any Gr 37%; Gr≥3 1%), cough (Black pts: any Gr 35%, Gr≥3 0%; non-Black pts: any Gr 37%, Gr≥3 0%), and hypokalemia (Black pts: any Gr 35%, Gr≥3 0%; non-Black pts: any Gr 23%, Gr≥3 4%). Cytokine release syndrome was reported in 25% (Gr3–5 0%) of Black pts *vs* 51% (Gr3 1%, Gr4–5 0%) of non-Black pts. ICANS was reported in 1 Black pt (5%; Gr1) and 8 non-Black pts (8%; Gr3 3%, Gr4–5 0%). The most common infection in Black pts was pneumonia (any Gr 30%, Gr≥3 25%) and in non-Black pts was COVID-19 (any Gr 26%, Gr≥3 13%). LINKER-MM1 enrolled a proportion of African American pts broadly consistent with US demographic representation. Response rates in Black pts were numerically higher *vs* non-black pts; PFS and OS were similar. Other than neutropenia, toxicity was similar in Black and non-Black pts.

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A PROSPECTIVE, OBSERVATIONAL STUDY OF PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA TREATED WITH IXAZOMIB IN REAL-WORLD SETTINGS IN GREECE: THE 'OL-ORAL' STUDY

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Introduction. Ixazomib (IXA) combined with lenalidomide (LEN) and dexamethasone (DEX) (IRd) is approved for adults with relapsed/refractory multiple myeloma (RRMM) after ≥1 prior therapy. The main objective of this study was to generate real-world data (RWD) on effectiveness, safety, medication adherence, health-related quality of life (HRQoL) and satisfaction with therapy in RRMM patients treated with IRd in routine clinical settings in Greece.

Methods. RRMM patients prescribed IRd for the first time, after 1-3 prior therapies, per the approved label, were eligible and consecutively enrolled. Patients refractory to bortezomib, pre-treated with IXA, and having received >1 IRd cycles, were excluded. Data were collected by routine assessments, patient-reported outcomes and chart review at study enrollment and at ~6, 12 and 24 months after IRd treatment initiation. HRQoL and patient satisfaction with IRd were assessed utilizing the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) and the Cancer Therapy Satisfaction Questionnaire (CTSQ), respectively.

Results. From Sep-2018 to Jun-2021, 49 eligible patients (57.1% males; mean age 70.4) were enrolled in the study by 16 hospitals. Prior to IRd, 75.5% of patients had received proteasome inhibitors (PIs) (73.5% bortezomib; 8.2% carfilzomib), 67.3% immunomodulatory drugs (IMiDs) (61.2% LEN; 12.2% thalidomide; 2.0% pomalidomide), and 24.5% autologous stem cell transplantation. Treatment with IRd was initiated a median (interquartile range; IQR) of 3.4 (1.7-4.4) years after MM diagnosis. At IRd initiation, 83.7% of patients had ECOG performance status 0-1, while 46.9% had relapsed, 44.9% relapsed & refractory, and 8.2% refractory MM; 46.9% were refractory to IMiDs (LEN in all cases) and none to PIs. IRd was initiated as 2nd/3rd/4th line in 65.3/22.4/12.2% of patients, at the label-recommended dosage in 32.7%; IXA/LEN/DEX were started at a lower dose in 16.3/46.9/55.1% of patients. Over a median (IQR) observation period of 8.6 (5.9-21.1) months, a median (IQR) of 8.0 (5.0-20.0) IXA-containing cycles were received. Median PFS & OS was 22.1mo & NR respectively. Adherence to IXA was high at both 6- and 12-month visits, with none of the prescribed ixazomib capsules missed in 96.9% and 100% of patients, respectively. Clinical and patient-reported outcomes are presented in Table 1. In the overall population, no statistically significantly changes were observed from enrollment at any of the post-baseline timepoints for the EQ-5D index, EQ-Visual Analogue Scale (VAS) score and CTSQ domain scores. The 12- and 24-month IXA continuation rate among evaluable patients was 42.6% (20/47) and 15.2% (7/46), respectively. IXA-related AE rate was 44.9%. A total of 16 IXA-related serious AEs were reported for 22.4% of the patients; each reported in <5% of patients.

Conclusions. The IRd combination in RRMM patients as a 2nd to 4th line treatment in Greek routine settings, provides efficacy and safety results similar to those reported in TOURMALINE-MM1 trial (Moreau et al, N Engl J Med 2016), as well as in other European RWD (Leleu et al, Future Oncol 2024), with high levels of adherence while it maintains patients' QoL, despite the less favorable higher proportion of LEN-refractory patients in OL-ORAL.

Table 1. Clinical and patient-reported outcomes of IRd-treated patients with RRMM.

Number of disease/response assessments, median (IQR)		
Overall ($n_{assessments}$=288)	N=49	5.0 (3.0-7.0)
IRd as 2nd line ($n_{assessments}$=183)	N=32	4.0 (2.0-6.0)
IRd as ≥3rd line ($n_{assessments}$=105)	N=17	5.0 (4.0-8.0)
Achievement of ≥PR[a], n (%)		
Overall	N=38	22 (57.9)
IRd as 2nd line	N=23	14 (60.9)
IRd as ≥3rd line	N=15	8 (53.3)
Time to 1st documentation of ≥PR[a], months, median (IQR)		
Overall	N=22	1.9 (1.3-2.6)
IRd as 2nd line	N=14	1.9 (1.6-2.5)
IRd as ≥3rd line	N=8	2.0 (1.0-3.2)
KM-estimated PFS (confirmed PD)[b]		
Median (95% CI) time (months)	N=49	22.1 (16.8-NA)
6-month PFS rate (95% CI)	N=49	75.8 (60.5-85.8)
12-month PFS rate (95% CI)	N=49	72.0 (55.4-83.3)
KM-estimated OS[c]		
Median (95% CI) time (months)	N=49	Not reached
6-month OS rate, % (95% CI)	N=49	89.7 (77.1-95.6)
12-month OS rate, % (95% CI)	N=49	87.1 (73.4-94.0)
24-month OS rate, % (95% CI)	N=49	83.8 (68.4-92.1)
High adherence with Ixa (80-100%), n (%)		
At 6 months post-baseline	N=32	31 (96.9%)
At 12 months post-baseline	N=19	19 (100.0%)
UK-weighted EQ-5D utility index score, median (IQR)		
At enrollment	N=45	0.73 (0.58-0.85)
At 6 months post-baseline	N=23	0.75 (0.69-1.00)
At 12 months post-baseline	N=10	0.88 (0.81-1.00)
EQ-VAS score, median (IQR)		
At enrollment	N=45	70.0 (60.0-80.0)
At 6 months post-baseline	N=24	70.0 (60.0-90.5)
At 12 months post-baseline	N=10	85.0 (70.0-95.0)
CTSQ Expectations of Therapy (ET) domain score, mean (SD)		
At enrollment	N=43	62.9 (17.9)
At 6 months post-baseline	N=24	66.4 (18.1)
At 12 months post-baseline	N=10	78.0 (13.4)
CTSQ Feelings about Side Effects (FSE) domain score, mean (SD)		
At enrollment	N=43	60.6 (19.3)
At 6 months post-baseline	N=24	66.4 (20.0)
At 12 months post-baseline	N=10	71.3 (15.4)
CTSQ Satisfaction With Therapy (SWT) domain score, mean (SD)		
At enrollment	N=43	73.3 (15.7)
At 6 months post-baseline	N=24	75.0 (15.7)
At 12 months post-baseline	N=10	82.5 (12.4)

[a]Confirmed response only; [b]Censoring rate: 67.3; [c]Censoring rate: 85.7%. Patients alive at end of follow-up period were censored on the date of last contact. Abbreviations: CI, confidence interval; CTSQ, Cancer Therapy Satisfaction Questionnaire; EQ-5D, EuroQol 5-dimensions; EQ-VAS, EuroQol Visual Analogue Scale; IQR, interquartile range; IRd, ixazomib, lenalidomide and dexamethasone; KM, Kaplan-Meier; N, number of patients with available data; n, number of patients with variable; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory multiple myeloma; SD, standard deviation.

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EFFICACY AND SAFETY OF ISATUXIMAB, CARFILZOMIB AND DEXAMETHASONE (ISAKD) IN MULTIPLE MYELOMA PATIENTS AT FIRST RELAPSE AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION AND LENALIDOMIDE MAINTENANCE: RESULTS FROM THE REAL-LIFE AENEID STUDY

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In the randomized, phase 3 IKEMA trial the triplet isatuximab, carfilzomib and dexamethasone (IsaKd) provided a superior clinical benefit over carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma (MM) after 1-3 prior treatments. In that study, however, the number of patients who had progressed after frontline lenalidomide was very low and their specific clinical outcome was not evaluable. The real-life, AENEID study (A rEtrospective, observatioNal, multicEnter study of Isatuximab, carfilzomib and Dexamethasone as second line treatment in multiple myeloma patients relapsed/refractory after an initial therapy including lenalidomide) aims to evaluate the efficacy and safety of IsaKd in this specific subset of patients, poorly represented in IKEMA trial. In this setting, the present analysis refers to 82 patients who received, from April 2022 to September 2024, at least one cycle of IsaKd, as second line treatment at first relapse after induction therapy (mainly bortezomib-thalidomide-dexamethasone), autologous stem-cell transplant (ASCT) and lenalidomide maintenance, outside of clinical trials. Median age at IsaKd initiation was 62 years (range 43-73). Median duration of lenalidomide maintenance was 20 months (range, 1–60). Sixty-seven patients (81.7%) were symptomatic and 15 (18.3%) showed biochemical relapse. At IsaKd start, 38 patients (46.3%) were in ISS stage I, 23 (28.1 %) in stage II, 12 (14.6 %) in stage III, while in 9 patients (11%) ISS was not reported. Cytogenetics was available for 50 patients (61%), thirteen of whom were classified as high risk (26%), considering the same criteria of IKEMA trial [presence of del(17p) or t(4;14), or t(14;16)]. Extramedullary-disease (EMD) was reported in 16 cases (19.5%). With a median follow-up of 12.9 months (range, 1-77), overall response rate, at least very-good partial response and median progression-free survival (PFS) (Figure 1A) of our real-world cohort were lower than in IKEMA study [79.3% *vs* 86.6%, 56.1% *vs* 72.6% and 24.4 *vs* 35.7 months, respectively]. This was likely due to the well-known poor prognostic weight of lenalidomide-refractoriness (len-R) developed by all our patients during maintenance and, possibly, to a quite relevant percentage of EMD (19.5%). Median overall survival (OS) (Figure 1B) was not reached, as in the pivotal trial, while 1-year OS probability was 85.1%. Regarding safety, infusion reactions occurred at first administration of isatuximab in 9 patients (10.9%), all grade 1-2 and promptly resolved. Hematological toxicity included grade 3/4 thrombocytopenia (30.5%), lymphocytopenia (19.5%), neutropenia (17.1%) and anemia (10.9%). Pneumonia (any grade) occurred in 13.4% of cases. Cardiac toxicity included grade 1-2 hypertension (13.4%). The OPTIMISMM and EMN011 trials (investigating pomalidomide and dexamethasone-based combinations with bortezomib or carfilzomib, respectively) are among the few ones to report the outcome of len-R patients after one line of therapy. Median PFS of patients treated with IsaKd in our analysis appeared better than in the randomized OPTIMISMM trial (24.4 *vs* 17.8 months, respectively) and similar to that reported in phase 2 EMN011 study (24.4 *vs* 26 months, respectively). Overall, our real-world data show that IsaKd may be a valuable option in the specific subset of len-R and anti-CD38 naïve MM patients, relapsed after a first line therapy including ASCT and maintenance.

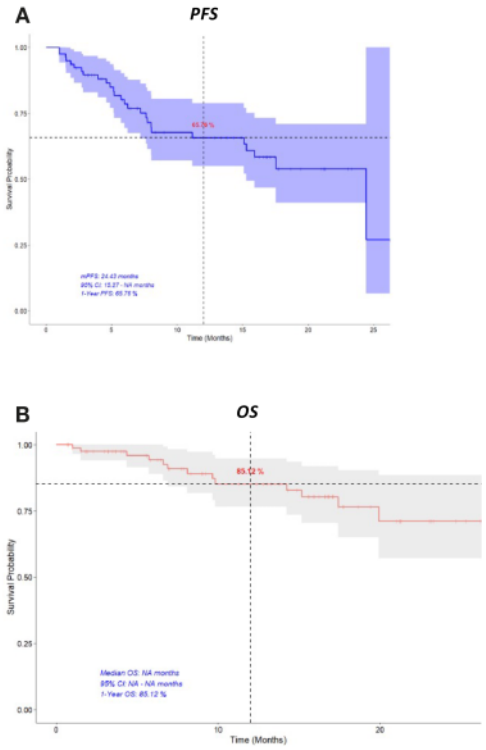

Figure 1.

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EVALUATION OF ATTRITION RATES IN REAL-LIFE SETTING: A SINGLE-CENTER SURVEY IN THE LAST 12 YEARS (2012-2024)

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Background. For multiple myeloma (MM), the proportions of patients reaching the subsequent line of therapy (LOT) decline gradually and real-world data describing the attrition rates of LOT in real-life in Italy are limited.

Methods. MM patients who had been hospitalized and received at

least one LOT from Jan- 2012 to Jan-2024 at AOU Policlinico Rodolico San Marco in Catania were retrospectively recruited. Demographic and clinical characteristics were retrieved by electronic records of an internal registry available since 2008. The Cox proportional hazards regression model was applied to analyze the risk factors of frontline treatment attrition.

Results. A total of 707 newly diagnosed MM were included in the survey, with 421 (59.5%) patients receiving only the first LOT. The combination of bortezomib, thalidomide with dexamethasone/prednisone was the most common frontline treatment before 2017, while daratumumab-based regimens constituted most frontline treatment in 2020 and beyond. The attrition rates from the first to the fourth LOT exhibited a gradual upward trend (46%, 27%, 14% and 5%, respectively in 2012-2017 versus 69%, 20%, 9% and 2% in 2018-2024). MM who underwent autologous stem cell transplantation (ASCT) and received lenalidomide-based maintenance showed lower attrition rates across all LOTs (range 12–16%) than MM without ASCT (range 13%–28%) in 2012-2017, but not in 2018-2024 where attrition rates were comparable among patients treated with ASCT+lena maintenance (range 2-16%) or front-line continuous therapy based on daratumumab and/or lenalidomide (range 3-20%). Median overall survival in the 2012-2017 cohort was 57.4%, significantly lower than 2018-2024 cohort (67.0%), mainly due to the wide use of daratumumab-based first line regimens, described by Del Fabro at the same conference. The multivariate Cox regression model revealed that ISS stage III (HR 2.17, p<0.001), aggressive clinical presentation with elevated LDH or extra-medullary disease (HR 3.15, p<0.001), comorbidities such as amyloidosis (HR 1.62, p=0.02) and any-grade infections in the first year (HR 3.62, p=0.001) were independent risk factors for MM patients attritted from the frontline treatment in 2018-2024 cohort.

Conclusions. In this study, the attrition rates were generally high and increased gradually across all LOTs. Nearly half of MM patients received only one LOT, and higher tumor burden and any-grade infections in the first year may be associated with fewer subsequent LOTs and reduced OS.

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CLINICAL OUTCOMES AND SAFETY OF DARATUMUMAB POMALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED IN AN ITALIAN REAL-LIFE MULTICENTER RETROSPECTIVE STUDY

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Multiple myeloma is a bone marrow cancer caused by the uncontrolled proliferation of plasma cells and characterized by an unpredictable clinical and laboratory course. This retrospective study examines the real-world efficacy and safety of Daratumumab (Dara) combined with pomalidomide (P) and dexamethasone (d) (DaraPd) as a salvage therapy for relapsed/refractory multiple myeloma (RRMM) patients (pts) outside of controlled clinical trials, in accordance to marketing approval. A total of 108 RRMM pts from 10 italian centers were enrolled in the study after receiving at least two cycle of DaraPd as salvage treatment between February 2023 and December 2024. Pts included in the study had experienced relapse after at least one prior lines of therapy, which included immunomodulatory drugs (IMiDs) and a proteasome inhibitors (PIs) or were double refractory. The treatment regimen consisted of Daratumumab s.c. (1800 mg) administered according to the recommended dosing schedule, Pomalidomide at 4 mg daily for 21 days of each 28-day cycle, and Dexamethasone 40 mg weekly.

Table 1. Clinical outcomes and safety of Daratumumab Pomalidomide and Dexamethasone in relapsed/refractory Multiple Myeloma patients treated in an italian real-life multicenter retrospective study.

Features at second line initiation	Total cohort
Median age, years (range)	68,5 (46-87)
Male, n (%)	44 (59.2%)
R-ISS II-III	92 (85,3%)
Glomerular filtration rate ≤40 ml/min, n (%)	10 (9.2%)
Glomerular filtration rate ≤60 ml/min, n (%)	35 (32.4%)
High genetic risk MM, n (%)	33 (30,6%)
Extramedullary disease, n (%)	8 (7,3%)
Bone's disease (osteolisis) n (%)	83 (76,8%)
Medullary infiltration > 50%, n (%)	12 (11%)
One prior line patients n (%)	44 (40,7%)
Primary refractory, n (%)	4 (3,6%)
Early relapse, n (%)	56 (51,9%)
Prior ASCT, n (%)	79 (73,1%)
Prior Lenalidomide therapy, n(%)	88 (81%)
Not exposed to PI n (%)	5 (4,5%)
Exposed to double PI n (%)	42 (39%)
Tetra-refractory (double PI and double IMIDs) n (%)	24 (22,2%)
DaraPD in, n (%):	
II line therapy	44 (40,7%)
III line therapy	59 (54,6%)
>III	5 (4,6%)
Type of first line therapy, n (%):	
DVTD	2 (1,8%)
VTD	60 (55,5%)
VRD, RD	6 (5,5%)
Other (VCD, PAD, VD, VMP, Trial..)	40 (37%)
Type of 2nd line therapy, n (%):	
KRD-KD	45 (41,6%)
RD	17 (15,7%)
Other (EloRD,XRD, Trial..)	46 (42,7%)
Overall response rate, n (%)	101 (93,5%)
Complete response or >, n (%)	13 (12,1%)
Very good partial response, n (%)	40 (37%)
Partial response, n (%)	55 (50,9%)
Time to best response, months, median (range)	3 (1-14)
Initial dose Pomalidomide 4 mg, n (%)	95 (87,9%)
Reduction dose Pomalidomide, n (%)	38 (35,1%)
Time to reduction dose Pomalid., months, median (range)	4 (1-5)
Hematological toxicity, n (%)	67 (63,8%)
Grading 1-3 (1-5), n (%)	47 (70,2%)
No-hematological toxicity, n (%)	24 (22,2%)
infective and pneumonia	23 (95,3%)

Responders were defined as pts who achieve at least a partial remission (PR). Of the 108 enrolled patients, 59.2% were males, median age 68,5 years and 14.7% classified as stage I disease according to R-ISS. The median number of prior therapies was 2 (1-4), with 51.9% of patients exhibiting refractory disease. Additonally, 73.1% of patients had under-

gone ASCT. Cytogenetic data from fluorescence in situ hybridation (FISH) analysis we available for 87.3% of patients, with 69.4% showing favorable cytogenetic profiles. Contrast, 30.6% classified as high-risk due to aberrations such as t(4;14), t(14;16), gain(1q21), t(11;14), and del(17p). As of December 2024, all pts were evaluable for response. The median number of DaraPd cycles administered was 13 (range 2–23). The overall response rate (ORR) was 93.5% with 67% achieving a complete response or better. After a median follow-up of 21.5 months (range 5-23), disease progression or death occurred in 7 pts, resulting in a median PFS of 13.3 months and a median PFS, in the pts in first relpased, of 22.1 months. The expected PFS in pts with first relapse, not frankly refractories, without high cytogenetic and functional risk, was 26.4 months. Univariable analyses indicated a shorter PFS for patients with elevated LDH (HR=1.8; p=0.003), high-risk cytogenetic abnormalities (HR=2.53; p=0.001), refractory disease (HR=1.53; p=0.03), R-ISS stage III (HR=2.47; p=0.0001). Cox multivariable analysis identified high-risk cytogenetic abnormalities (HR=2.84 p=0.0001) and elevated LDH (HR=2.36; p=0.003) as independent prognostic factors for PFS. The cumulative 2-year-overall survival (OS) probability rate was 62.9%. with significative differences observed in Cox multivariate analysis for pts with high-risk high-risk cytogenetic abnormalities (HR=2.82; p=0.013), elevated LDH (HR=3.35; p=0.002) and creatinine clearance <60 ml/min (HR=2.58; p=0.006). The safety profile was acceptable, with 63,8% incidence of hematological adverse events (neutropenia and thrombocytopenia), wich were generally grade 1-3 (70.2%), and without an increase in infection rate. In conclusion, this comprehensive real-world study confirms the safety and efficacy of DaraPd as a viable salvage therapy for patients with RRMM who have undergone at least one treatment regimens and in the future, by optimizing the efficacy of the therapeutic algorithm, it will increase PFS.

P55

OUTCOMES OF SECOND-LINE THERAPY IN FUNCTIONAL HIGH-RISK MULTIPLE MYELOMA PATIENTS REFRACTORY TO QUADRUPLET INDUCTION: A MULTI-CENTER REAL-LIFE STUDY

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Introduction. Functional high risk multiple myeloma (FRMM), characterized by refractoriness or early relapse after first line induction therapy, is a critical unmet clinical need due to poor outcomes and limited survival of these subjects. To date, daratumumab-based quadruplet regimens are widely used as induction treatment for transplant eligible MM patients; however, incidence and characteristics of FRMM after daratumumab-based regiments are still unexplored, as well as its clinical management with second-line therapies. In this multi-center real-life retrospective study, we investigated clinical characteristics and outcomes of second-line therapies in FRMM patients previously treated with daratumumab-based quadruplets.

Methods. A total of 62 FRMM consecutive patients across 13 Italian Hematology Units were enrolled, and clinical characteristics are summarized in Figure 1A (median follow-up, 14 months; range, 11.6-16.3 months). Patients initiated second-line therapy outside clinical trials for refractory or early relapsed disease within 18 months of daratumumab-bortezomib-thalidomide-dexamethasone (Dara-VTD) induction or 12 months after frontline autologous stem cell transplantation (ASCT). High genetic risk MM was defined per IMWG criteria, including chromosome 1q and 1p abnormalities.

A

Features at second line initiation	Total cohort N = 62
Median age, years (range)	60 (40-71)
Male, n (%)	34 (55)
ECOG scale, n (%)	
0-1	49 (79)
≥ 2	11 (14)
Glomerular filtration rate ≤40 ml/min, n (%)	11 (18)
High genetic risk MM, n (%)	28 (45)
Extramedullary disease, n (%)	17 (27)
Dara-VTD cycles before 2nd line, n (%)	
1-2	5 (8)
3-4	41 (67)
5-6	16 (25)
Primary refractory , n (%)	47 (76)
Early relapse, n (%)	15 (24)
Prior ASCT, n (%)	13 (21)
Prior Lenalidomide maintenance, n(%)	4 (6)
Type of 2nd line therapy, n (%)	
KRD	53 (86)
Chemotherapy protocols	5 (8)
Other	4 (6)
Overall response rate, n (%)	38 (61)
Complete response, n (%)	8 (13)
Very good partial response, n (%)	18 (29)
Partial response, n (%)	12 (19)
Overall progressions after 2nd line therapy, n (%)	24 (39)
Progression free survival, median, months (range)	NR (1-27)
One-year PFS, %	54
Deaths, n (%)	15 (24)
Overall survival, median, months (range)	NR (2-28)
One-year OS, %	72
Time to best response, months, median (range)	2 (1-24)
Consolidation with ASCT, n (%)	16 (26)

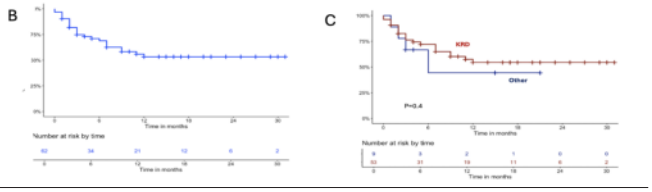

Figure 1.

Results. Our cohort exhibited several high-risk features, with 45% of patients with high genetic risk and 27% with extramedullary disease (EMD). Advanced disease stages were prevalent, with 63% and 33% classified as R-ISS stages II and III, respectively. Carfilzomib-lenalidomide-dexamethasone (KRD) was predominantly employed as second-line treatment (86% of patients), while chemotherapy-based regimens, such as D-PACE or PAD regimens, accounted for 8% of cases. The overall response rate (ORR) was 61%, with 42% of very good partial response (VGPR) or better. Median progression-free survival (PFS) was not reached (NR; Figure 1B) and the estimated 12-month PFS was 54%. Similarly, median overall survival (OS) was NR, with a 12-month OS of 72%. Finally, KRD could improve clinical outcomes compared to other protocols (median PFS, NR *vs* 6 months; p=0.4; Figure 1C); however, longer follow-up is needed to confirm this preliminary result. At the time of data cut, 34% of patients were still on second-line therapy, and 26% proceeded to consolidation ASCT.

Conclusion. In conclusion, second-line management of FRMM following anti-CD38-based induction is challenging and variable across centers, because of the lack of international treatment algorithms. Carfilzomib-based regimens, such as KRD, demonstrated a certain activity, especially in lenalidomide-naïve patients, but outcomes remain suboptimal for this ultra-high-risk population. In contrast to the phase III ASPIRE trial, where KRD achieved a median PFS of 26.3 months in a conventional MM population, FRMM patients continue to exhibit a dismal prognosis with currently available therapies. Therefore, integrating next-generation therapies, such as bispecific T-cell engagers (BiTEs) or CAR-T cells, into earlier treatment lines might be of great clinical benefit in these high-risk subjects. Larger perspective trials are needed to better define FRMM management.

P56

SUPPORTING TREATMENT DECISION-MAKING FOR LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA PATIENTS POST-DRD IN ITALY: A MULTI-CRITERIA DECISION FRAMEWORK

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Background. Multiple Myeloma (MM) is a rare haematological malignancy affecting B lymphocyte plasma cells and is the second most commonly diagnosed blood cancer in Europe. Despite significant therapeutic advancements, a substantial unmet medical need exists for MM patients not eligible for autologous stem cell transplantation (NSCT) who relapse after first-line therapy with the combination of daratumumab, lenalidomide and dexamethasone (DRd). According to the EHA-ESMO guidelines, three therapeutic options currently approved in Europe are recommended for lenalidomide-refractory patients: carfilzomib and dexamethasone (Kd), pomalidomide, bortezomib, and dexamethasone (PVd) and selinexor, bortezomib, and dexamethasone (SVd). This analysis aimed to identify key criteria in treatment choice and assess the value of the three therapeutic options from an Italian multi-stakeholder perspective.

Methods. Following ISPOR good practices, a multiple-criteria decision analysis (MCDA) framework using the Measuring Attractiveness by a Categorical-Based Evaluation Technique (MACBETH) method was applied. Preferences were elicited from 24 Italian stakeholders, including haematologists, methodologists, decision-makers and a patient representative. Decision criteria were identified through targeted literature reviews and a multi-stakeholder workshop and finalized with a pragmatic literature review to assess data availability for each alternative. Based on literature and public information, a value was associated with each alternative for each criterion (*i.e.*, performance matrix). Stakeholders were asked to weigh the importance of each criterion and sub-criterion and to score different performance levels through an online structured questionnaire. Results from the questionnaires were analysed and discussed during a final multi-stakeholder workshop.

Results. The final MCDA framework comprised five main criteria: acquisition cost, efficacy, organizational impact, route of administration and safety. Within the safety criterion, six sub-criteria related to grade 3+ adverse events were considered: peripheral neuropathy, diarrhoea, nausea, fatigue, anaemia, and thrombocytopenia. Efficacy emerged as the most critical criterion, with a median weight of 38.1%. Safety was the second most important criterion (26.8% median weight), with peripheral neuropathy being the most relevant sub-criterion (34.9%). Based on elicited preferences, SVd was ranked as the most valuable therapy with a global score of 72, followed by PVd (44) and Kd (26), on account of its clinical efficacy. No significant differences in preferences were observed between clinicians and non-clinicians. Sensitivity analyses confirmed the robustness of these results, showing consistent rankings across different stakeholder groups and scenarios.

Conclusions. This analysis provides valuable insights into the post-DRd treatment options for MM, supporting decision-making from an Italian multi-stakeholder perspective. SVd emerged as the preferred alternative for NSCT patients who relapse after first-line therapy with DRd. These findings highlight the need for continued research and development of therapeutic options to address the unmet needs of MM patients, particularly those who are refractory to lenalidomide and have limited treatment options.

P57

FROM SPAIN TO THE WORLD: EXPERIENCE WITH TALQUETAMAB AS MONOTHERAPY IN RRMM PATIENTS OUTSIDE CLINICAL TRIALS, THE BITAL STUDY

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Introduction. Pre-Approval Access programs (PAA) facilitate patient (pts) access to certain drugs. Talquetamab (TAL), a GPRC5D-targeted bispecific antibody, was granted in November 2022 by Spanish

health authorities for the treatment of adult pts with relapsed refractory multiple myeloma (RRMM), triple-class exposed (TCE), and after all available treatment options have been exhausted. Between November 2022 and 2024, 215 pts from 87 academic and non-academic sites initiated treatment within PAA. We present the characteristics of the first pts included in the BiTAL study, which aims to collect the experience of pts treated within the PAA for TAL in Spain.

Materials and Methods. This is an ongoing retrospective non-interventional multicenter study. Data collection period was from September to October 2024. Eligible pts had initiated treatment with TAL monotherapy, at least one dose, outside clinical trials through PAA in Spain. Pts were aged > 18 years; diagnosed with RRMM TCE and received the first dose of TAL in monotherapy at least 30 days before study initiation.

Results. 24 pts from 17 sites were evaluable at data cut-off. Pts characteristics are described in Table 1. 50% of pts presented with clinically significant comorbidities including cardiovascular (29.2%), diabetes (16.7%), renal insufficiency and history of severe infections (12.5% each). The incidence of high-risk cytogenetics and extramedullary disease was 12.5% and 4.2%, respectively. The median number of previous lines of therapy was 5. The percentages of pts having received 3, 4, and ≥5 prior lines were 4.2%, 25%, and 41.7%, respectively. 79.2% of pts were triple-class exposed and 37.5% pts had been previously treated with a BCMA-targeted therapy. Triple-class refractory disease was present in 62.5% of the pts and 29.2% had penta-drug refractory disease.

Conclusions. The BiTAL study has the potential to present the longest cohort of TAL-treated patients with RRMM TCE outside clinical trials. Pts included to date exhibited diverse demographic profiles and comorbidities, reflecting high heterogeneity in real-world settings. Most pts had undergone multiple prior lines of therapy, reflecting the importance of individual pts profiles when tailoring therapeutic strategies.

Table 1. Patients' demographic and clinical characteristics at inclusion.

	N = 24
Age (years), median (IQR)	65.5 (57.0-73.8) *
Age (years) categorization, n (%)	
<65	9 (37.5)
65-75	7 (29.2)
>75	4 (16.7)
NA	4 (16.7)
Sex, n (%)	
Female	9 (37.5)
Time from diagnosis (years), median (IQR)	7.9 (4.0-8.9) ^
ECOG, n (%)	
0-1	15 (62.5)
≥2	4 (16.7)
NA	5 (20.8)
Creatinine clearance (ml/min), n (%)	
> 60	17 (70.8)
30-60	1 (4.2)
NA	6 (25.0)
Charlson Index, n (%)	
0-1	9 (37.5)
≥ 2	10 (41.7)
NA	5 (20.8)
Type of myeloma (heavy chain), n (%)	
IgG	8 (33.3)
No IgG (IgA, IgD, IgE, IgM)	7 (29.2)
NA	9 (37.5)
Plasmacytoma type, n (%)	
Bone-related	6 (25.0)
Extramedullary	3 (12.5)
Cytogenetic abnormality risk, n (%)	
Standard	4 (16.7)
High	1 (4.2)
t(4;14)	1 (4.2)
t(14;16)	0
del(17p)	1 (4.2)
ISS, n (%)	
I (Mß2 < 3,5 mg/l and albumin = 3,5 g/dl)	5 (20.8)
II (Mß2 < 3,5 mg/l and albumin < 3,5 g/dl or Mß2 < 3,5 mg/l and albumin <5,5 g/dl)	8 (33.3)
III (Mß2 = 5,5 mg/l)	4 (16.7)
NA	7 (29.2)
Number of prior lines to talquetamab, median (IQR)	5.0 (4.0-6.0) "

IQR, interquartile range; NA, data not available; ECOG, Eastern Cooperative Oncology Group; ml, milliliters; min, minutes; Ig, immunoglobulin; ISS, International Staging System; Mß2, Beta-2-microglobuline; * N=20; ^ N=8; " N=19.

P58

PREVALENCE AND PROGNOSTIC SIGNIFICANCE OF FUNCTIONAL HIGH RISK MULTIPLE MYELOMA IN TRANSPLANT ELIGIBLE PATIENTS: A REAL LIFE EXPERIENCE

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Background. In the last 2 decades, the improvement of multiple myeloma (MM) risk stratification and the introduction of novel therapies dramatically changed prognosis, being able to reach high rates of deep responses, and doubling overall survival (OS). Despite this, some patients show early relapse, even if risk at diagnosis is standard, highlighting the need of a dynamic assessment.

Methods. This was a retrospective, single center study that included 84 patients who underwent first-line treatment followed by autologous stem cell transplantation (ASCT) from 2016 to 2020. Our aims was to observe the prevalence of "functional high risk MM" (early relapse, ER), defined as relapse within 18 months from ASCT and to compare baseline characteristics and outcome of ER patients with late relapse/non relapse group (NER).

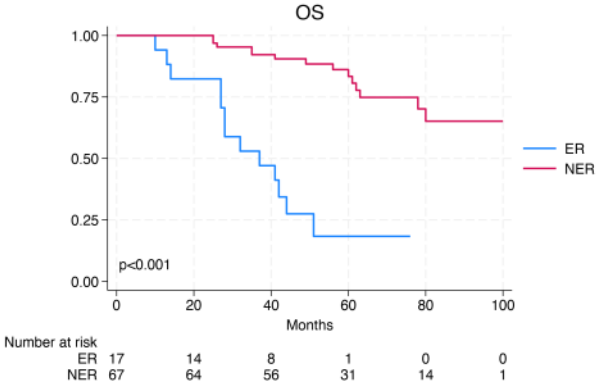

Figure 1.

Results. At a median follow-up of 53.5 months after ASCT, 17/84 patients (20%) experienced early ER, 27 (32%) relapsed later and 40 (48%) had no disease recurrence (48%). ER group had a trend to older age (68 *vs* 62 years, p=.058). No significant differences were detected regarding laboratory parameters at diagnosis (LDH, anemia, creatinine, calcemia), staging according to ISS, R-ISS and R2-ISS and incidence of "double and triple hits". The type of induction therapy before ASCT and the salvage treatment after first relapse of the ER group were comparable to the NER population. In terms of response to induction therapy pre-ASCT and 3 months post-transplant, the rate of responses < VGPR was similar between the 2 groups. As expected, PFS1 of ER patients is 0% compared to 78% for NER patients at 3 years and dropped to 53.5% (CI 38.9-66.0) at 5 years in NER group. The PFS2 of ER patients is significantly reduced compared to NER: ER 23.5% (CI 7.3-44.9) *vs* NER 79.3% (CI 59.6-90.1) at 3 years; ER 8.8% (CI 0.7-30.3) *vs* NER 52.2% (CI 31.7-69.1) at 5 years (p<0.001). The OS of ER patients is significantly worse than NER patients: ER 52.9% (CI 27.6-73.0) *vs* NER 92.2% (CI 82.2-96.7) at 3 years and ER 18.3% (CI 3.6-41.8) *vs* NER 83.4% (CI 69.9-91.2) at 5 years (p<0.001). (Figure 1.) In univariate analysis older age is associated with a significant reduction in PFS1 and OS (p=0.03 and p=0.05, respectively). Patients with late relapse have a sig-

nificant prolongation of PFS2 and OS (p<0.001 and p<0.001, respectively). Patients with "double or triple hit myeloma" have a reduction in PFS2 (p=0.08). Achieving a VGPR (compared to CR) in one of the phases of sequential therapy significantly reduces PFS1 (p=0.03) and OS (p=0.05)

Conclusions. In our study ER patients represented one fifth of the transplant-eligible patients and cannot be recognized at diagnosis on the basis of staging and clinical and cytogenetic features. Response to salvage treatments and OS were extremely poorer in comparison with NER patients. Reaching CR remains a significant favourable prognostic factor for both ER and NER patients. ER patients remain an "unmet clinical need" requiring new treatments and new technologies in risk assessment at diagnosis and in response evaluation after therapy.

P59

REAL-WORLD BISPECIFIC ANTIBODY THERAPY FOR MULTIPLE MYELOMA: INSIGHTS FROM DUTCH NATIONWIDE REGISTRY

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Background. Bispecific antibodies (BsAbs) are approved for treating relapsed or refractory multiple myeloma (RRMM) after three or more prior lines of therapy (LOT), if triple class exposed (TCE). Real-world data are crucial to assess effectiveness and safety outside clinical trials.

Methods. This nationwide multicenter observational study collects real-world data on teclistamab (TEC; anti-BCMA) and talquetamab (TAL; anti-GPRC5D) for RRMM patients in a compassionate use program. It focuses on infection occurrence, preventive measures, treatment schedule adjustments, and quality of life (QoL) data collected at multiple intervals using EORTC QLQ-C30 and QLQ-MY20 questionnaires.

Results. As of October 8th, 2024, 259 RRMM patients received TEC and 22 received TAL across 25 hospitals in the Netherlands. Currently, 131 patients are included in the registry. Patients had 2 to 12 prior LOT (median 4), all were TCE, and 66% were triple class refractory. Four patients had prior BCMA CAR-T treatment, and twelve were treated sequentially with TEC and TAL. Seven patients did not start BsAb therapy due to rapid disease progression. Analysis of 110 TEC-treated patients showed an ORR of 62%, with 55% at least VGPR, at a median follow-up of 6.7 months. Four RRMM patients with secondary AL amyloidosis achieved rapid CR, with 3 patients showing an ongoing response at 5 months of median follow-up. Seven patients previously treated with BCMA CAR-T or TAL had an 71% ORR, all at least VGPR, at a median follow-up of 14 months. CRS was reported in 54% of patients, mostly grade 1-2, however 2% of patients experienced CRS grade 3 or higher. 25% of patients received tocilizumab. Six percent of patients experienced ICANS, all grade 1-2. Inflammatory pain flare occurred in 14% of patients. Infections occurred in 62% of patients, 33% of patients were hospitalized due to infections. Eighty percent of patients were treated with prophylactic IVIG. Some patients did not respond to TEC treatment and were treated for a brief duration, and therefore did not receive IVIG. After six months of therapy 98% of patients received IVIG prophylaxis. Prophylactic antibiotics were given to 95% of patients. All patients started treatment with a standard step-up dosing schedule (in hospital), followed by weekly administrations at the outpatient clinic. At 6 months follow-up TEC dosing intervals were extended to biweekly in 47%, four-weekly in 13%, and six-weekly in 2% of patients. Therapy was discontinued in 58% of patients due to progressive disease (45%), infections (8%), and toxicity (5%). Seven patients treated with TAL had an ORR of 71%, with 14% at least VGPR, at a median follow-up of 14 months.

Fifty percent of patients in the registry fail to meet the inclusion and exclusion criteria for the MajesTEC-1 and MonumenTAL-1 clinical trials, highlighting the need for studying real-world patient populations to ensure broader applicability and effectiveness of the treatments in clinical settings. QoL data are limited but expanding. Updated efficacy, safety data, long-term outcomes and further analysis on dosing schedules will be presented at the meeting.

Conclusion. This nationwide registry of BsAb treatment in RRMM showed similar efficacy to clinical trials. Infectious complications were common, but hospitalization rates were lower, likely due to prophylactic measures and extended dosing intervals. QoL data collection will reveal the impact of these therapies on patients' lives.

Special conditions

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COMPARISON OF ISATUXIMAB-POMALIDOMIDE-DEXAMETHASONE VERSUS ELOTUZUMAB-POMALIDOMIDE-DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS: A TARGET TRIAL EMULATION USING REAL-WORLD DATA

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The lack of randomized comparisons between isatuximab-pomalidomide-dexamethasone (IsaPd) and elotuzumab-pomalidomide-dexamethasone (EloPd) in relapsed/refractory multiple myeloma (RRMM) poses a challenge. This study applied target trial emulation (TTE) to real-world data (RWD) to compare regimens' efficacy and safety. In the original population, the overall response rate (ORR) was 66.8%, with IsaPd showing a significantly lower probability of non-response compared to EloPd (23.1% versus 44.6%; OR=0.37; p<0.001). However, after the inverse probability of treatment weighting (IPTW) adjustment, the difference in ORR was no longer significant, with ISS stage II, no prior Daratumumab exposure, and high-risk FISH profiles independently associated with non-response. In unadjusted analysis, IsaPd demonstrated a significant progression-free survival (PFS) benefit (17.5 *vs* 7.9 months for EloPd; HR=0.55, p=0.001), but this difference became non-significant after IPTW adjustment. Similarly, overall survival (OS) was significantly better with IsaPd in unadjusted analysis (HR=0.57, p=0.007), but the difference was not significant after adjustment. Safety analysis revealed a statistically significant higher rate of infections associated with IsaPd, even after adjustment. This study underscores the TTE utility in addressing gaps between RWD and clinical trial data to enable rigorous comparisons of treatment regimens. Nevertheless, CART-cell and bispecific antibodies are reshaping the treatment landscape for this challenging patient population.

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EFFICACY AND TOLERBILITY OF MELFLUFEN IN RELAPSED MULTIPLE MYELOMA, A SINGLE CENTER REAL LIFE EXPERIENCE

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Melphalan flufenamide (melflufen), a first-in-class alkylating peptide-drug conjugate, is approved in Europe in combination with dexamethasone for triple-class refractory relapsed/refractory multiple myeloma (RRMM) patients with ≥3 prior lines of therapy and without prior autologous stem cell transplantation (ASCT) or with a time to progression at least 3 years from ASCT. We report the outcomes of 8 patients treated at a single center. Our cohort received a median of 3.5 (2-6) prior lines of therapy before melflufen. Median age was 68.5 years (range 56-81), 3 patients (37.5%) were ≥70 years old, four patients had an extramedullary (EMD) disease (two intracranial, one hepatic, one paraosseus), one had a plasmacellular leukemia, none of the patients had renal insufficiency. All patients were triple-class refractory RRMM patients, seven (87.5%) were exposed to novel proteasome inhibitors, eight (100%) were exposed to lenalidomide, seven (87.5%) to pomalidomide, eight (100%) to anti-CD38 monoclonal antibodies, two patients were previously treated with Elotuzumab, two patients received belantamab, one was treated with Talquetamab. Autologous transplantation was used prior to melflufen in three patients at least 4 years before this treatment. Melflufen treatment was initiated at a median of 76.5 months from diagnosis (range 13-112). Patients received melflufen in combination with dexamethasone, one patients received additional radiotherapy. All patients received the full melflufen dose at first cycle. Major side effects were hematologic toxicities, mainly anemia ≥G3 (2 patients), thrombocytopenia ≥G3 (3 patients) and neutropenia (≥G3, 2 patients) that were clinically manageable with appropriate dose delays, dose reductions, and supportive care with growth factors and transfusions. In particular, dose reduction (50%) was applied in 3 patients. One patient needed a temporary therapy delay (about two months) for hematological toxicity. The overall response rate (ORR) was 37.5% (3 patients achieved PR). Among the patients that achieved PR two had EMD (intracranial and paraosseous) and were previous exposed to 3 LOT, one had plasmacellular leukemia and was exposed to 2 LOT. One patient achieved MR, two patients reached SD, the remaining two patients progressed and received further lines of therapy (one was treated with DCEP polichemotherapy followed by selinexor-bortezomib and dexamethasone regimen; the other was treated with isatuximab pomalidomide and dexamethasone as bridge to CAR-T cell therapy). One patient died of pneumonia. Three patients discontinued therapy for progression (2 patients) or toxicity. Median OS was not reached, predicted OS at 8 months was 87%. Overall, the safety profile of melflufen plus dexamethasone is generally comparable to that of other doublet combinations in patients with heavily pretreated relapsed/refractory multiple myeloma. Our little cohort resembles in real life the results of the HORIZON clinical trial that included heavily pretreated RRMM patients demonstrating that the melflufen plus dexamethasone doublet could be beneficial for RRMM patients with manageable toxicity.

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REAL-WORLD ANALYSIS OF TECLISTAMAB TREATMENT FOR RELAPSED REFRACTORY MULTIPLE MYELOMA IN TWO BELGIAN UNIVERSITY HOSPITALS

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Introduction. T-cell redirection therapies, including bispecific antibodies and CAR-T cells, are transforming the treatment landscape of relapsed/refractory multiple myeloma (RRMM), offering remarkable and durable responses. Teclistamab (Tec) is the first BCMA × CD3 bispecific antibody approved for RRMM treatment, based on the MajesTEC-1 phase 1/2 trial. Recently introduced in Belgium, we report on our real-world experience.

Methods. We conducted a retrospective analysis to assess the efficacy and tolerability of Tec in 36 patients treated at two Belgian academic centers, comparing real-world outcomes with those from clinical trials. Tec was administered weekly at 1.5 mg/kg after two step-up doses (0.06 and 0.3 mg/kg), following standard guidelines. High-risk (HR) cytogenetics were defined by t(4;14), t(14;16), and/or del(17p). Responses were evaluated according to IMWG 2016 criteria, with survival analyses performed using the Kaplan-Meier method. Adverse events (AEs) were graded per CTCAE v5.0, and CRS/ICANS were graded per ASTCT criteria.

Results. From December 12, 2022, to October 10, 2024, 36 patients received at least one dose of Tec. The median age was 67 years (range: 54–85), with 56% female patients. High-risk cytogenetics were observed in 36%, ISS stage III in 30%, circulating plasma cells in 33%, and extramedullary disease (EMD) in 36%. ECOG performance status was 1–2 in 80% of patients. Patients had received a median of 3 prior lines of therapy (LOT) (range: 2-11); 53% had undergone autologous stem cell transplantation. All were triple-class exposed; 50% were penta-exposed, and 44% were penta-refractory. All patients were refractory to their last LOT, with no prior exposure to BCMA-directed therapies. At a median follow-up of 10.7 months (range: 2-25), the overall response rate (ORR) was 89%, with 76% achieving at least a very good partial response (VGPR). The median time to first and best response was 34 and 81 days, respectively. Median progression-free survival (PFS) was 24.1 months, but only 4.3 months for patients with EMD. At the time of analysis, 10 patients (28%) had died, predominantly due to progressive disease. Median overall survival (OS) was not reached. All patients experienced at least one AE, with grade ≥3 events in 77%. CRS occurred in 53% of patients (no grade ≥3), all during step-up dosing in cycle 1. ICANS was observed in 5 patients (16%), with grade 3 in 1 case. Cytopenias were common: anemia (100%/36% grade ≥3), neutropenia (74%/47.1%), thrombocytopenia (69%/27.7%), and lymphopenia (80%/69%). Infectious episodes occurred in 22 patients (28%), with grade ≥3 infections in 50%. Immunoglobulin substitution was administered to 92% of patients.

Conclusions. Our real-world data demonstrate that teclistamab achieves comparable efficacy and safety outcomes to those reported in pivotal trials and other real-world studies. The toxicity profile was consistent with previous reports. These findings also underscore the urgent need for novel strategies to improve outcomes in patients with EMD

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REAL-LIFE DATA ON SAFETY AND EFFICACY OF AUTOLOGOUS STEM CELL TRANSPLATATION IN ELDERLY PATIENTS WITH MULTIPLE MYELOMA

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Introduction and Aim. Multiple myeloma (MM) is a disease characterized by the proliferation of monoclonal plasma cells in the bone marrow, leading to clinical symptoms. Among the treatment options, autologous stem cell transplantation (ASCT) plays a significant role. Although there is no strict age limit for ASCT, its applicability in patients over 65 years of age is debated. The aim of this study is to examine the impact of age on the outcomes of autologous stem cell transplantation in MM patients aged above and below 60, as well as its effect on survival analyses.

Materials and Methods. The study includes 361 MM patients diagnosed according to the criteria of the International Myeloma Working Group (IMWG) and who underwent autologous stem cell transplantation at Ankara University Faculty of Medicine, Department of Hematology, between January 2012 and December 2023. Statistical analyses were performed using the SPSS program.

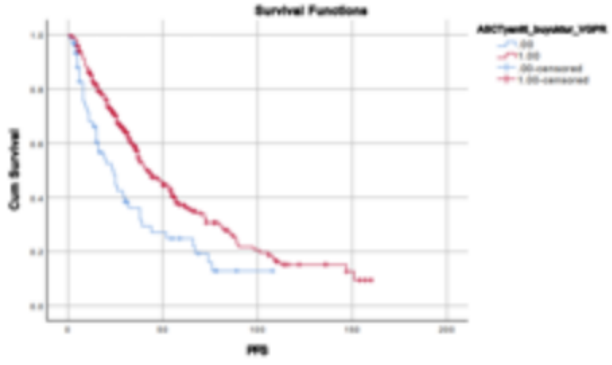

Figure 1. Relationship between PFS (months) and post-transplant response ≥ VGPR and <VGPR.

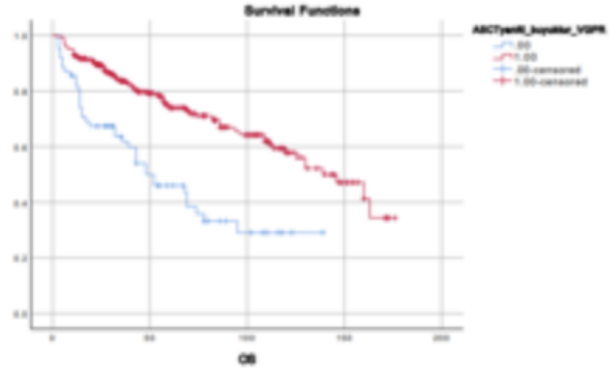

Figure 2. Relationship between OS (months) and response of ≥VGPR and <VGPR at 100th day after transplantation.

Results. There were no significant differences between age groups in terms of R-ISS distributions, extramedullary involvement, high-risk cytogenetic features, the number of transplanted CD34+ cells, transplant response distributions, overall survival (OS), progression-free survival (PFS), and R-ISS staging ($p>0.05$). However, responses at day 100 post-transplantation had a significant impact on OS and PFS, with patients achieving CR or VGPR showing longer OS and PFS ($p<0.001$). No significant difference was found between age groups. The 100-day response post-transplant was significantly associated with OS and PFS, but there was no age-related difference.

Conclusion. In comparisons between patients aged under and over 60, no statistically significant difference was found in terms of overall survival (OS) and progression-free survival (PFS). This indicates that age does not negatively affect the success of autologous stem cell transplantation (ASCT). Additionally, neutrophil and platelet engraftment times did not differ based on age, suggesting that engraftment success is not age-dependent. However, the post-transplant response, especially achieving complete response (CR) or very good partial response (VGPR), played a crucial role in both overall and progression-free survival, emerging as key factors in determining treatment success.

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DEXAMETHASONE, CYCLOPHOSPHAMIDE, ETOPOSIDE, AND CISPLATIN (DCEP) AS A SALVAGE OPTION IN THE ERA OF NOVEL AGENTS: A SINGLE CENTER REAL LIFE EXPERIENCE

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Multiple myeloma (MM) still remains an incurable disease and one challenge is how to manage pts that have failed monoclonal antibodies, immunomodulatory drugs and proteasome inhibitors. Moreover, novel therapies with CAR-T or bispecific antibodies are restricted to fit pts with adequate bone marrow reserves and adequate hepatic, renal and cardiac function. Polichemotherapy including dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) is one of the salvage options that could be employed in pts with R/R disease, and that may bridge them to other novel therapies. Here we describe a single-center retrospective analysis to assess the role of DCEP chemotherapy in R/R MM pts. Between 2012 and 2025, 59 R/R MM pts received DCEP regimen: 8 (13.5%) after one line of therapy (LOT), 15 (25%) after two LOT, 28 (48%) after three LOT and the remaining (8 patients, 13.5%) after more than 4 LOT. On the basis of the year when a patient was exposed to DCEP therapy, patients were divided in three groups: patients treated before 2016 (group A, 23 pt), patients treated from 2017 to 2021 (group B, 24 pt) and patients treated from 2022 to present (group C, 12 pt). The division into groups corresponds to the European authorization for the use of new IMIDs and monoclonal antibodies (group B), and after approval of bispecific antibodies and CAR-T cell therapies (group C). The median age at DCEP was 69 years, and DCEP treatment was initiated at a median of 59 months from diagnosis (range 3-300). Among group A, six pts received just one previous LOT, two pts two LOT, twelve pts three and three pts four or more LOT; among group B 2 pts received one LOT, nine pts two LOT, ten pts three LOT and three pts more than four LOT; among group C, three pts received 2 LOT, three pts received 3 LOT, six pts received 6 LOT before DCEP. After 4-6 DCEP cycles

(median number of cycles 3, range 1-6), ORR (≥ PR) was 44%, 22 pts (37%) achieved PR, 4 patients (7%) VGPR, 1 patient (1.5%) CR. After DCEP, 31 patients received one further line of therapy (4 pt of group A, 7 of group B, 5 of group C), 8 pts received two LOT (5 group A, 2 group B, 1 group C) 8 three LOT or more (3 group A, 3 group B, 2 group C). After a median follow-up of 6 months, 12 patients (22%) died due to progressive disease: 5 (9%) in group A, 5 (9%) in group B, 2 (4%) in group C. No treatment-related deaths were registered. Median PFS was 3 months (4 months for group A, 3 months group B, 3 months group C); median OS was 6 months (6 months group A, 5 months group B, 11 months group C, Figure 1). There was no significant difference in PFS or OS among the different groups. Infusional regimen was well tolerated with no life-threatening adverse events. Non hematological side effects mainly included pneumonia (14 pt ≥G3, 24%). The majority of patients developed ≥Grade 3 haematological toxicity during treatment; 46 pt had ≥G3 neutropenia (79%), 38 pt had ≥G3 thrombocytopenia (65%), 38 patients had ≥G3 anemia (65%). Toxicities were managed with antibiotic therapy, antiviral therapy, transfusions, and growth factors for white blood cells and red blood cells. This is the largest dataset of MM patients treated with DCEP regimen reported to date, and confirms that even with current novel therapies an ancient infusional well tolerated regimen could retain a role in patients with R/R disease and could be used as a bridge to novel therapeutic options.

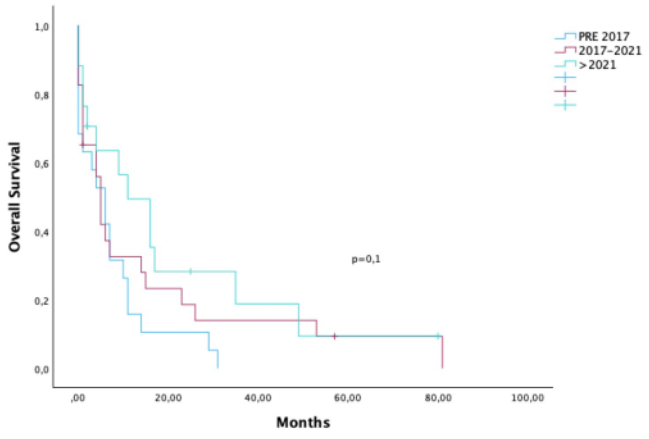

Figure 1.

P65

IS IT TIME TO FIGHT MULTI-REFRACTORINESS IN PATIENTS WITH FIRST RELAPSE IN MULTIPLE MYELOMA IN ITALY?

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First-line Multiple Myeloma (MM) therapy is rapidly evolving, more and more including anti-CD38 monoclonal antibodies as daratumumab (dara) in association with lenalidomide (R) and/or proteasome inhibitors so, prospectively, most patients (pts) will be exposed/refractory to many drugs with limited therapeutic options at relapse. Nevertheless, the burden of multi-refractory pts depends on the time of therapeutic regimens approval by national regulatory agencies, on the time to progression of the various therapies as well as on attrition rate. Consequently, multi-refractory patient burden will not be the same in different countries, being for example very different in Italy and USA for the abovementioned reasons. The aim of this study is to recognize the current burden of MM patients who are refractory now or may become refractory to drugs used in first-line therapy in Italy, analysing our single tertiary centre MM population. We would like to define a current and a near future refractoriness scenario in a real-life MM population. From 2010 to 2024, we treated 476 patients among whom 324 relapsed and 152 did not. In the 324 relapsed pts median age was 71 years (range 30-93), 84 patients (25%) had PS ≥ 2, 110 patients (34%) were high-risk cytogenetic and 255 (79%) were intermediate-high risk R-ISS. One hundred nine pts (33.5%) were transplant eligible and 137 pts (42%) were enrolled in clinical trials. Moreover, 159 (49%) received frontline R based continuous (cont) therapy resulting R-refractory (ref) at relapse, 6 (2%) dara-R based cont therapies resulting double-refractory, 4 (1%) receiving dara based cont ones resulting dara-refractory and 155 (48%) fixed duration treatments being only exposed at relapse. Out of 169 pts on cont therapy, 32 (19%) stopped it for adverse events, resulting exposed but not refractory. Splitting these 324 pts into 3 groups according to years of relapse (first period: 2010-2015, 117 pts; second period: 2016-2021, 146 pts; third period: 2022-2024, 61 pts), their refractory status spread as follows: 42 pts (36%) were R-ref in the first period, 87 (60%) in the second and 30 (50%) in the third period; dara-R-ref was recognized in 6 (10%) pts only in the third period; dara-ref in none pts, 1 (1%) and 3 (5%) in the 3 periods, respectively (Figure 1). Second line therapy was administered in 243 pts: 94 PI-based, 77 R-based, 8 pomalidomide-based, 50 antiCD38-based (DaraPD 3, DaraVD 6, DaraRd 31, IsaKd 9, IsaPd 1), 2 bispecific antibodies and 12 others. On the other hand, 152 pts are still on therapy without relapse. Out of these, 59 (63%) pts are receiving R-based treatment so they could become R-ref at first relapse, 23 (15%) dara-R becoming double-ref, 7 (5%) dara becoming dara-ref and 26 (17%) fixed therapy remaining only exposed. In conclusion, only exposed pts are decreasing over time, due to the major spread of cont frontline therapies in MM landscape although they could increase again since most current trials are proposing a fixed term therapy. However, the highest burden of refractoriness that we currently observed in MM in first relapse consisted of the R exposure/refractoriness. Considering the available regimens and the timing of new therapies approval for real practice and their time to progression, the challenging problem will continue to be R exposition/refractoriness rather than multi-refractoriness, that will be low for some years to come.

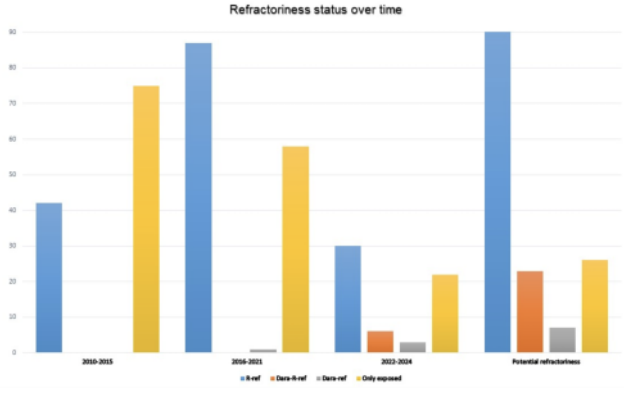

Figure 1.

P66

MASS SPECTROMETRY (MALDI-TOF) IS MORE INFORMATIVE THAN IMMUNOFIXATION ANALYSIS IN REFERENCE TO BONE MARROW FLOW CYTOMETRIC MEASURABLE RESIDUAL DISEASE (FLOW-MRD) ASSESSMENT IN MULTIPLE MYELOMA

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Background and aim. MRD negativity is currently the optimal goal for treatment success in MM1. To assess the monoclonal (M) protein, serum SPEP (detection limit (DL); 0.5-1 g/L), IFE (DL; 0.05–0.1 g/L), or clonal plasma cells in bone marrow by flow cytometry (FC) (10-5-6) or NGS (10-5-6) analyses are alternatives. Serum-based tests are preferable due to their non-invasiveness. However, increased use of monoclonal antibodies as part of anti-MM therapy complicates serum M protein assessments. In this prospective analysis, we aim to present a comparative analysis of MALDI-TOF and flow-MRD tests among patients receiving immunotherapy.

Methods. Patients' inclusion criteria: Cases on anti-myeloma therapies include mAbs such as daratumumab and teclistamab and have achieved at least VGPR to confirm CR were subjected to marrow MRD by FC and serum MALDI-TOF. FC: Antibody panels, which consisted of CD38.FITC/CD81.PE/ CD19.ECD/ CD117.PC7/ CD138.APC/ CD56.APCA700/ CD27.A750/CD45.KO and cKAPPA.FITC/ cLAMBDA.PE/CD19.ECD/ CD27.PC7/CD138.APC/CD45 were used at the Ankara University FC Lab. At least 100.000 leukocytes were evaluated in each tube (sensitivity: 10-4). The data were evaluated using the Navios device (Beckman Coulter, Miami, USA) with a 3 laser 10 color (3L10C) analysis feature. The analyses were conducted using Kaluza software. MALDI-TOF: The samples were analyzed either at Mayo Clinic (prior to 2024) or at Acıbadem Labs by the Bruker rapifleX MALDI Tissue-Typer device. Initially the light chains were used with serum resin to bind to the constant region. Non-binding proteins were removed. The samples were analyzed by MALDI after the bonds between the light and heavy chains were broken using the elution buffer. For the enrichment of target molecules in drug interactions, IgG K or L Thermo Capture select resin was used. Statistical analysis: IFE, FC, and MALDI-TOF results were compared with Fisher's exact test.

Results. Until now, 12 MM patients with samples analyzed at the Mayo Clinic (n=6) and the Acıbadem (R&D) Laboratory (n=6) have been included. The M/F ratio was 9/3; the median age was 59.5. (29-70). Seven patients (58.3%) have received only one line of treatment. Two patients (16.7%) were analyzed after completion of planned treatment. Six patients had received daratumumab, and one patient was receiving teclistamab. MALDI, FC, and IFE results are summarized in Table 1. Comparison of these results showed a significant correlation between MALDI and FC-MRD (p=0.03), while no significant relationship was observed between IFE and MALDI or between IFE and FC-MRD. (p>0.5). Some of the discordances were attributable to the immunotherapeutics detectable in serum.

Discussion. In our analysis, among four cases, all method results were concordant. Discordancies were either due to antiCD38 or bispecific antibodies in the blood or lower specificity of IFE or higher sensitivity of FC-MRD than MALDI. In addition, the ability of MALDI to detect MRD in a patient where MRD was not detected by FC is delayed clearance of serum M proteins than disappearance from BM. In conclusion, in cases where IFE cannot distinguish serum M protein MALDI positivity may ameliorate the need for BMA. FC-MRD can be delayed until MALDI analysis reveals no M proteins.

Table 1. Detailed data analyses and comments on test results of the patients.

No	Age	Sex	MM type	mAb	Line of therapy	Active Treatment	IFE	FC-MRD	MALDI TOF	interpretation
1	53	M	IgG L	None	2	No	1	1	1	Quantitative FU MALDI: 0.04-0.017
2	29	M	IgG K	DARATUMUMAB	1	Yes	1	0	0	Drug effect
3	67	M	L	DARATUMUMAB	1	Yes	1	1	1	IgG K was positive. MRD positive with L enrichment.
4	65	M	K	DARATUMUMAB	1	Yes	1	0	0	Drug effect
5	50	M	IgG K	TECLISTAMAB	1	Yes	1	0	0	Drug effect
6	68	M	IgG K	DARATUMUMAB	2	Yes	0	0	0	Drug effect; previously IFE and MALDI were positive.
7	47	M	K	None	1	Yes	1	0	0	IFE is less specific
8	55	M	IgA L	None	2	Yes	0	1	1	IFE is less sensitive
9	70	M	IgA K	None	2	Yes	0	1	0	FC-MRD is more sensitive
10	65	F	IgG L	None	1	No	1	0	0	IFE is less specific
11	61	F	L	DARATUMUMAB	1	Yes	1	0	0	FC-MRD is negative with L enrichment. (IFE IgGK) concordant
12	58	F	L	DARATUMUMAB	2	Yes	1	1	1	

Special conditions

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A REAL-WORLD RETROSPECTIVE-PROSPECTIVE ANALYSIS OF SECONDARY IMMUNODEFICIENCY AND RISK OF INFECTION IN PATIENTS WITH AL AMYLOIDOSIS TREATED WITH DARATUMAMAB-BASED INDUCTION REGIMENS. A MULTICENTER ITALIAN EXPERIENCE

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Anti-CD38 monoclonal antibody Daratumumab (D) proved effective in AL amyloidosis (AL), both in the newly diagnosed and the relapsed setting. D in combination with Cyclophosphamide, Bortezomib and Dexamethasone is now the standard frontline treatment (Tx) of AL, based on the results of the ANDROMEDA trial. We have conducted an observational analysis of 153 newly diagnosed AL patients (pts) treated with D-based induction regimens since Jan 2020 in 24 Italian centers, with the aim to evaluate incidence, severity and timing of infections (Inf) from the start of Tx until the next line or autologous stem cell transplant (ASCT), and to identify clinical risk factors for Inf. At induction initiation, median age was 66 (IC 58-75). 13.8% of pts had concurrent symptomatic multiple myeloma (MM), including the presence of CRAB symptoms and/or ≥60% bone marrow plasma cells (BMPCs). Cardiac involvement was reported in 66% (32% stage IIIa/IIIb), renal in 71.2% (11.8 % stage III), nephrotic-range proteinuria (≥3.5 g/24 h) in 42.3%, severe renal failure (eGFR<30 ml/min) in 12% of pts. 21% had severe hypogammaglobulinemia (HG) (IgG <400 mg/dL) at Tx initiation. Notably, 76.7% of pts with HG had nephrotic syndrome secondary to renal AL. Induction regimen was D-CyBorD in 78.4% of pts. 48.4% of pts were started on D maintenance after induction. With a median follow-up of 14 months, 32.7% of pts had discontinued Tx (induction +/- maintenance), mainly (58%) after achieving ≥VGPR upon completion of therapeutic program. 48.4% of pts presented ≥1 all-grade Inf, 13.7% had ≥2 events. 11.8% had ≥1 G≥3 events. Overall, 94 Inf were reported (53.2% bacterial, 44.7% viral, 2.1% fungal), 48.9% referable to upper respiratory tract Inf, mainly low-grade (G1/2). Most frequent G≥3 events included pneumonia (8/18) and sepsis (5/18). Inf accounted for Tx discontinuation in only 4 cases. 3 fatal Inf occurred. Among 81 cases evaluated for hematologic responses, most all-grade (92.5%) and G≥3 (83.3%) Inf occurred in responsive pts. Namely, 66.6%/55.6% of all-grade/G≥3 Inf occurred in ≥VGPR. The median time from the start of induction to Inf was 109 days. 90.4% of Inf occurred on D-based Tx (18% during maintenance), the remaining 9.6 % in the Tx-free interval until the next line or ASCT. 53.4% of 103 evaluated pts were reported to have IgG <400 mg/dL at any timepoint during the observation period, but only 17.5% received Ig replacement (IgRT), based on recurrent/severe Inf (14/18) or low Ig (8/18). By univariate Cox regression analysis, older age (≥75), concurrent MM (CRAB and/or ≥60% BMPCs), and low s-albumin (<3 g/dL) emerged as the clinical variables significantly associated with increased risk of G≥3 Inf. BMPCs ≥60% attained a borderline statistical significance (p=0.06). Baseline IgG levels, hematologic response at the time of Inf and organ involvement (type, grade, number of organs), nephrotic proteinuria had no statistically significant impact on the risk of Inf. By multivariate analysis, independent predictors of risk of G≥3 Inf were age ≥75, (HR 3.59, p=0.009), concurrent MM (HR 3.26, p=0.02), s-albumin <3 g/dL (HR 2.52, p=0.055). In conclusion, in pts treated with D-based induction the rate of severe Inf is low, despite severe HG affecting more than half of pts at Tx initiation and/or during subsequent Tx, to a large extent secondary to Ig urinary loss. Assessment of risk factors (age, disease burden, s-albumin) may help inform the decision on IgRT in this setting.

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VENOUS THROMBOEMBOLISM RISK SCORES IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING DARATUMUMAB, LENALIDOMIDE, AND DEXAMETHASONE

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The combination of daratumumab, lenalidomide, and dexamethasone (DaraRD) dramatically improved survival in multiple myeloma (MM), nonetheless risk of venous thromboembolism (VTE) remains high. Various VTE risk assessment models (RAMs) have been developed to predict the risk of VTE and guide thromboprophylaxis in MM, but the accuracy of VTE-RAMs in dara-exposed MM is limited or unknown. In a retrospective, real-life, unselected cohort of MM patients (pts) con-

secutively treated with DaraRD in a large tertiary hospital, we aimed to assess (i) the performance of available VTE RAMs (IMPEDE-VTE, SAVED, PRISM, and HER-CAT scores); (ii) the feasibility and safety of thromboprophylaxis with low molecular weight heparin for 6 months followed by aspirin (LMWH-ASA), as per institutional guidelines. Kaplan-Meier method and Concordance-Index (C-index) were adopted to estimate risk scores' prognostic accuracy. We included 96 pts consecutively treated at our institution between July 1st, 2018 and September 30th, 2023. Median age was 74 years, male sex 59.1%, 47 pts (49%) had newly-diagnosed transplant eligible MM (NTE-MM), and 49 pts (51%) relapsed/refractory MM (RRMM). After a median follow up of 365 days (IQR, 323 to 365), 10 pts (10.4%) experienced a VTE event, of which 5 pts (10.6%) in NTE-MM, and 5 pts (10.2%) in RRMM group, respectively. Eight VTE events (8.3%) occurred within first 6 months from DaraRD initiation while on LMWH prophylaxis, and 2 VTE (2%) occurred in patients on aspirin. Four pts (4.2%) had a hemorrhagic event (HE), 4 (8.3%) in NTE-MM and 0 (0%) in RRMM, respectively. Two HE occurred during LMWH prophylaxis, whereas 2 HE occurred after a VTE event while pts were receiving full-dose anticoagulant treatment. Overall, two (2.1%) patients died at 244 days and 360 days since the start of Dara-Rd, respectively (median 365 days, IQR 365, 365). None of the patients who experienced VTE or bleeding died. The accuracy of the IMPEDE-VTE, SAVED, PRISM and HER-CAT scores was generally poor, with C-Index values ranging from 0.43 (95% confidence intervals [95%CI]0.30 to 0.56) and 0.53 (95%CI: 0.38 to 0.68) (Table 1). The LMWH-ASA protocol was completed by 89.5% of the cohort. During the first 6 months of DaraRd, 7 pts (7.3%) discontinued LMWH: 6 pts (6.3%) due to a VTE event and 1 pts (1%) due to a HE. Then, 82 pts (89.5%) switched to aspirin. Main causes for not starting aspirin were VTE in 6 pts (6.3%), MM progression in 5 pts (5%), other reasons in 2 pts (2%). In the present study, for the first time to our knowledge, we report a real-life experience of contemporary patients with either NTE-MM or RRMM consecutively treated with DaraRd in a single tertiary-care center. Our study confirms the high VTE risk in MM patients. Despite the availability of several VTE RAMs, none of them demonstrated a satisfactory predictive accuracy in Dara-exposed MM. The LMWH-ASA prophylactic protocol seemed to be safe and feasible although with low effectiveness. Considering the relevant thromboembolic burden associated with MM and MM-directed therapies, identification of novel reliable risk factors (both patient-, disease-, and treatment-specific) for VTE with the development of novel RAMs is of utmost importance to guide clinical and thromboprophylaxis management in this population.

Table 1. Predictive accuracy of risk scores.

Score	C-index (95% CI)
IMPEDE-VTE	0.43 (0.30 to 0.56)
SAVED	0.53 (0.38 to 0.68)
EHR-CAT	0.51 (0.35 to 0.65)
PRISM	0.52 (0.50 to 0.54)

Footnote: 95%CI: 95% confidence intervals

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OBSERVATION OR TREATMENT FOR SMOLDERING MULTIPLE MYELOMA? A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED STUDIES

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Background. Smoldering multiple myeloma (sMM) is an asymptomatic precursor condition to multiple myeloma (MM). While observation has traditionally been the standard of care for sMM, emerging evidence suggests that early therapeutic intervention with anti-myeloma regimens may delay progression and improve outcomes especially in high-risk patients.

Methods. A systematic database search (end-of-search: December 16, 2024) identified literature on randomized clinical trials evaluating treatments for sMM compared to observation or no antimyeloma-treatment medication. Pooled poportions, odds ratios (OR), hazard ratios (HR), and 95% confidence intervals (CI) were calculated using random-effects models.

Results. Upon evaluation, 7 articles were deemed eligible, representing 5 randomized clinical trials investigating sMM pre-treatment with anti-myeloma regimens compared to observation, placebo or non-anti-myeloma therapy. These trials collectively involved 844 patients. All of the 5 included studies reported PFS results (without high heterogeneity, I2=42%, p=0.14), where a statistically significant 60% reduced pooled risk for disease progression or death (HR=0.40, 95% CI: 0.29-0.55) for patients that underwent treatment compared to those that did not was revealed. An exploratory sensitivity analysis involving trials with only treatment-naïve control arms and trials with only observation controls, revealed that risks for disease progression or death were 63% lower (HR=0.37, 95% CI: 0.25-0.56) and 66% lower (HR=0.34, 95% CI: 0.21-0.56) for patients treated compared in these subgroups, respectively. Furthermore, time-to-progression (TTP) was reported in 3 studies; the pooled efffect estimate revealed a statistically significant 58% reduced risk for progression to symptomatic MM (HR=0.42, 95% CI: 0.29-0.61) for patients that underwent treatment compared to those that did not. Moreover, the pooled overall response rate (ORR) was 58% (95% CI: 43% - 73%) stemming from 4 out of the 5 studies and ranging from 37% to 79%. Only 2 trials reported mature OS outcomes were the pooled effect estimate showed a 45% lower risk for death (HR=0.55, 95% CI: 0.37-0.82) in sMM patients who were on treatment during asymptomatic disease compared to those on observation. Finally, all of the five included studies reported grade 3-4 adverse events between trial arms. The odds for a grade 3-4 AE for those on anti-myeloma treatments was as 3.5 times as high (OR=3.53, 95% CI: 1.14, 10.91) compared to those on observation, placebo or non- anti-myeloma regimens. Moreover, the pooled proportion of grade 3-4 AEs in the treatment arms was 40% (95% CI: 35% - 45%). There were no statistically significant differences observed in the odds of second primary malignancies (SPMs) between treatment arms and control arms (OR=1.54, 95% CI: 0.57-4.17).

Conclusion. This meta-analysis of 5 randomized clinical trials involving 844 patients highlights the significant benefits of early treatment in sMM, across key clinical outcomes. However, these benefits were accompanied by an increased risk of grade 3-4 adverse events in the treated population. These findings underscore the efficacy of early anti-myeloma therapy in reducing disease progression and improving survival outcomes, while highlighting the need for careful monitoring and management of treatment-related toxicities.

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MORTALITY RATE OF PATIENTS WITH MAYO STAGE IV AL AMYLOIDOSIS IN PHASE 3 VITAL TRIAL PLACEBO ARM IS REPRESENTATIVE OF REAL-WORLD MORTALITY PER MATCHED MAYO CLINIC COHORT

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Introduction. Amyloid light chain (AL) amyloidosis is a rare, progressive, and typically fatal disorder caused by misfolded immunoglobulin light chains (LCs) that aggregate and form amyloid that deposits in organs, leading to organ damage and failure. Despite recent treatment advancements, patients (pts) with newly diagnosed AL amyloidosis and significant cardiac involvement experience high rates of early mortality (Mayo 2012 Stage IV, median overall survival 6-11 months [mos]). Birtamimab is an investigational humanized monoclonal antibody designed to neutralize soluble toxic LC aggregates and clear deposited amyloid by inducing phagocytosis. The Phase 3 VITAL clinical trial (NCT02312206) evaluated birtamimab + standard of care (SoC) *vs* placebo (PBO) + SoC in treatment-naïve pts with newly diagnosed AL amyloidosis and cardiac involvement. The study was terminated based on a futility analysis of the primary endpoint (time to all-cause mortality [ACM] or cardiac hospitalization ≥91 days after 1st study drug infusion). Post hoc analysis of ACM over 9 mos revealed a significant survival benefit (hazard ratio [HR]=0.413 [95% confidence interval: 0.191, 0.895]; p=0.021) in Mayo Stage IV pts, which was consistent across all key baseline variables (Gertz *et al.* Blood 2023). The objective of this analysis was to compare the observed mortality rate in the VITAL Mayo Stage IV PBO group with a matched cohort of pts from the Mayo Clinic, a center of excellence for AL amyloidosis treatment.

Methods. Real-world data were derived from chart records at the Mayo Clinic for pts with Mayo Stage IV AL amyloidosis receiving SoC from Jan 2012 to May 2017. To match the two pt populations, Mayo Clinic pts with the following criteria were excluded: diagnosis ≥90 days prior to arrival at the Mayo Clinic, Mayo Stage I-III disease or no stage information, N-terminal pro-brain natriuretic peptide (NT-proBNP) >8500 pg/mL, stem cell therapy within 1 yr of diagnosis, exposure to birtamimab, or exposure to daratumumab in analysis period (9 mos). Kaplan-Meier mortality rate estimates were compared via Cox HR. Pts who died were censored at the last assessment they were known to be alive.

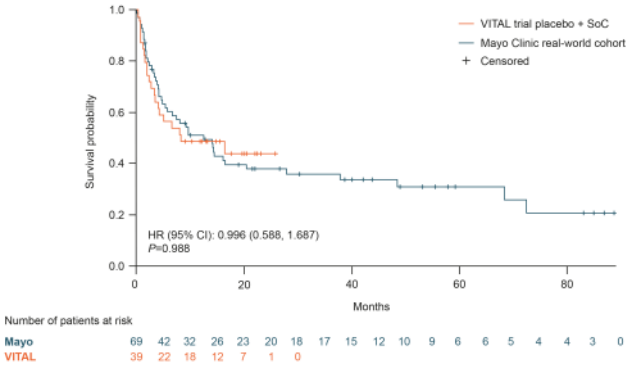

Figure 1.

Results. Overall, 881 pts with AL amyloidosis were identified in Mayo Clinic chart records; 69 were matched to VITAL Mayo Stage IV PBO pts (n=39) after applying exclusion criteria. Baseline characteristics were generally balanced between VITAL PBO and Mayo Clinic pts, including median (quartile [Q]1, Q3) age at AL amyloidosis diagnosis of 64 (57, 68) yrs *vs* 66 (58, 74) yrs, baseline difference between involved and uninvolved serum free light chains (dFLC) of 57.4 (35.5, 106.3) mg/dL *vs* 54.6 (33.3, 98.0) mg/dL, troponin T of 0.09 (0.06, 0.13) ng/mL *vs* 0.07 (0.05, 0.12) ng/mL, and NT-proBNP of 5415 (4054, 8073) pg/mL *vs* 4330 (3451, 5575) pg/mL, respectively. Kaplan-Meier estimates of time to ACM were similar between the two groups (Figure 1). The proportion of VITAL Mayo Stage IV PBO pts surviving at 9 mos was 49% *vs* 52% in the matched Mayo Clinic cohort.

Conclusions. Mortality was comparable between Mayo Stage IV VITAL PBO pts and a matched Mayo Clinic real-world population. These data demonstrate that the VITAL Mayo Stage IV PBO pt cohort generally represents an historical control population of newly diagnosed, treatment-naïve Mayo Stage IV pts with NT-proBNP ≤8500 pg/mL, further reinforcing the survival benefit observed in birtamimab-treated Mayo Stage IV pts in VITAL.

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DARATUMUMAB-BASED TREATMENTS IN STAGE IIIB AL AMYLOIDOSIS: REAL LIFE EXPERIENCE FROM ANCONA TERTIARY CENTER

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Light chain (AL) Amyloidosis is a rare protein misfolding disorder causing insoluble fibrils deposition in tissues with consequent organ dysfunction and failure mostly of heart and kidney. Recently, anti-CD38 monoclonal antibody daratumumab (dara) became frontline therapy backbone in non-stage IIIB amyloidosis, with significant haematological and organ responses translating into improved outcome. However, patients (pts) with stage IIIB cardiac disease have historically a median overall survival (OS) of 5 months so recent clinical trials as EMN22 are trying to evaluate dara also in this setting. We retrospectively analysed 38 pts treated in Ancona tertiary centre from 2016 to 2024, aiming to evaluate the real life use of dara-based regimens in AL Amyloidosis pts, mostly stage IIIB. Median age was 69 years (range 38-86) and median follow-up was 32 months (2-72.5 months). Seventeen pts (45%) had primary and 21 (55%) secondary amyloidosis. Cardiac involvement was recognized in 27 pts (71%; 4% stage I, 11% stage II, 48% stage IIIA and 37% stage IIIB); kidney involvement in 20 (52%) and liver in 5 (13%). Frontline therapy was dara-cyclophosphamide-bortezomib-dexamethasone (Dara-CyBorD) in 16 patients (42%), cyclophosphamide-bortezomib-dexamethasone (CyBorD) in 17 (45%), bortezomib-dexamethasone (VD) in 3 (8%), melphalan-prednisone in 1 (3%) and rituximab-CyBorD in 1 (3%). Out of 27 pts with cardiac involvement, 83% non-stage IIIB pts obtained ≥ haematological VGPR, with or without dara, 66% among stage IIIB treated with dara and 33% without dara. Cardiac response was detected in 33% of non-stage IIIB pts with dara (*vs* 67% without), but none of stage IIIB obtained a cardiac response, with a mortality rate of 83% *vs* 67% in dara *vs* non-dara subgroups. Three patients (11%) developed infections, mainly pneumonia followed by sepsis and COVID-19, being only one grade 5. Nine pts died for heart failure (33%) and one for secondary malignancy (4%). In cardiac stage IIIB pts median PFS was 3 *vs* 24 months in dara *vs* non-dara subgroups (p=0.056) and median OS of 3 *vs* 25 months (p=0.016), respectively. Median PFS was NR *vs* 57 months in the same two subgroups of non-stage IIIB pts

(p=0.122), respectively. Stepwise Cox regression analysis selected dara use (HR 12.7, p < 0.001) and stage IIIB (5.5, p=0.020) as factors negatively affecting OS whereas response ≥VGPR (HR 6.2, p=0.013), and cardiac response (HR 4.8, p=0.031) as factors positively affecting OS. Compared to ANDROMEDA trial data, our real life experience confirmed that, pts with stage < IIIB amyloidosis receiving dara- had higher haematological response rate which however did not translate into better OS although it was similar to that reported in ANDROMEDA. Compared to EMN22 trial, that used dara monotherapy in stage IIIB rather than association, our stage IIIB pts had similar hematological but worse cardiac responses and higher mortality due to cardiac failure. Whether cardiac failure is due to disease progression or to toxicity of the combination therapy is still an open question. In conclusion, despite small sample size, our real life data showed that, by adding dara to CyBorD, outcome of advanced stage cardiac amyloidosis was not improved since early mortality, mostly due to heart failure, is still the major problem. Pending therapies able to eliminate pre-existing amyloid fibrils, early diagnosis represents the best tool to improve outcome of pts with cardiac amyloidosis, so far.

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POSITIVE IMPACT OF BOTH ENZYME REPLACEMENT AND SUBSTRATE REDUCTION THERAPY ON MGUS IN TWO PATIENTS WITH GAUCHER DISEASE

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Introduction. Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by defective beta glucocerebrosidase that leads to the accumulation of glucosylceramide in macrophages, generally presenting with splenomegaly, anemia, thrombocytopenia and/or bone involvement. The correlation between GD and an increased onset of plasma cell dyscrasias, both monoclonal gammopathies of uncertain significance (MGUS) and multiple myeloma (MM) at a younger age has already been described. Most commonly suggested mechanism was associated to a pro-inflammatory microenvironment due to abnormal macrophage activation caused by glycolipid storage, resulting in chronic B-cell stimulation.

Methods. Multicentric prospective observational study was conducted at our center, screening 600 MGUS patients for Gaucher disease. Four MGUS patients were diagnosed with GD, and an additional fifth patient was diagnosed shortly after the enrolment was closed. All five patients were started on treatment with periodical disease follow-up. Interestingly in two cases there was evidence of improvement in terms of reduction of the level of monoclonal protein in course of treatment.

Results. At the time of GD diagnosis, both patients were of young age, pediatric and adult patient in it late-30s. The 4-year-old child presented with splenomegaly, anemia, and presence of a 0.1 g/dl IgG-K monoclonal protein (MP) in serum protein electrophoresis, while serum free light chain assay was within the normal range. Enzyme replacement therapy (ERT) with imiglucerase was started and one year after he showed complete resolution of anemia, significant reduction in spleen size, and disappearance of the MP, with the negativization of serum immunofixation test. The 38-year-old woman presented with thrombocytopenia, splenomegaly, mild anemia, and a monoclonal IgG-K component of 1.19 g/dl, with the serum free light chain assay within the normal range. Two months after substrate reduction therapy (SRT) with eliglustat, follow-up exams evidenced resolution of anemia and initial improvement of both thrombocytopenia and reduction in the MP (1.05 g/dl) (Figure 1).

Conclusions. The accumulation of glucosylceramide in GD leads to chronic macrophage stimulation with the subsequent release of pro-inflammatory cytokines, resulting in B cell activation and potential development of both polyclonal and monoclonal gammopathies. In our study, we demonstrated that therapy, both ERT and SRT, at an early age led to a reduction and even disappearance of the MP, thus potentially eliminating the chronic inflammation stimulus and preventing both ulterior B-cell activation and development of lymphoid and plasma cell disorders. Given the increased prevalence of MGUS (1-35%) and MM (0.4-4%) in patients with GD the impact of both enzyme replacement and substrate reduction therapy on MP level needs further studies and longer follow-up.

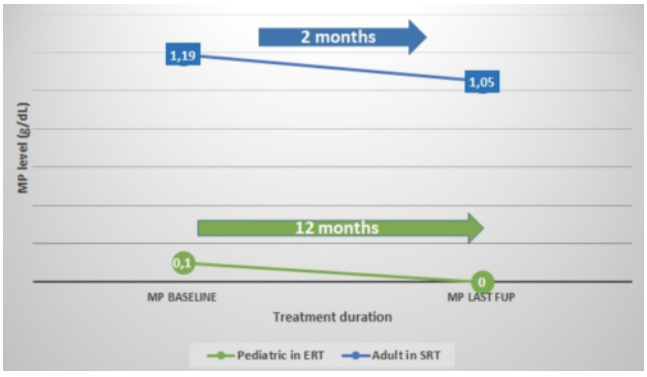

Figure 1.

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VACCINATION STRATEGIES AND ANTIMICROBIAL PROPHYLAXIS IN PATIENTS WITH MULTIPLE MYELOMA: A REAL-WORLD PRACTICE SURVEY AMONG EMN-ITALY CENTERS

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Patients with hematological malignancies have an increased risk of infections, including those preventable by vaccines like influenza and invasive pneumococcal disease. This risk starts to rise at the MGUS stage and is much higher in patients with active disease, especially when starting anti-myeloma therapy. A population study showed a tenfold increased risk of viral infections and a sevenfold increased risk of bacterial infections in multiple myeloma patients. Severe immune suppression, particularly during uncontrolled disease, contributes to this higher susceptibility, worsened by the immunosuppressive effects of anti-myeloma treatments that impair T-cell function and antibody production. Vaccination during periods of minimal immunosuppression could help reduce infection risk, but cultural differences among healthcare professionals can impact vaccine compliance.This study aimed to evaluate attitudes toward vaccinations and the use of antimicrobial prophylaxis in various centers affiliated with the European Myeloma Network (EMN-Italy). A survey question-

naire assessing vaccine uptakes and general opinion about vaccination was provided to 107 EMN-Italy centers between September 2024 and December 2024. Responses from 68 centers (63%) were received. All respondents reported informations about vaccine strategies and the use of antimicrobial prophylaxis in the centers. Prior to starting chemotherapy, 72% of clinicians verify the vaccination history of patients, paying particular attention to the pneumococcal (96%), inactivated anti-influenza virus (91%), varicella-zoster virus (85%), Haemophilus influenza (42%) and Hepatitis B virus (35%). Meningococcal vaccination is offered to only 18% of patients. There is minor attention to vaccinations for diphtheria, tetanus, and pertussis (DTP) or measles, mumps, and rubella (MMR). Influenza vaccination is recommended in 85% of centers, while pneumococcal vaccination is advised for all patients in 56% of centers. However, 25% of centers limit pneumococcal vaccination to patients over 65 years of age. Vaccination status against SARS-CoV-2 is assessed in 95% of centers, and nearly all provide the anti-SARS-CoV-2 booster dose even during maintenance therapy. Additionally, 88% of centers recommend the new recombinant subunit vaccine for Varicella-Zoster Virus in patients with Multiple Myeloma who are eligible for treatment, with antiviral prophylactic therapy being maintained in 61% of cases. The evaluation of the QuantiFERON test before starting therapy is performed in 31% of cases and in 52% of patients with a history of lung disease. Regarding antiviral prophylaxis, treatment with acyclovir at a dose of 400 mg per day is used in 43% of patients, while 40% of patients receive 400 mg twice daily. A minority of centers (2%) use antiviral prophylaxis with valacyclovir at a dose of 500 mg per day. Prophylaxis with Sulfamethoxazole/ Trimethoprim is administered in 64% of centers and in 33% only in selected cases. The use of immunoglobulins is reserved for patients with IgG levels <3.5 g/dL and a history of infections in 59% of centers, with 86% of cases involving intravenous immunoglobulins. This survey highlights a strong focus among clinicians on vaccination and antimicrobial prophylaxis in patients with multiple myeloma who are candidates for treatment. The responses reveal a heterogeneity in practices, emphasizing the need for guidelines to standardize this critical aspect of care in multiple myeloma patients.

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TREATMENT PATTERNS OF BONE-TARGETED AGENTS FOR THE PREVENTION OF SKELETAL-RELATED EVENTS IN MULTIPLE MYELOMA IN BULGARIA: A CROSS-SECTIONAL CHART REVIEW STUDY

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Background. Lytic bone lesions are a frequent consequence of multiple myeloma (MM), occurring in up to 90% of patients during the course of the disease. Myeloma bone disease (MBD) increases the risk of skeletal-related events (SREs). In a real-world study (Ria M *et al*. Int J Clin Exp Med 2013) between 46% and 76% of patients experienced SREs within 2 years from their initial anti-myeloma therapy. Myeloma treatment guidelines recommend the use of bone-targeted agents (BTAs, i.e. bisphosphonates or denosumab) for SRE prevention. The aim of this study was to describe the patterns of MBD, associated pain management and SRE incidence in a real-world setting of hematology clinics in Bulgaria.

Methods. This was a cross-sectional patient review of structured and unstructured data documented in electronic health records (EHRs) from eight hematology clinics in Bulgaria. The study included ≥18-year-old patients with a hospitalization for MM (ICD-10 code C90.0) and a BTA prescription specifically for MM. The primary objective was to describe patients' demographic and clinical characteristics and the details of MBD management. Secondary objectives included descriptions of the incidence of SREs and osteonecrosis of the jaw (ONJ), and pain management. The study period was 01-Jan-2019 to 31-Dec-2022.

Table 1. Overview of patient demographics and study results.

	Denosumab N=177	ZA N=440	Both [a] N=115
Age (years), mean (SD)	65.9 (10.5)	66.2 (9.4)	63.6 (9.6)
Age categories, n (%)			
≤65 years	78 (44)	193 (44)	58 (50)
>65 years	99 (56)	247 (56)	57 (50)
Female sex, n (%)	93 (53)	233 (53)	63 (55)
First recorded therapy [b], n (%)			
Anti-myeloma treatment + BTA	143 (81)	347 (79)	78 (68)
Anti-myeloma treatment only	30 (17)	71 (16)	19 (17)
BTA only	4 (2)	22 (5)	18 (16)
BTA administrations during study, n (%)			
Anti-myeloma treatment + BTA	171 (97)	6 (92)	96 (83)/112 (97)
BTA only	6 (3)	34 (8)	19 (17)/3 (3)
BTA treatment duration (days) [c], median (Q1, Q3)	39 (0, 115)	60 (0, 142)	60 (0, 197)/ 84 (0, 157)
Cumulative SRE incidence (patients) n (%)	56 (32)	153 (35)	46 (40)
Previous SRE	39 (22)	71 (16)	35 (30)
SRE during BTA	16 (9)	30 (7)	3/7 (9)
≤65 years, n	5	15	0/4
>65 years, n	11	15	3/3
SRE after discontinuation of BTA	1 (<1)	Missing	1
SRE both before and during BTA	4 (2)	Missing	0
Type of SRE (patients) [d], n (%)			
Radiation to bone	7 (4)	51 (12)	13 (11)
Spinal cord compression	32 (18)	95 (22)	26 (23)
Surgery to bone	28 (16)	46 (10)	17 (15)
Fractures (excluding proximal femoral)	23 (13)	28 (6)	15 (13)
Fractures (proximal femoral)	2 (1)	5 (1)	1 (1)
Type of SRE (occurrences) [d], n	107	279	89
Radiation to bone	7	71	14
Spinal cord compression [e]	32	95	26
Surgery to bone	35	65	26
Fractures (excluding proximal femoral)	30	42	22
Fractures (proximal femoral)	3	6	1
Cumulative ONJ incidence (patients), n (%)	0 (0)	5 (1)	2 (2)
during BTA treatment	0 (0)	1 (<1)	0 (0)
Analgesic use, n (%)	46 (26)	242 (55)	41 (36)
Opioid	26 (15)	173 (39)	14 (12)
Non-opioid	22 (12)	69 (16)	27 (23)

BTA, bone-targeted agent; SD, standard deviation; SRE, skeletal-related event; ZA, zoledronic acid
[a] Both = ZA and denosumab at different times. Where appropriate, the first shown number corresponds to the denosumab treatment period and the second shows the ZA treatment period in patients receiving both treatments sequentially.
[b] Recorded therapy at or after first documented MM hospitalization during study period (baseline).
[c] In cases where the duration of treatment is 0 days, the patient may have received only a single dose or the subsequent doses were administered at least 60 days after the first dose, which was longer than the pre-defined discontinuation threshold.
[d] Shows the number of SRE before and during the study period, including the period after BTA discontinuation.
[e] Only the first occurrence was counted.

Results. The EHRs included a total of 732 patients; n=177 received denosumab, n=440 received zoledronic acid, and n=115 sequentially received zoledronic acid and denosumab. The patient demographics are shown in Table 1. In 83%, 84%, and 84% in the three groups, respectively, a BTA either alone or in combination with their anti-myeloma treatment was documented as first recorded therapy. The median (Q1, Q3) time from MM diagnosis to the initiation of denosumab was 8 (4, 37) days, for zoledronic acid it was 31 (12, 128) days, and in the cohort that received both BTAs it was 246 (130, 374) days for denosumab and 40 (10, 114) days for zoledronic acid, suggesting zoledronic acid was used first in most patients.The median (Q1, Q3) duration of BTA administration was longest in patients receiving both BTA types sequentially. BTAs were prescribed mostly in preventive intent, as only 22%, 16%, and 30%, respectively, had experienced previous SRE. New SRE occurred in 9%, 7%, 9%, respectively; 2% of denosumab patients experienced an SRE before and during the study. Table 1 shows details on the SRE incidence overall and by SRE type. Seven cases of ONJ were identified but only one occurred during BTA use (in the zoledronic acid cohort). Analgesics were used in 26%, 55%, and 36%, respectively; the need for opioid analgesics was highest in the zoledronic acid only group

(39%; Table 1).

Conclusions. Patients with MM are at very high risk of SRE. In our study of real-life clinical practice in Bulgaria, only a minority (<10% in all cohorts) of MM patients prescribed use of BTAs in the preventative setting experienced an SRE.

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CYTOMEGALOVIRUS INFECTION AFTER AUTOLOGOUS TRANSPLANTATION IN PATIENTS WITH MULTIPLE MYELOMA EXPOSED TO DARATUMUMAB

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Cytomegalovirus (CMV) infection is a common complication after autologous hematopoietic stem-cell transplantation (ASCT), nonetheless CMV disease is rare. Among multiple myeloma (MM) patients (pts), factors such as bortezomib-exposure and CD34+ selection identify high-risk pts. Recently, the anti-CD38 monoclonal antibody daratumumab (dara) has become the backbone treatment for many MM. Besides efficacy, some series reported an increased incidence of viral infections in Dara-exposed MM. To date, less in know about CMV infection in dara-exposed MM undergoing ASCT. We report a retrospective, single-center analysis of MM pts that consecutively underwent single or tandem-ASCT following daratumumab, bortezomib, thalidomide, and dexamethasone (dara-VTd) induction at our institution between January 1st, 2022 and September 30th, 2024. Pts were followed for at least 100 days after ASCT. Active CMV-DNA monitoring was performed by real-time quantitative PCR on a weekly basis for the first month after ASCT, thereafter weekly until 2 consecutive negative determination. CMV infection was defined as detection of CMV-DNA in peripheral blood. Indication for anti-CMV pre-emptive therapy (PET) were either a single CMV-DNA determination >10.000 cp/mL or a >0.5 log increase in 2 consecutive determination. CMV disease was defined as detection of CMV-DNA together with clinical symptoms and/or signs of organ involvement. Fifty-four pts were included in the analysis, median age was 62 years (range 39-70), 29 pts (54%) were female. At diagnosis 13 pts (24%) were ISS 3 stage, 8 pts (15%) were R-ISS 3, and 21 pts (39%) had high risk FISH abnormalities. After a median of 4 dara-VTd cycles (range 4-6), 50 pts (93%) underwent leukapheresis with cyclophosphamide 4 gr/mq whereas 4 pts (7%) received only G-CSF. After a median of 254 days (range 165-336) from start of induction, 54 pts (100%) underwent ASCT (Figure 1). After a median of 21 days (range 7-49) from ASCT, 36 pts (67%) had CMV infection. No primary CMV infection was observed among 2 seronegative pts. Notably, 13 pts (24%) required PET (median duration of PET 13 days, range 7-24), whereas only 1 pts (2%) had CMV disease (interstitial pneumonia). After a median of 392 days (range 302-502) from start of induction, all 22 pts initially candidate to tandem-ASCT for high-risk disease could actually receive tandem-ASCT. (Figure 1). After a median of 21 days (range 14-35) from ASCT, 14 pts (64%) had CMV infection. No primary CMV infection was reported. Notably, 5 pts (23%) required PET (median duration of PET 28 days, range 14-56), whereas only 1 pts (5%) had CMV disease (interstitial pneumonia). No difference emerged in CMV infection between single *vs* tandem-ASCT. In univariate analysis of characteristics at first ASCT, logistic regression found that higher levels of NK cells correlated with lower risk of subsequent CMV infection (Odds Ratio 0.87, 95% CI 0.77-0.98, p=0.03), whereas higher risk of PET was associated with older age (Odds Ratio 1.14, 95% CI 1.02-1.32, p=0.04), lower IgM levels (Odds Ratio 0.00032, 95% CI 2.7 $x10^{-8}$– 0.0069, p=0.001), and lower CD4+/CD8+ ratio (Odds Ratio 0.08, 95% CI 0.005-0.61, p=0.04). In this real-life cohort, dara-based induction before ASCT resulted in high rates of CMV infection. Few pts with CMV infection required PET and CMV disease was rare. No primary CMV infection was reported. Some characteristics of pts before ASCT might identify higher risk pts.

Table . Characteristics of patients at single- and tandem-ASCT.

Characteristics of patiens	single ASCT	tandem ASCT
N	54	22
Time to single ASCT (days, range)	254 (165-336)	392 (302-502)
WBC/uL (median, 95% IC)	4685 (3402-5617)	4940 (3750-5645)
Lymphocytes/uL (median, 95% IC)	1045 (652-1257)	1400 (1060-1815)
IgG (mg/dL) (median, 95% IC)	4.39 (3.44-6.56)	5.96 (3.75-7.76)
IgA (mg/dL) (median, 95% IC)	0.26 (0.21-0.34)	0.23 (0.16-0.35)
IgM (mg/dL) (median, 95% IC)	0.187 (0.17-0.22)	0.28 (0.22-0.42)
CMV IgG U/ml (median, 95% IC)	140 (118-178)	155 (117-172)
CMV IgM U/ml (median, 95% IC)	0 (0-0)	0 (0-0)
CMV DNA copie/ml (median, 95% IC)	0 (0-0)	0 (0-0)
EBV IgG U/ml (median, 95% IC)	117 (36-374)	90 (36-329)
EBV IgM U/ml (median, 95% IC)	0 (0-0)	0 (0-0)
EBV DNA copie/ml (median, 95% IC)	0 (0-0)	0 (0-0)
% CD4+ T-cells (median, 95% IC)	37.4 (28.2-43.7)	16.9 (15-21.7)
% CD8+ T-cells (median, 95% IC)	47.5 (37.7-53.4)	61.1 (49.4-69.6)
CD4+/CD8+ (median, 95% IC)	0.81 (0.58-1.13)	0.27 (0.24-0.45)
% CD19+ B-cells (median, 95% IC)	4.67 (1.39-8.37)	13 (5.62-19)
% NK cells (median, 95% IC)	4.06 (2.47-9.41)	5.94 (4.24-9.3)
Conditioning regimen		
melphalan 200 mg/mq (%)	48 (89%)	20 (91%)
melphalan 140 mg/mq (%)	6 (11%)	2 (9%)
CD34+ cells infused (10^6/Kg) (median, 95% IC)	5.17 (4.32-5.49)	5.11 (4.63-5.28)
Neutrophils engraftment (median, 95% IC)	11 (10-12)	10 (10-11)
Febrile neutropenia (%)	38 (70%)	14 (64%)
Invasive fungal infection (%)	1 (2%)	0 (0%)
WBC/uL +1 month (median, 95% IC)	5480 (4033-7098)	5765 (4765-7080)
Lymphocytes /uL +1 month (median, 95% IC)	990 (498-1648)	1170 (848-2003)
WBC/uL +2 month (median, 95% IC)	5620 (3925-7488)	5000 (3693-5928)
Lymphocytes/uL +2 month (median, 95% IC)	2080 (1623-2743)	1590 (950-1850)
WBC/uL +3 month (median, 95% IC)	4585 (3600-6010	4410 (3155-5350)
Lymphocytes/uL +1 month (median, 95% IC)	1400 (995-2100)	1280 (775-1705)
CMV infection (%)	36 (67%)	14 (64%)
Days to first CMV-DNA+ (median, range)	21 (7-49)	21 (14-35)
Duration of CMV infection, days (median,range)	21 (7-49)	25 (7-63)
PET (%)	13 (24%)	5 (23%)
Duration of PET, days (median, range)	21 (7-42)	28 (14-56)
CMV disease (%)	1 (2%)	1 (5%)
MM disease response rates (%)	54 (100%)	22 (100%)
Partial response	0 (0%)	0 (0%)
VGPR	12 (22%)	2 (9%)
CR	17 (31%)	11 (50%)
sCR	25 (46%)	9 (41%)

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SAFETY OF DECADE PLUS USE OF IGPRO20 IN THE REAL WORLD: POST-MARKETING PHARMACOVIGILANCE REPORT

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Introduction. IgPro20 (Hizentra®, CSL Behring) is a subcutaneous human immunoglobulin approved since 2010 for the treatment of primary and secondary immunodeficiency, and since 2018 for maintenance therapy in chronic inflammatory demyelinating polyneuropathy (CIDP). We investigated spontaneous reports of thromboembolic events (TEEs) and infections in patients having received IgPro20.

Methods. The CSL Behring safety database was used to retrieve all post-marketing cases (since product launch in 2010 until 31 May 2023), which registered adverse events from the 'Opportunistic infections' (broad) and 'Embolic and thrombotic events' Standardized MedDRA Queries. Reporting rates of adverse events are presented as cases per 100 patient years of exposure to IgPro20,calculated by dividing the total

amount of IgPro20 sold by the estimated weekly CIDP (20g) or immunodeficiency (10g) dose. The indication for IgPro20 use was based on the reporter designation.

Results. The reporting rate of TEEs was 0.36 (estimate based on CIDP dose) or 0.18 (estimate based on immunodeficiency dose) per 100 patient years. Infections were reported with a rate of 1.27 (CIDP dose estimate) or 0.63 (immunodeficiency dose estimate) per 100 patient years; the most frequent were COVID-19, Influenza and Herpes Zoster (respectively, 0.31, 0.27 and 0.09 per 100 patient years (CIDP dose estimate) or 0.15, 0.13 and 0.05 per 100 patient years (immunodeficiency dose estimate). For 36 TEE cases (6.9% of all reported TEE cases) and for 88 infection cases (4.8% of all reported infection cases), the reported indication was CIDP. Patient exposure for IgPro20 was estimated to be between 144,000 patient years based on the CIDP and 287,000 patient years based on the immunodeficiency dose.

Conclusions. Spontaneous reports of adverse events, collected over a period of more than ten years, show that adverse events of interest in patients having received IgPro20 (including TEEs and infections) were rare, including in patients with CIDP and immunodeficiency.

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