3rd European Myeloma Network Meeting

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ABSTRACT BOOK
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Looking at evolution of SMM into MM, two main patterns can be inferred. One where the tumor does not change, implying it biologically is a MM from the start and early treatment may be beneficial; and another where the genomic composition of the tumor changes, implying the tumor was actually indolent at the time of diagnosis and treatment strategy may be aimed at eradication before the acquisition of aggressive subclones.

Recent evidence suggests there is an advantage when treating SMM early, and studies are evaluating whether a more aggressive diagnosis approach -or even MGUS screening- may be beneficial for the patient. However, this will need to be paralleled by a better understanding of the biology of the tumor, and genomic prognostication may help better prognostication and treatment choices in MGUS/SMM patients.
However, they represent an important limitation for periodic disease monitoring because it entails an aggressive procedure. Moreover, recent findings are showing that a single BM aspirate is unable to reflect the complex MM heterogeneity. Recent advances in flow cytometry, microfluidics and "omics" technologies have made possible the detection and isolation of circulating tumor cells (CTCs), which offers a promising and minimally invasive alternative for tumor assessment and metastasis study. CTCs are detectable in premalignant and active MM states and its enumeration has strong prognostic value, to an extent that it is challenging current stratification systems. In addition, CTCs reflect with high precision both intra and extramedullary disease at the phenotypic, genomic and transcriptomic levels. Despite the high resemblance between tumor clones in distinct locations, some subtle (not random) differences might shed some light onto the metastatic process. Thus, it has been suggested that a hypoxic and pro-inflammatory microenvironment could induce an arrest in proliferation forcing tumor cells to recirculate. In my presentation, I will summarize data on the characterization of MM CTCs as well as their clinical and research potential.

**EXTRAMEDULLARY DISEASE**

Beksac, Meral

High risk or ultra-high risk Multiple Myeloma are observed among 15 to 10% of newly diagnosed Multiple Myelona(NDMM). These constitute the group of patients which are the most difficult to treat. Cytogetic, molecular and clinical parameters define such high risk patients at diagnosis. Among clinical findings extra-medullary plasmacytoma(EMP), plasma cell leukemia (PCL) can be recognized. The incidence of EMP at diagnosis ranges between 7-18% (1) However incidence increases at later phases of disease to reach 70%. Central nervous system or liver plasma cell infiltration has been reported at autopsy highly frequently (1) Classification of EMP is not standardized yet. It is of great importance to exclude solitary plasmacytoma and para-osseous (PO) expansion of bone plasmacytomas from soft-tissue plasmacytoma(1,2). Table 1 is adapted from a recent review from the Mayo Group(3).

| Table 1. Classification of EMD adapted from Bansal et al (Blood Cancer Journal 2021) |
|-------------------------------------------------|
| Solitary plasmacytoma with no marrow involvement | Biopsy proven single plasmacytoma with no marrow plasma cell infiltration |
| Solitary plasmacytoma with minimal marrow involvement | Solitary plasmacytoma with < 10% clonal plasma cells in bone marrow |
| Bone associated EMD with MM (EMM) | Extra-medullary para-osseous (PO) myeloma extending from bone and growing contiguous |
| Bone independent EMD with MM (EMM) | Isolated extra-osseous plasmacytoma (EMP) not contiguous with any bone lesion |
| Organ infiltrating EMD | Diffuse or nodular infiltration in liver, central nervous system, skin, lymph node etc |
| Plasma cell leukemia | Presence of clonal plasma cells in circulation (>5% or > 2 x 10^9/L) |

**Treatment**: Apart from radiotherapy there is no standard treatment of EMD(4). Until recent there are no prospective trials aiming to analyze efficacy in particular among patients presenting with EMD at diagnosis. Montefusco et al performed a meta analysis comparing outcome of EMD patients versus those without EMD among eight prospective NDMM GIMEMA trials(5). IMID- or PI-based therapy in patients (n = 2332) with NDMM included 267 patients with soft-tissue plasmacytomas (PO, n = 243; EMD, n = 12; not classified, n = 12). Median PFS and OS were similar (PFS: 26.1 months and 25.2 months; OS: 70.1 months and 79.9 months) In patients with EMD and without plasmacytomas, respectively. Another retrospective analysis by the Balkan Myeloma Study Group among 226 patients showed higher complete response among those presenting with PO involvement versus EMP at diagnosis (34.2 % vs. 19.3 %; p<NS) and relapse (54.5 % vs. 9 %; p=0.001) following a median of two lines of treatment(6). Also PO disease had a better response when recognized at initial diagnosis of myeloma than at relapse (51.7 vs. 38.9 months). In addition, OS was also better for PO involvement compared to EMP at diagnosis (not reached vs. 46.5 months). EMP at relapse had the worst prognosis with a PFS of (9.1 months) and overall survival (11.4 months).

Since anti-CD38 monoclonal antibodies in particular combined with Carfilzomib or Pomalidomide are highly effective against advanced myeloma cells we have attempted to treat a patient presenting with pleural EMD. Our results in view of the published similar reports favour this combination as a bridging therapy to stem cell transplantation(10).

Among recent randomized clinical trials EMD is gradually being recognized as a risk factor but response rate and durations are rarely reported. The ICARIA study comparing the efficacy of Isatuximab in the Pomalidomide-dexamethasone backbone is an exception and EMD results have been reported at two Congresses(9). Among 307 RRMM patients randomized to two study arms: Isa-Pd (n=154) or Pd (n=153). At study entry, soft-tissue plasmacytomas were present in 24 (7.8%) patients of those, 14 (9.1%) patients were in the Isa-Pd and 10 (6.5%) patients in the Pd arm. Limited to only EMD patients PFS was improved by adding Isa to Pd: HR: 0.22, 95% CI: 0.07-0.69. Median PFS was 4.57 (95% CI: 2.40-not calculable [NC]) months in the Isa-Pd arm versus 1.56 (95% CI: 0.95-4.47) months in the Pd arm. A multivariate analysis of PFS adjusted for ISS stage, cytogenetics risk, and number of prior lines was performed. The difference in the HR after adjustment (adjusted hazard ratio of 0.39, 95% CI: 0.119-2.582 versus 0.211-1.199) indicates that the prognostic factors may have influenced the treatment effect in favor of Isa-Pd arm, but the adjusted HR was still in favor of the Isa-Pd arm. The overall response rate also improved with 50% (7/14) and 10% (1/10) responders in the Isa-Pd and Pd arms, respectively. Very good partial response occurred in 21.4% (3/14) of patients in the Isa-Pd arm and 10% (1/10) of patients in the Pd arm.

The prospective phase 2 EMN19 study (acronym ANTARES) is currently ongoing to evaluate the efficacy of Daratumumab combined with Cyclophosphamide Bortezomibe and Dexamethasone among both NDMM and first relapse MM presenting with EMD excluding PCL. Results are expected to be presented in 2022.

**Autologous Stem Cell Transplantation**: The multi-center, multi-national retrospective study of the Balkan Myeloma Group included patients who received autologous SCT (44%) following their EMD diagnosis. In the multivariate analysis, PO, EMD at diagnosis, ISS-1 and undergoing ASCT improved OS independently(6).

Within the EBMT Registry data on clinical and cytogenetic data from 488 patients with NDMM and EMD (PO, n=374; EMP, n=114; both, n=27) high-risk cytogenetics were over-expressed (41%)(7). Outcomes following single autologous SCT were significantly worsened in the presence of high-risk cytogenetic abnormalities, whereas a tandem autologous transplant strategy was shown to offset the poor prognosis. A analysis on EMD effect among 3744 NDMM patients reported no difference in 3-year PFS following first-line autologous SCT between those with single sites of EMD (any location) and those with diffuse EMP(8). However, single EMP involvement was associated with worse 3-year OS compared with no EMD, which worsened still further when multiple sites of organs were involved. (8)

Depth of response measurement must include functional imaging among patients presenting with EMD. PET-CT has contributed to an increase in the incidence of EMD both at diagnosis and at relapse. Patients responding in the marrow and a reduction in M protein secretion may continue to harbour clonal plasma cells outside of the marrow. PET-CT metabolic response has been developed to quantify and standardize such cases(11).**Novel Treatments**: Recently CAR-T treatments have provided unprecedented high and durable responses among advanced and highly refractory myeloma patients. The incidence of EMD among such patients is higher that at diagnosis. In the KARMA study as presented at ASH 2020 EMD incidence was 40 % with a rate (24 % vs 39%) and median duration (9.2 vs 11.1 months) of complete response inferior to those without EMD. Thus CAR-T is a potential treatment approach which is currently far from being curative. BITEs are also moving forward and there are anecdotal cases achieving good quality responses with Telcistamab or Talquetamab. Currently the unmet need for treatment of high risk myeloma including patients presenting with EMD is still unanswered. Based on experience among advanced patients are promising and novel immunotherapeutic approaches integrated into the induction may provide a breakthrough in this area(4,12).

1. Blade J, de Larrea C F, Rosiñol L, Cibeira M T, Jiménez R, Powles R. Solitary plasmacytoma in Multiple Myeloma: incidence, mechanisms of extramedullary spread and treatment approach. J Clin Oncol 2011 29:28, 3805-3812
MINIMAL RESIDUAL DISEASE IN PERIPHERAL BLOOD ASSESSED BY MASS SPECTROMETRY

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Despite the high rates of complete response (CR) achieved with the current treatments, patients with multiple myeloma (MM) continue to relapse due to the presence of undetected disease. Disease identification in patients with standard CR using more sensitive techniques (flow cytometry and sequencing) has been named “minimal” or “measurable” residual disease (MRD) and numerous studies have demonstrated its capacity to identify patients at a higher risk of progression and/or death. However, the evaluation of MRD in MM might ignore distant foci or extramedullary disease and hemodiluted BM samples could produce false negative results. Further, the procedure to obtain a BM sample is painful, which prevents to perform it frequently. Therefore, there alternative methods for MRD assessment in more accessible and representative samples, such as peripheral blood (PB) need to be tested.

Mass spectrometry (MS) is an analytic method based on the measurement of mass-to-charge ratio of ionic species. Each monoclonal protein (MP) is characterized by a unique sequence of amino acids that is specific to each plasma cell clone (and MM patient), thus permitting single-clone tracking overtime with high sensitivity and specificity. The Spanish Myeloma Group GEM/PETHEMA has investigated the use of QIP-MS to assess treatment response vs standard and BM-based MRD analysis by next generation flow (NGF). In the GEM-ESAR trial for patients with high-risk smouldering MM, the presence of an MP was evaluated by flow cytometry and QIP-MS (targeting with light chain (FLC) - QIP-FLC-MS) vs conventional serum protein electrophoresis (SPEP) and immunofixation (sIFE) in 77 patients. When the analysis of FLCs was added to QIP-lg-MS, the percentages of positive cases increased from 80% to 85% post-induction, from 60% to 68% post-asCT and from 56% to 63% post-consolidation. Importantly, among patients achieving at least CR, the percentage of positive cases by QIP-lg-MS + QIP-FLC-MS was 60%, 38% and 43% post-induction, post-asCT and post-consolidation, respectively. More recently, results from 186 newly diagnosed MM patients enrolled in the GEM2012MENOS65 trial have been presented. As compared to SPEP/IFE, QIP-MS detected the paraprotein in a higher proportion of cases at each time point: 63% vs 52% post-induction, 46% vs 36% post-asCT and 35% vs 27% post-consolidation. Importantly, QIP-MS identified the MP in a cohort of patients in standard CR and this was associated with a significantly shorter progression free survival (PFS) (p=0.0008).

As compared to NGF, the percentage of concordant results was around 80% at all time points analyzed and both techniques exhibited a similar prognostic value in terms of PFS throughout the treatment: post-induction (NGF: p=0.012; QIP-MS: p=0.015), post-asCT (NGF: p=0.015; QIP-MS: p=0.057) and post-consolidation (NGF: p=0.001; QIP-MS: p=0.005).

In conclusion, from our results, MS-based methods can detect the MP in serum with a higher sensitivity as compared to conventional SPEP/IFE. As compared to NGF in BM, MS in PB displays a fair degree of concordance and is associated with a comparable prognostic value. However, more data are needed to define the final role of MS in the follow-up of patients with MM.

HOW TO INCORPORATE MRD IN CLINICAL TRIALS

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Depth of response is the key element to evaluate treatment efficacy and predict survival. Eradicating all tumor cells is necessary to cure most malignancies and this requires achieving and maintaining the deepest response possible. Both next generation flow (NGF) cytometry, and next generation sequencing (NGS) affords a sensitivity of 10-6. Patients that achieve a negative MRD status at the level of 10-5 or 10-6, display significantly longer progression-free (PFS) and overall survival (OS) when compared to those with positive MRD. The prognostic impact of MRD apply to newly-diagnosed transplant eligible and ineligible MM as well as relapsed/refractory Multiple Myeloma: Analysis of High-Risk Subgroups in the KarMMa Study. Blood 2020 suppl: 3234a

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months to minimize the risk of false-negative results. Mass spectrometry is also emerging as a potent technique to detect low levels of paraprotein as a surrogate for residual disease. In addition imaging techniques, particularly PET-CT, has an important role for MRD assessment outside of the BM. Currently MRD has been incorporated in numerous clinical trials with different aims: 1. to evaluate treatment efficacy; 2. to compare two treatment approaches; 3. adapted therapy intensity according to MRD follow-up; 4. to adapt maintenance duration; 5. to introduce Early Rescue Intervention (ERI) strategies. The implantation of MRD should help in avoiding over and under treatment and may become a surrogate biomarker for accelerated drug development and operational care.

**HOW TO TREAT HIGH RISK PATIENTS**

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Whilst outcome has improved for most multiple myeloma patients, the treatment of high-risk and ultra-high-risk disease remains challenging. Recent evidence regarding molecular diagnostics as well as retrospective and novel prospective data regarding improvements with innovative treatment approaches will be discussed in this presentation.

**HOW TO TREAT UNFIT AND FRAIL PATIENTS**

Cook, Gordon

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Therapeutic options have greatly expanded over recent years defining new standards of care in multiple myeloma (MM). However, MM is a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced a heterogeneous disease as are the patients it affects. As the median new standards of care in multiple myeloma (MM). However, MM is a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals.

**TREATMENT AT RELAPSE: WHAT TO DO FIRST?**

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Over the last years and because of the introduction of novel drugs, autologous stem cell transplant as well as maintenance as part of the first line of therapy, together with the better knowledge of the disease biology and new techniques to measure the residual disease, the duration of the response after the diagnosis is longer than in the past. However, most patients will finally progress and we have to consider some patients and disease-based factors in order to make the right choice: i) chronological age; ii) frailty; iii) organ function; iii) risk status; iv) life style and family support and v) treatment history.

The first consideration at the moment of the relapse is if we should treat biochemical or clinical relapses and it is highly recommended to treat at the biochemical relapse with the only exception of indolent diseases at the diagnosis (ISS-1, anaemia as the only myeloma defining event…). The second consideration is to evaluate the treatment history and the refractoriness to the previous drugs. Today, most patients at the moment of first relapse, are exposed to proteasome inhibitors and immunomodulatory drugs and refractory to lenalidomide and over the last months, some patients are also exposed to the anti-CD38 monoclonal antibodies.

According to the most recent guidelines and phase 3 clinical trials, if the patient is eligible for anti-CD38 monoclonal antibodies because the patient is naive or sensitive, the optimal choices are carfilzomib-dexamethasone plus either daratumumab or isatuximab or pomalidomide-dexamethasone plus daratumumab. If the patient is not eligible for anti-CD38 monoclonal antibodies, the possibilities would be either pomalidomide-dexamethasone plus bortezomib or Selinexor-dexamethasone plus bortezomib. Of note, venetoclax-dexamethasone alone or in combination will be reserved for patients with t(11;14). These recommendations would be applicable to patients in first relapse. There are some other combination recommended for third line and beyond, and based on pomalidomide-dexamethasone, if the patient has not been previously exposed, in combination with either isatuximab or elotuzumab although it is also possible to combine with cyclophosphamide.

In summary, we have to follow the current guidelines for the management of MM at first relapse although the treatment landscape is rapidly evolving and phase 3 trials are ongoing with the objective of incorporating the BCMA-targeted therapy at first relapse.

**AL AMYLOIDOSIS: MECHANISMS OF DISEASE AND BIOMARKERS**

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Light chain (AL) amyloidosis is caused by usually small B cell, usually plasma cell, clones that produces a monoclonal light chain (LC) causing organ toxicity, aggregating and forming deposits in tissues.

Biomarkers of clonal and organ involvement play a key role in the diagnosis, treatment stratification and in the therapeutic strategy, including response assessment. Serum and urine immunofixation (IFE) and free LC (FLC) measurements are used to detect the amyloid LC. Investigation of chromosomal abnormalities in plasma cells including response assessment. Serum and urine immunofixation (IFE) and free LC (FLC) measurements are used to detect the amyloid LC. Investigation of chromosomal abnormalities in plasma cells offers precious information for the choice of treatment. Patients with t(11;14) have poorer outcomes with bortezomib and dexamethasone (BDex) with/without cyclophosphamide. These patients can be treated with BDex plus melphalan, daratumumab-bortezomib combinations, and possibly in the future with venetoclax. On the other hand, gain1q21 is associated to a dismal outcome after first-line melphalan and dexamethasone or after lenalidomide or daratumumab-based regimens in relapsed/refractory disease. Patient survival is best predicted by cardiac biomarkers that are also used for stratification in clinical trials and to predict cardiac toxicity with stem cell transplant. Proteinuria and estimated glomerular filtration rate are used to assess the risk of dialysis. The replacement of 24h-proteinuria with urinary albumin/creatinine ratio for renal staging has been recently proposed.

Hematologic response (HR) is assessed by IFE and FLC measurement and organ response (OR) by changes in NT-proBNP and proteinuria,
according to validated response criteria. Organ response can also be graded or combined with HR in a composite HR and OR model. Novel technologies will improve our ability to assess deep HR, as new methods for identification of amyloid LC and next generation flow cytometry for minimal residual disease identification (MRD). It has been shown that in patients who attain complete response the absence of MRD is associated with a higher probability of also attaining OR. This indicates that very small, undetectable concentrations of the amyloid LC can sustain persistent organ dysfunction. Finally, it is under investigation the possible additional prognostic role of advanced cardiac imaging at diagnosis and after treatment. Clinical observation assisted by biomarkers and advanced imaging will improve our knowledge of the mechanisms of disease in cardiac amyloidosis, giving a better perspective of the role of organ toxicity and amyloid load.

**LIGHT CHAIN DEPOSITION DISEASE**

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Light chain deposition disease (LCDD) is a very rare, non-amyloid variant of the deposition diseases seen in monoclonal gammapathies. LCDD is one of the non-amyloid Monoclonal immunoglobulin deposition diseases next to heavy chain (HCDD), or combined light and heavy chain deposition disease (LHCDD).

The underlying clone in LCDD, most commonly plasmacell but can be lymphoid, is mostly small (median 10% BM infiltration) and therefore LCDD can be considered as one of the Monoclonal Gammapathies of Renal Significance (MGRS). Often there is only light chain as the circulating monoclonal component, most often kappa, followed by IgG heavy chain.

The clinical presentation is markedly different from AL Amyloidosis; LCDD virtually always presents with kidney involvement while cardiac, liver and other organs are involved in a minority of patients only. Up to 30% of patients present with End Stage Renal Disease at diagnosis.

LCDD is diagnosed by demonstrating monoclonal light chain (mostly kappa) deposits in a biopsy of an involved organ (most commonly the kidney). Of importance, renal prognosis among those diagnosed in 4 or 5 Chronic Kidney Disease is better among patients with LCDD than renal AL amyloidosis. In the latter, end stage kidney disease is rarely reversible, while in LCDD improvements can be seen even in patients that start treatment in stage 4 CKD. Achievement of a durable hematological CR or VGPR is associated with significant and ongoing improvements in renal function in most patients. However, LCDD patients that do not achieve a CR or VGPR will most likely to experience progressive renal failure. Also, prognosis is better in patients with less CKD compared to stage 4 or 5 CKD at diagnosis. Therefore, timely diagnosis and achievement of a rapid and durable deep hematological response are important goals in LCDD.

There are no prospective data on optimal treatment for this rare disease. Based on retrospective data, clone direct therapy including proteasome inhibitor based induction followed by High Dose Melfalan + autologous stemcell rescue have yielded high and deep responses (both hematological and renal) in retrospective series. Some small reports have shown favourable results of daratumumab. Renal transplantation has been performed successfully in patients in a hematological remission, but is unsuccessful if patients have active hematological disease.

**IMMUNOTHERAPY**

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Cellular Immunotherapy involving CAR T cells, TCR transduced T cells and T cell engaging antibodies are increasingly used for the treatment of multiple myeloma. Currently, only one, maybe two CAR T cell products are approved for clinical use in patients with relapsed / refractory multiple myeloma (for the 3 lines of prior therapy and progression under the last treatment). One bispecific antibody, which is also targeting BCMA on myeloma cells, will soon be approved for clinical use in heavily pretreated patients with multiple myeloma.

Due to the fact that T cell fitness and repopulation potential of T cells is clearly increased in earlier lines of therapy, there are increasing studies now testing CAR T cells and bispecific antibodies in earlier lines of treatment of multiple myeloma. We need additional studies in early relapse frontline therapy with CAR T cells and bispecific antibodies to optimize their anti-myeloma potential and on the other hand future trials will have to study whether the higher T cell fitness and longer persistence of CAR T cell might also increase toxicity of CAR T cells and/or bispecific antibodies when used in frontline therapy or for early relapse. We also have to screen whether the hematotoxicity, which is a significant side effect, of CAR T cell therapy and T cell engaging antibodies will be reduced if the patient is less heavily pre-treated.

So in summary, we urgently need more trials with T cell engaging antibodies, CAR T cells and also TCR transduced T cells in earlier lines of therapy, including randomized trials comparing CAR T cells and bispecfic antibodies to high dose chemotherapy and autologous stem cells transplantation and thus to further define the role of the novel immunotherapies in early lines of therapy for multiple myeloma.

**COVID-19 AND MYELOMA**

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The disease- and treatment-induced immunosuppression in MM accounts for a two-fold higher risk for infection with the SARS-CoV-2 virus, an increased risk for a prolonged, severe symptomatic disease, and an increased mortality. Most pts are aware of these risks and show a higher compliance with vaccination recommendations compared to the general population.

Several studies revealed differences in the humoral and cellular immune response between pts with MGUS, SMM, and MM, with normal median antibody titers in MGUS, moderately impaired response in SMM, and significantly reduced antibody response in MM, albeit with a wide variation in titers between individual pts. Pts with active, poorly controlled disease and those exposed to CD38 and BCMA-targeting treatments frequently show no or reduced SARS-CoV-2 antibody responses. The EMN issued a consensus that MM pts should ideally be vaccinated before onset of active disease and/or during periods of well controlled disease. A third dose should be administered after an interval of approximately 6 months, and early data in immunocompromised pts show a vaccination response in several previously poorly responding pts after a forth dose. An open question pertains to the role of the interrelationship between the innate, humoral and cellular immune system. Neutralizing antibodies provide the best proxy for protection, although specific thresholds associated with protection against infection are unlikely to be established given the many factors associated with infection control. Antibody titers decline with time from vaccination and more so in vaccinated pts compared to those who have been infected and vaccinated, mandating booster shots in time intervals that need to be established. Pts may present without measurable antibody titers but with detectable cellular immunity or vice versa, although in most reports, correlations between antibody and cellular response were noted. Data suggest that SARS-CoV-2 specific memory B and T cells persist for prolonged periods.

One of the threads to patient protection is the substantial mutational activity of the SARS-CoV-2 virus with reduced neutralizing capacity of vaccine induced antibodies against recent variants of concern, particularly the omicron variant, posing vaccinated pts at risk for breakthrough infections. Recent research efforts resulted in new prophylactic treatments for pts with high risk for severe COVID-19 disease (Table 1) that have been shown to reduce the incidence of severe complications.
Osteolytic bone disease is the most common complication of multiple myeloma. Bone targeted agents should be administered in all newly-diagnosed myeloma patients with myeloma-related bone disease. Zoledronic acid should be given even in newly-diagnosed patients without bone disease and it is preferred over other bisphosphonates due to its survival advantage. Zoledronic acid is administered monthly. However, once patients achieve VGPR or better, the treating physician may consider decreasing frequency of dosing to every 3 months or based on osteoporosis recommendations (every 6 months or yearly), or even to discontinue therapy if the patient has received one year of monthly zoledronic acid. Bisphosphonates should be re-administered at a monthly schedule at the time of relapse if new evidence of bone disease is present.

Denosumab can also be considered for the treatment of myeloma-related bone disease, particularly in patients with renal impairment. In the largest placebo-controlled trial for myeloma patients to-date, denosumab was compared to zoledronic acid. Although, there was no difference regarding time to first skeletal-related event (SRE), a landmark analysis at 15 months showed a superiority of denosumab. Denosumab may also prolong PFS among newly-diagnosed patients with bone disease, who are eligible for autologous transplantation. Denosumab should be administered as a subcutaneous injection of 120mg at monthly intervals continuously, according to its label. Dosing de-intensification or drug holiday or discontinuation might be considered only after 24 months of treatment and if patient has responded to anti-MM treatment defined as VGPR or better. Discontinuation of denosumab is challenging due to the rebound phenomenon observed in osteoporosis patients. In this case, and until further data is available on myeloma patients, a single dose of iv bisphosphonate (i.e. zoledronic acid) is recommended at least 6 months after the last denosumab dose in order to prevent a potential rebound effect.

Balloon kyphoplasty and vertebroplasty are recommended for patients with painful vertebral compression fractures. Radiotherapy should be considered for uncontrolled pain due to impeding or symptomatic spinal cord compression and due to pathological fractures. Surgery should be considered for prevention and restoration of long-bone pathological fractures, vertebral column instability and spinal cord compression with bone fragments within the spinal route.

### Table 1.

| Medicine                        | Mode of Action       | Administration                                      | EMA/FDA approved |
|---------------------------------|----------------------|-----------------------------------------------------|------------------|
| Nirmatrelvir and Ritonavir (Paxlovid) | Antiviral            | 2 tablets Nirmatrelvir plus 1 tablet Ritonavir twice daily for 5 days | Yes/EUA         |
| Molnupiravir (Lagevrio)         | Antiviral            | 4 tablets twice daily for 5 days                    | EUA*/EUA        |
| Remdesivir (Veklury)            | Antiviral            | 200 mg IV infused over 30-120 min, Yes/Yes then day 2 and thereafter: 100 mg i.v. q/day for 5 days (10 days max) | Yes/Yes         |
| Sofrovimab (Xevudy) Monoclonal antibodies | Antiviral            | 500mg through an infusion over 30 minutes | Yes/EUA        |
| Tixagevimab (Evusheld**) Monoclonal antibody cocktail | Monoclonal antibody | 300mg of Tixagevimab and 300mg administered in 2 separate consecutive i.m. injections | EUA/Submitted/EUA |
| Bebtelovimab Monoclonal antibody | Monoclonal antibody | 175mg through an infusion over 30 minutes | No/EUA         |

*EUA: Emergence use authorization, **approved for pre-exposure prophylaxis also, extended half-life, repeat administration in 6 months

**BONE DISEASE**

Terpos, Evangelos

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Osteolytic bone disease is the most common complication of multiple myeloma. Bone targeted agents should be administered in all newly-diagnosed myeloma patients with myeloma-related bone disease.
**BEST ABSTRACTS - ORAL PRESENTATIONS**

**B01 STROMAL CELL–NEUTROPHIL INTERACTIONS PROMOTE A PRO-TUMOR ENVIRONMENT IN MULTIPLE MYELOMA**

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Cancer development and progression are accompanied by alterations in the local microenvironment. In multiple myeloma (MM), interactions between myeloma cells and their niche are considered critical for disease pathobiology. Recently, we showed that the MM bone marrow (BM) is characterized by inflammatory mesenchymal stromal cells (iMSCs) that transcribe MM survival factors such as IL6, as well as myeloid cell modulation factors such as CCL2, ANX1, C3 and chemokines that bind CXCR1 and 2. As myeloid cells have been implicated in the pathophysiology of various malignancies, we hypothesized that iMSCs attract and influence myeloid populations in the MM BM. Using flow cytometry, we observed increased expression of CXCR1/2 on CD15+ neutrophils in MM compared to those of controls. In addition, BM neutrophils in MM were activated, as evidenced by a switch to the active form of CD11b and the shedding of CD62L. As these findings suggested possible neutrophil – iMSC interactions, we set out to identify MM-associated alterations in neutrophils by scRNA sequencing of the full BM granulocytic lineage (n = 6 MM, and 4 controls). Immature and mature neutrophils in MM had increased transcription of genes encoding receptors for iMSC-derived signals, including ILAR, FPR and C3AR1. Moreover, we confirmed the activated state of neutrophils through elevated transcription of OSM, SLPI, and IL1B. These data suggest a contribution of iMSCs to neutrophil activation. This was confirmed by coculture of iMSCs and naive neutrophils, which lead to shedding of neutrophilic CD62L. Further analysis of our transcriptional data revealed that a subpopulation of activated MM neutrophils expressed interferon (IFN)-response genes, including IFIT1, IFIT2 and ISG15. Importantly, by analyzing single cell immune datasets of MM bone marrow, we observed IFN-responsive neutrophils to be the only hematopoietic population transcribing TNFSF13B, encoding the MM-survival factor BAFF. Stimulation of naive neutrophils with IFNγ or IFNα induced TNFSF13B transcription, but did not lead to BAFF secretion. This led us to hypothesize that BAFF release by activated neutrophils might be regulated by the inflammatory stromal environment. To test this hypothesis we cultured IFNγ-stimulated neutrophils in the presence of either non inflammatory MSCs or IL11-activated iMSCs. Whilst the presence of iMSCs could induce BAFF release by neutrophils, non-inflammatory MSCs did not have this effect. Together these data suggest that stromal – immune interactions in MM are driving a tumor-supportive environment by inducing local release of plasma cell survival factors.

**B02 COMBINATION OF SUBCUTANEOUS TECLISTAMAB WITH DARATUMUMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): RESULTS FROM A PHASE 1B MULTICOHORT STUDY**

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**B03 SKELETAL-RELATED EVENTS AND ABNORMAL MRI PATTERN AT DIAgnOSIS ARE ASSOCIATED WITH INFERIOR OVERALL SURVIVAL IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA**

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Introduction: Skeletal related events (SREs) remain a devastating consequence of multiple myeloma bone disease (MMBD). The presence of osteolytic disease increases the risk of SREs, which include pathologic fractures, spinal cord compression (SCC) and need for surgery or radiotherapy to bone.

Methods: In this context, we conducted this single-center, prospective, observational study to determine the incidence of SREs among MM patients who received treatment with novel agents during first-line therapy (NDMM) and explore possible correlations with disease characteristics, imaging finding and patient prognosis.

Results: Overall, data from 370 patients with NDMM according to the International Myeloma Working Group criteria are included in the present analysis. 200 (54%) were males, whereas 99% were Caucasian. The median age at diagnosis was 65 (range 31-92). One third (n=120) had an ECOG performance status (PS) of 0, 27% (n=100) a PS of 1, 8% (n=30) a PS of 2 and 32% (n=120) a PS of 3-4. One third were ISS stage 1 (34%), one third were ISS stage 2 (35%) and another third were ISS stage 3 (31%). 214 patients (58%) had IgG myeloma subtype, 90 patients had IgA (24%) and 62 patients had light-chain myeloma (17%). At diagnosis, the patients were evaluated for the presence of MMBD with at least one of the following imaging modalities: whole body X-rays (WBXR), whole body low dose computed tomography (WBLDCT) and magnetic resonance imaging (MRI). Based on the WBXR, 73 patients (20%) had no osteolytic lesions, 48 patients (13%) had 1 to 3 lytic lesions and 223 patients (60%) had more than 3 lytic lesions at diagnosis. According to WBLDCT, only 12 (3%) patients had no osteolytic lesions, whereas 7 (2%) patients had 1 to 3 lytic lesions and 76 (20%) had more than 3 lytic lesions (data available for 95 patients). Based on MRI findings, 38 patients (16%) had normal MRI pattern, 151 (40%) had focal MRI pattern, 139 (38%) patients had diffuse MRI pattern and 22 (6%) had variable MRI pattern at diagnosis. Regarding treatment regimens at first line, 161 patients received IMiD– based regimens, 152 patients received PI-based treatments, 24 patients received PI and IMiD-based regimens, whereas 33 patients received therapy based on alkylating agents. SREs were observed in 183 patients at diagnosis: 154 (154/370 42%) patients presented with pathological fractures (110 with vertebral fractures, 29 with rib fractures and 15 with fractures of the long bones; 6 patients had both vertebral and 14 long bone or rib fractures), while 11 (11/370 3%) needed radiotherapy, 9 (9/370 2%) surgery to bone and 9 (9/370 2%) patients presented with spinal cord compression. The incidence of SREs at diagnosis was higher in patients with osteolytic lesions. Among patients with SREs at Diagnosis, 92.4% showed new SREs during the disease course with WBLDCT. Among those without SREs at diagno- sis, 72.2% showed new SREs with WBLDCT. Importantly, patients with abnormal MRI pattern, who did not present with SREs at diagnosis, had statistically significant improved median overall survival in comparison with patients who had abnormal MRI pattern or presence of SREs at diagnosis (9.2 vs 6.3 years, p=0.048).

Conclusion: Approximately one half of NDMM patients presented with SREs at diagnosis. The presence of SRE or abnormal MRI pattern was associated with inferior survival. SREs lead to functional impairment and increased mortality rates; therefore early detection and prompt management is essential.
In the phase 1 MajesTEC-1 trial, teclistamab (Tec), a B-cell maturation antigen x CD3 T cell redirecting bispecific antibody, showed an overall response rate of 65% at 6.1-month follow-up. Daratumumab (Dara) is a monoclonal antibody that targets CD38 and is approved for the treatment of MM. In MM cell lines, the lytic activity of Tec was enhanced by pretreatment and combination treatment with Dara; thus, the combination of both agents may improve efficacy in RRMM by targeting discrete yet complementary antigens. We present data on patients (pts) with RRMM who received Tec + Dara in the phase 1b TRIMM-2 study (NCT04198195).

Eligible pts were ≥18 years of age, had a MM diagnosis, and received ≥3 prior lines of therapy (LOT; including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double refractory to a PI and IMiD. Receipt of anti-CD38 therapy ≤90 days was not allowed. The primary objectives were to identify the RP2D for the Tec + Dara combination and to assess safety of the combination. This analysis focuses on subcutaneous (SC) cohorts in the study. Responses were assessed by IMWG criteria and adverse events (AEs) by CTCAE v5.0 (cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]) were graded per ASTCT guidelines.

33 pts received SC Tec + Dara in different dosing cohorts: Dara 1800 mg + Tec 1500 μg/kg weekly (n=21), + Tec 3000 μg/kg weekly (n=5), + Tec 3000 mg biweekly starting Cycle 3 Day 1 (C3D1; Tec 150 mg weekly in C1, + Tec 3000 μg/kg biweekly (n=5), 9 pts in the Dara 1800 mg + Tec 1500 μg/kg weekly cohort switched to Tec 3000 μg/kg biweekly dosing after C3D1. As of Jun 22, 2021, median follow-up across the cohorts was 3.6 months (range 0.1–10.4). Median age was 67 years (range 51–78) and 57.6% were female. Median number of prior LOT was 5 (range 2–16); 69.7% were triple-class exposed (prior Dara in all 69.7%) and 60.6% were penta-drug exposed. The most common AE was CRS (54.5%; all grade 1); median duration was 2 days (range 1–6), and median duration was 2 days (range 1–7). Other AEs (≥30%) were neutropenia (36.4%; all grade 3); thrombocytopenia (36.4%; grade 3/4 33.3%), anemia (36.4%; grade 3/4 24.2%), diarrea (36.4%; grade 3/4 3.0%), nausea (30.3%; all grade 1/2), and pyrexia (30.3%; all grade 1/2). Overall, 66.7% of pts had grade 3/4 AEs. Infections occurred in 51.5% of pts (grade ≥3 24.2%). No ICANS events were reported. One pt in the Dara 1800 mg + Tec 3000 μg/kg weekly cohort died from treatment-unrelated bacterial pneumonia during C1, and 1 pt in the Dara 1800 mg + Tec 1500 μg/kg weekly cohort died from progressive disease.

Responses are shown in the Table. Across the cohorts, median time to first response was 1.0 month (range 0–1.9). Median duration of response was not reached. Tec + Dara treatment led to proinflammatory cytokine production and T cell activation. The Tec pharmacokinetic profile was similar to that reported in the MajesTEC-1 study. The combination of Tec + Dara had a manageable safety profile and showed preliminary efficacy in pretreated pts with MM. These findings warrant further investigation, and the randomized phase 3 MajesTEC-3 study will evaluate Tec + Dara vs Dara, pomalidomide, and dexamethasone or Dara, bortezomib, and dexamethasone in patients with triple-class exposed RRMM and no direct head-to-head trials were performed to evaluate cilta-cel and other relevant treatments.

### Objective
To perform meta-analyses to derive single summary effect estimates for overall survival (OS) and progression-free survival (PFS) using pooled ITCs that evaluated cilta-cel versus PCT in patients with triple-class exposed RRMM.

### Methods
ITCs comparing the effectiveness of cilta-cel versus PCT were not available. OS and PFS were included in this analysis. The data cut-off date for CARTITUDE-1 was February 2021, and data for PCT were based on the following sources: (i) Flattiron, a largely US community-based MM registry; (ii) long-term follow-up data from POLLUX (NCT02076009), CASTOR (NCT02136134), and EQUULEUS (NCT01998971), three global RRMM daratumumab randomized clinical trials; (iii) MAMMOTH, a retrospective study based in the US, and (iv) a representative German patient registry maintained by OncologyInformationService. The PCT group for each ITC comprised pts who fulfilled key eligibility criteria for the CARTITUDE-1 trial and was made comparable to CARTITUDE-1 using inverse probability of treatment weighting, resulting in ITCs that were appropriate for meta-analysis. The meta-analysis used a robust variance estimation to account for the use of CARTITUDE-1 in each pairwise ITC. The main meta-analyses included all patients treated with cilta-cel in CARTITUDE-1 compared with PCT. Sensitivity analyses considered ITC effect estimates based on all patients enrolled in CARTITUDE-1. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are reported for pooled summary effect estimates.

### Results
Based on available data, the main meta-analyses included four ITCs for OS and three ITCs for PFS. Significant improvement in OS (HR: 0.21, 95% CI: 0.13–0.34) and PFS (HR: 0.2, 95% CI: 0.07–0.63) was observed with cilta-cel versus PCT (Figure). Results of the main meta-analyses were confirmed with sensitivity analyses that included all enrolled patients.

### Conclusions
Cilta-cel demonstrated a significant OS and PFS advantage versus PCT in the meta-analyses, highlighting its potential as an effective treatment in patients with triple-class exposed RRMM.
**B06  SUBCUTANEOUS TALQUETAMAB IN COMBINATION WITH DARUTUMUMAB IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM): PHASE 1B RESULTS**

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MM remains incurable with most patients (pts) relapsing or becoming refractory to standard therapies, highlighting the need for novel agents. Talquetamab (Tal) is a bispecific antibody that binds to G protein-coupled receptor family C group 5 member D (GPRC5D), a receptor highly expressed on plasma cells with limited expression in healthy tissue, and CD3 to redirect T cells to GPRC5D-expressing MM cells. In the phase 1 Monumental-1 study, an overall response rate of 70% at median 6.3-month follow-up was observed at the recommended phase 2 dose (RP2D) of Tal in pts with RRMM. Daratumumab (Dar) is a monoclonal antibody that targets CD38 and is approved for treatment of MM. In preclinical studies, Dar accelerated Tal-mediated lysis of MM cells, suggesting the potential to increase clinical activity in pts with RRMM when the agents are combined. We report initial findings for pts with RRMM who received Tal + Dar in the phase 1b multicohort TRIMM-2 study (NCT04101895).

Eligible pts (≥18 years) had MM and received ≥3 prior lines of therapy (LOT; including a proteasome inhibitor [PI] and immunomodulatory drug [IMiD]) or were double refractory to a PI and an IMiD. Pts who received anti-CD38 therapy ≤90 days were excluded. The primary objectives were to identify the RP2D of Tal in combination with Dar and to characterize the safety at the RP2D. Responses were assessed by IMWG criteria. Adverse events (AEs) were graded per CTCAE v5.0 (cytokine release syndrome [CRS] and immune effector cell-associated toxicities) and were graded per ASTCT criteria. Infections were defined as grade 3 associated with neutropenia (39.1%; grade 3/4 21.7%), anemia (34.8%; grade 3/4 21.7%), CRS (34.8%; all grade 1/2), and skin exfoliation (30.4%; all grade 1/2). Grade 3/4 AEs were reported in 78.3%. Median time to CRS onset was 2.5 days (range 2–5 days) and median duration was 2 days (range 1–3 days). Infections occurred in 34.8% of pts (grade 3/4 17.4%). Skin disorders were reported in 65.2% of pts (grade 3/4 13.0%), including nail disorders in 17.4% (all grade 1/2). Two ICANS events were reported (grade 1 [concurrent with CRS] and grade 3); both resolved and did not recur. One pt in the Dara 1800 μg + Tal 400 μg/kg biweekly cohort died from disease progression. Responses are shown in the Table. The median time to first response across the cohorts was 1.0 month (range 0.9–2.4), and median duration of response was not reached. Tal pharmacokinetics was similar to that reported in the Monumental-1 study. Proinflammatory cytokine production and T cell activation were observed after Tal + Dara treatment.

The combination of Tal with Dara was well tolerated, with a safety profile comparable to the monotherapies. The combination showed promising efficacy in pts with RRMM, supporting further clinical development of Tal + Dara combination therapy.

| Dara range μg/kg weekly (n=4) | Daratumumab | Combination |
|-------------------------------|-------------|-------------|
| Tal 400 μg/kg weekly | Tal 400 μg/kg biweekly (n=5) | Tal 800 μg/kg biweekly (n=8) |
| Partial or complete response | 3 | 3 | 7 |

Very good partial response or better | 3 | 3 | 6 |

**B07  SAFETY AND EFFICACY OF CITLACABTAGENE AUTOLEUCEL, A CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY DIRECTED AGAINST B-CELL MATURATION ANTIGEN IN PATIENTS WITH MULTIPLE MYELOMA AND EARLY RELAPSE AFTER INITIAL THERAPY: CARTITUDE-2 RESULTS**

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Introduction: CARTITUDE-2 (NCT04133636) is a phase 2, multicohort study evaluating the safety and efficacy of ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor T-cell (CAR-T) therapy with two B-cell maturation antigen (BCMA)-targeting single-domain antibodies, in patients with multiple myeloma (MM) in various disease settings.

Objective: To present the first results from cohort B of CARTITUDE-2, which enrolled patients following early relapse after initial therapy that included a proteasome inhibitor (PI) and immunomodulatory drugs (IMiDs) or lenalidomide (Len).

Methods: Eligible cohort B patients had MM, received 1 prior line of therapy (PI and IMiD required), had disease progression ≤12 months after autologous stem cell transplantation (ASCT) or frontline therapy, and were naive to CAR-T or anti-BCMA therapies. A single cilta-cel infusion (target dose: 0.75×10^6 viable T cells/kg) was given ≤5–7 days after initiation of lymphodepletion (300 mg/m² cyclophosphamide and 30mg/m² fludarabine daily for 3 days). The primary objective was minimal residual disease (MRD) negativity at 10⁻⁵. Adverse events were graded by Common Terminology Criteria for Adverse Events version 5.0 (cytokine release syndrome [CRS] and immune effector cell associated neurotoxicity syndrome [ICANS]) using American Society for Transplantation and Cellular Therapy (ASTCT) criteria.

Results: As of April 15, 2021, 18 patients (median age: 57.0 years [range: 44–67]; 78% men) received cilta-cel. Median follow-up was 4.7 months (range: 0.6–13.5), and median time from diagnosis to enrollment was 1.1 years (range: 0.5–1.9). Two (11.1%) patients had high cytogenetic risk and 5 (27.8%) had bone marrow plasma cells >30%; 14 (77.8%) patients had prior ASCT, and 15 (83.3%) were refractory to their prior therapy. Overall response rate was 88.9% (95% CI: 65.3–98.6) with 2 complete responses (CR) achieved by 27.8% (95% CI: 7.9–55.3) and 2 very good partial response (VGPR) achieved by 66.7% (95% CI: 41.0–86.7). Median time to first response was 0.9 months (range: 0.9–2.6), median time to best response was 1.4 months (range: 0.9–11.8), and median time to ≥CR was 1.8 months (range: 0.9–11.6). Of 13 patients with ≥3 months follow-up, 5 (38%) achieved ≥CR. All MRD-evaluable
patients (n=9) were MRD negative at 10⁻⁵ (Figure). Hematologic treatment emergent adverse events (TEAEs) in ≥20% of patients were neutropenia (88.9%), thrombocytopenia (61.1%), anemia (50.0%), leukopenia (27.8%), and lymphopenia (22.2%). CRS occurred in 15 (83.3%) patients (1 grade 4); median time to onset was 8 days (range: 5–11), and median duration was 4 days (range: 1–7). One patient had ICANS (grade 1). One patient experienced movement and neurocognitive TEAEs (grade 3) on Day 38 post ciltacel infusion. No deaths were reported post ciltacel infusion.

Conclusions: In patients who experienced early clinical relapse or treatment failure to initial therapy, a single ciltacel infusion resulted in early and deep responses with a manageable safety profile. Responses continue to deepen, and follow-up is ongoing. These findings support the investigation of ciltacel in earlier lines of therapy and incorporation into potentially curative frontline regimens.

Methods: In this context, we prospectively evaluated the development of NAbs against SARS-CoV-2 (ELISA, cPass™ SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA) in patients with MM at 30 days post vaccination with a third dose of the mRNA BNT162b2 vaccine (NCT04743388). Serum samples were collected on the date of the booster dose (just before vaccination) and 4 weeks after.

Results: The study population included 167 consecutive MM patients (58% males; median age: 68 years, IQR: 60-75 years) who were vaccinated with the booster BNT162b2 dose between September/October 2021, at the same vaccination center. All patients had been fully vaccinated with the two-dose BNT162b2. At the time of vaccination, the vast majority (93.4%) of patients were receiving anti-myeloma treatment. The booster dose significantly improved the humoral response in MM patients. More specifically, the median (IQR) of NAbs titer reached 96.7% (52.6-97.8%) as compared with 27.1% (13.9%-65.8%) before the third dose (p<0.001). Overall, 114 (68%) patients had less than 50% NAbs activity before the third dose. Among them, 75 (65.8%) patients increased their NAbs titer to at least 50% after the third dose. Interestingly, the patients who had achieved a NAbs titer of ≥50% at one month after the second vaccine dose were more likely to achieve a NAbs titer of ≥50% at one month after the third dose, as compared with those who had inferior antibody responses after the second dose (p=0.001). Fifty-seven (34%) patients had not developed a sufficient humoral response following the second vaccination (NAbs titer <30%). All of them presented with low NAbs titers before the third dose (median 14.5% (IQR 7.2%-23.3%)). The third vaccine dose boosted the median antibody response to 38.8% (IQR 15.6%-92.3%, p<0.001). At one month after the booster dose, 52/57 (56%) patients showed a NAbs titer above the positivity threshold (≥30%) and 26/57 (45.6%) showed a NAbs titer of ≥50%.

In the multivariate analysis, only the presence of a NAbs titer ≥30% at one month after the second dose (Odds Ratio (OR) 9.5, 95% Confidence Interval (CI): 3.3-27.6) and the treatment with anti-BCMA agents (OR 0.03, 95% CI: 0.003-0.27) emerged as significant predictive factors for a NAbs titer ≥50%. None of the patients who were under anti-BCMA therapy achieved a NAbs titer of ≥50% one month after the booster dose.

Conclusion: Our study demonstrated that a third BNT162b2 dose in patients with MM optimized the humoral response against SARS-CoV-2, as depicted by the significant increase in NAbs at one month post the booster dose. Importantly, ~46% of patients with suboptimal NAbs responses at one month following the two-dose BNT162b2 vaccination showed NAbs titers over 50% at one month after the booster dose. Taking also into consideration the defective immunity in patients with MM and the current COVID-19 outbreaks, self-protection measures, such as mask wearing and social distancing, remain particularly important.
**P01 ARGinine STARVATION IN MULTIPLE MYELOMA MICROENVIRONMENT CONVEYS BORTEZOMIB REFRACTORINESS VIA TLR4 PATHWAY.**

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**Background:** In multiple myeloma (MM) malignant plasma cells (PC) can induce metabolic changes in the local microenvironment that are closely related to drug resistance and disease progression. Arginine (Arg) is a non-essential amino acid which plays an important role in the immune-escape mechanisms and in BTZ resistance. Since our group has previously demonstrated that BTZ-resistant PCs upregulate TLR4 pathway as a stress responsive mechanism, and TLR4-driven cytokine production in starvation is under control of general control nonderepressible 2 (GCN2), a serine/threonine-protein kinase that senses amino acid deficiency through binding to uncharged transfer RNA, we aimed to investigate TLR4 signalling in response to Arg deprivation.

**Methods:** Our in vitro studies are carried out on three human myeloma cell lines (HMCLs) (U266, NCI-H929, OPM2) cultured in medium with different Arg concentrations: R100 (114 μM/mL) and R10 (11.4 μM/mL) and correspondent respectively to 100%, 25% and 10% of the arginine concentration in MM bone marrow, for 24h or 48h. Our study suggests that TLR4 pathway is part of adaptation to Arg deprivation in HMCLs and to convey bortezomib refractoriness.

**Results:** In bortezomib-refractory patients Arg-1 was increased in peripheral blood. Sera of MM, but not MGSU, patients conferred bortezomib-resistance to U266 cell line in an Arg-1 dependent manner, an effect partially reverted by treatment with nor-NOHA (an aspecific Arg-1 inhibitor). Treatment with recombinant Arg-1 for 24 hours conferred protection to U266 after treatment with 20nM bortezomib for 48 hours, associated to increased expression of TNFα, ATF4 and p62.

In HMCLs the progressive arginine deprivation induced delay in cell cycle until proliferation arrest (in total lack of arginine in culture media), with increase of G0-G1 length, associated decreased cell viability starting from R25. We next investigated if MM cells may adapt to Arg deprivation through unfolded protein response (UPR) system or GCN2 pathways. In the UPR system, higher levels of expression of metabolic-stress sensing protein PERK was observed only in NCI-H929 cells adapted to lower Arg deprivation (R25). Interestingly, we found an up-regulation of GCN2 protein expression in U266 cells already at R25 and in NCI-H929 only at R10 condition, associated to increased expression of TLR4 and its downstream effectors, involved in mitochondrial depolarization, suggesting a role of TLR4 pathway in preserving MM-PCs under arginine starvation. We finally tested the efficacy of bortezomib (BTZ) and carfilzomib (CFZ) in HMCLs cultured in R25 and R10 medium showed decreased PI-induced apoptosis and lower mitochondrial depolarization.

**Conclusions:** Our study suggests that TLR4 pathway is part of adaptation to Arg deprivation in HMCLs and to convey bortezomib refractoriness.

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**P02 PROGNOSTIC STRATIFICATION OF STANDARD RISK MULTIPLE MYELOMA DEFINED BY REVISED ISS**

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Current Multiple Myeloma (MM) prognostic stratification relies on high risk (HR) cytogenetic aberrations identified by interphase fluorescent in situ hybridization (FISH). According to Revised International Staging System (R-ISS) t(4;14), t(14;16) and deletion of 17p13 are considered HR aberrations, while all other abnormalities are considered standard risk (ST) changes. However growing evidence suggests that gain 1q21 (+1q) associates with dismal outcome while data on t(11;14) are conflicting. In addition, hyperdiploid MM characterized by trisomies involving of odd chromosomes is associated to sensitivity to lenalidomide treatment and favourable outcome.

The aim of this study was to evaluate the prognostic significance of specific MM genetic alterations including +1q, t(11;14) and 5-9-15 trisomy as surrogate of hyperdiploid MM in a cohort of standard risk MM patients according to R-ISS.

Starting from a cohort of 476 patients affected by newly diagnosed MM and followed in three referral centers, we identified by FISH 226 cases of standard risk MM after excluding HR changes. Patients’ characteristics including clinical and biological features at diagnosis, type of treatment and OS were collected.

The study cohort included 78 cases (34.5%) harboring t(11;14) confirmed by FISH while remnant 148 patients (65.5%) were t(11;14) negative. Within this subset, 40 cases displayed concomitant trisomy for chromosome 5-9-15 by FISH. Comparing t(11;14) to the other ST risk patients [non-t(11;14)], there were no differences in terms of ISS III stage, LDH levels, FLC ratio >100, hypercalcemia, renal injury, anaemia and bone disease at the diagnosis, while t(11;14) patients were characterized by higher frequency of bone marrow plasma cells >60% (p=0.001). Considering the treatments, no differences were found in type and median number of previous treatments [median lines #2 in t(11;14) subgroup and #1 in the non t(11;14) subgroup, p=0.2266]. Overall, chromosome 1 alterations, namely +1q and del1p were present in 35% and 7.5% of cases, respectively, with 8.9% of patients showing >Scopies of 1q. Of note +1q and del1p, were higher in the non-t(11;14) subgroup (39.9% vs 25.4%, p=0.0475 and 10% vs 2.7%, p=0.0594, respectively).

With a median follow-up of 32 months, median overall survival (OS) of the entire cohort was 102 months. Patient harboring t(11;14) showed reduced although not significant survival compared to non-t(11;14) cases (80 vs 156 months, p=0.0698). Interestingly the presence of +1q was associated to a worst outcome in the entire study cohort (57 vs 105 months, p=0.0018) and in the t(11;14) and non-t(11;14) subgroups separately (31 vs 84 months, p=0.0015 and 62 vs not reached, p=0.0074, respectively). The role of +1q in the ST MM was further confirmed from the fact that, excluding +1q, there is no significant survival difference between t(11;14) and non-t(11;14) (84 vs not reached, p=0.0099). However, patients with 5-9-15 trisomy, accounting for 27% of non-t(11;14) group, showed significantly better prognosis with respect to t(11;14) patients (p=0.0134).

In conclusion, standard risk MM identified by R-ISS represents a heterogeneous subgroup of patients. In this subgroup, the presence of gain1q impacts on overall survival, suggesting that this alteration might be helpful in the stratification of non-HR MM. Within standard risk, 5-9-15 trisomy used as hyperdiploid surrogate identifies a subset of patients with particularly favorable outcome, also compared to t(11;14) cases.
P03 RATIONALE AND DEVELOPMENT OF AN E-HEALTH APPLICATION TO DELIVER PATIENT CENTERED CARE DURING TREATMENT FOR MULTIPLE MYELOMA IN THE NETHERLANDS.

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Patients with newly diagnosed Multiple Myeloma (NDMM) face increasingly complicated treatment regimens, including many medications. E-health may support patients and health care providers during treatment, enhancing patient-centered care delivery. Therefore, we aimed to develop a multi-modality e-health application. Furthermore, we aimed to assess the usability and end-user experiences and to formulate additional requirements for improvement.

The application was developed following an iterative action-based methodology, the Design Thinking approach. Key end-users, including patients, hematologists, pharmacists and nurse specialists, were actively involved. Additional stakeholders, including information technology specialists, secretaries and managers, were consulted during an iterative development process. Before developing the application, the care pathway was evaluated and the ideal care pathway was defined, including integrating an e-health application. Second, the focus of development was determined and a solution ideated during recurring multidisciplinary meetings. Third, mockup display sketches of the intended application modules were recurrently discussed and optimized. Fourth, prototypes were tested and improved. Finally, a final prototype was tested during a pilot study with 18 patients and 7 healthcare professionals, evaluating usability, usage and qualitative experiences.

The application, ‘MM E-coach’, consisted of a newly developed mediation module (Figure 1), patient reported outcomes (PROs) and experiences questionnaire assessments, a messaging service, threshold-based alerts, information provision and a personal care plan. Following 8 weeks of use, the median system usability scale score was 60. Patients appreciated the medication overview and the healthcare professionals the outpatient clinic preparation module. Both appreciated the messaging service. Several recommendations for improvement were made, for example adding new or more flexible functionalities and improving the application view at a glance.

The MM E-coach has the potential to provide patient-centered care by supporting patients and caregivers during Multiple Myeloma treatment and is a promising application to be implemented in the Multiple Myeloma care pathway. Following the recommended improvements, a randomized clinical trial is being conducted to evaluate the clinical effectiveness in hospital practice.

P04 DARATUMUMAB PLUS BORTEZOMIB AND DEXMETHASONE VERSUS BORTEZOMIB AND DEXMETHASONE ALONE IN PATIENTS WITH PREVIOUSLY TREATED MULTIPLE MYELOMA: OVERALL SURVIVAL RESULTS FROM THE PHASE 3 CASTOR TRIAL

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Daratumumab (DARA) is a human IgGκ monoclonal antibody targeting CD38 approved in combination with standard-of-care regimens for pts with newly diagnosed multiple myeloma (NDMM) and as monotherapy and in combination with standard-of-care regimens for pts with relapsed/refractory multiple myeloma (RRMM). In the primary analysis of the phase 3 CASTOR study (median follow-up, 7.4 months), DARA plus bortezomib and dexamethasone (D-Vd) significantly prolonged progression-free survival (PFS) versus bortezomib and dexamethasone (Vd) alone in pts with RRMM, and key secondary endpoints (including time to disease progression, rate of very good partial response or better, overall response rate, and minimal residual disease [MRD]-negativity rates) were observed in a statistically significant benefit favoring D-Vd. Here, we report final overall survival (OS) and updated MRD-negativity and safety results after ~6 years of follow-up.

Methods: Pts with RRMM and ≥1 prior line of therapy were randomized 1:1 to receive D-Vd or Vd. All pts received up to 8 (21-day) cycles of Vd (1.3 mg/m² SC on Days 1, 4, 8, and 11; d 20 mg PO or IV on Days 1, 2, 4, 5, 8, 9, 11, and 12) plus bortezomib and dexamethasone (Vd) [hazard ratio (HR), 0.74; 95% confidence interval [CI], 0.59-0.92; P=0.0075 [crossing the prespecified stopping boundary of P=0.0323]], representing a 26% reduction in the risk of death with D-Vd (Figure). Median OS was 49.6 (95% CI, 42.2-62.3) months with D-Vd versus 38.5 (95% CI, 31.2-46.2) months with Vd. Prespecified subgroup analyses showed an OS improvement with D-Vd versus Vd across most subgroups, including pts aged ≥65 years; pts who had received 1 or 2 prior lines of therapy; pts with International Staging System stage III disease, high-risk cytogenetic abnormalities, or prior bortezomib treatment; and pts who were refractory to their last prior line of therapy. The most
pronounced OS benefit of D-Vd was seen in pts with 1 prior line of therapy (HR, 0.36; 95% CI, 0.39-0.80). D-Vd achieved significantly higher rates of MRD negativity (10^–5) versus Vd (15.1% vs 1.6%; P<0.0001). The most common (≥10%) grade 3/4 treatment-emergent adverse events (TEAEs; D-Vd/Vd) were thrombocytopenia (46.1%/32.9%), anemia (16.0%/16.0%), neutropenia (13.6%/4.6%), lymphopenia (10.3%/2.5%), and pneumonia (10.7%/10.1%). Rates of discontinuation due to TEAEs were low and similar between treatment groups (D-Vd, 10.7%; Vd, 9.3%). No new safety concerns were identified with extended follow-up.

Conclusion: Treatment with D-Vd significantly prolonged OS compared with Vd alone. These results, together with the OS results observed with DARA in combination with lenalidomide and dexamethasone in the phase 3 POLLUX study, demonstrate for the first time an OS benefit with DARA-containing regimens in RRMM. The greatest OS benefit of D-Vd was observed in pts with 1 prior line of therapy. Our results support early use of D-Vd to maximize pt benefit.

P05 DARATUMUMAB PLUS LENALIDOMIDE AND DEXAMETHASONE VERSUS LENALIDOMIDE AND DEXAMETHASONE ALONE IN PATIENTS WITH PREVIOUSLY TREATED MULTIPLE MYELOMA: OVERALL SURVIVAL RESULTS FROM THE PHASE 3 POLLUX TRIAL

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Introduction: Daratumumab (DARA) is a human IgG monoclonal antibody targeting CD38 that is approved in combination with standard-of-care regimens for pts with newly diagnosed multiple myeloma (NDMM) and as monotherapy and in combination with standard-of-care regimens for pts with relapsed/refractory multiple myeloma (RRMM). In the primary analysis of the phase 3 POLLUX study (median follow-up, 13.5 months), DARA plus lenalidomide and dexamethasone (D-Rd) provided a significant progression-free survival (PFS) benefit versus lenalidomide and dexamethasone (Rd) alone, and key secondary endpoints (including time to disease progression, rate of very good partial response or better, overall response rate, and minimal residual disease [MRD]–negativity rate) showed a statistically significant benefit favoring D-Rd. Here, we report final overall survival (OS) and updated MRD-negativity and safety results after ≥6 years of follow-up.

Methods: Pts with RRMM and ≥1 prior line of therapy were randomized 1:1 to receive D-Rd or Rd. All pts received 28-day cycles of Rd (R 25 mg PO on Days 1-21, d 40 mg QW). Pts in the D-Rd group also received DARA (16 mg/kg IV QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W thereafter). In both groups, pts were treated until disease progression or unacceptable toxicity. The primary endpoint was PFS; OS was a secondary endpoint.

Results: In total, 569 pts were randomized (D-Rd, n=286; Rd, n=283). The median (range) age was 65 (34-89) years; pts had received a median (range) of 1 (1-11) prior lines of therapy. At a median (range) follow-up of 79.7 (0.0-86.5) months, the POLLUX study showed a statistically significant and clinically meaningful improvement in OS with D-Rd versus Rd (hazard ratio, 0.73; 95% confidence interval [CI], 0.58-0.91; P=0.0044 [crossing the prespecified stopping boundary of P<0.0331]), representing a 27% reduction in the risk of death in the D-Rd group (Figure). The median OS was 67.6 (95% CI, 53.1-80.5) months in the D-Rd group versus 51.8 (95% CI, 44.0-60.0) months in the Rd group. Prespecified subgroup analyses showed an OS improvement with D-Rd versus Rd in most subgroups, including pts aged ≥65 years; pts who had received 1, 2, or 3 prior lines of therapy; pts with International Staging System stage III disease; and pts who were refractory to a proteasome inhibitor or to their last prior line of therapy. D-Rd achieved significantly higher rates of MRD negativity (10^–5) versus Rd (33.2% vs 6.7%; P<0.0001). The most common (≥10%) grade 3/4 treatment-emergent adverse events (TEAEs; D-Rd/Rd) were neutropenia (57.6%/41.6%), anemia (19.8%/22.4%), pneumonia (17.3%/11.0%), thrombocytopenia (15.5%/15.7%), and diarrhea (10.2%/3.9%). Rates of discontinuation due to TEAEs were comparable between treatment groups (D-Rd, 19.1%; Rd, 16.0 %). There were no new safety concerns identified with extended follow-up.

Conclusion: Treatment with D-Rd significantly prolonged OS compared with Rd alone. These results, together with the OS results observed with DARA in combination with bortezomib and dexamethasone in the phase 3 CASTOR study, demonstrate for the first time an OS benefit with DARA-containing regimens in RRMM. Our results support the use of DARA in pts with RRMM.
P06 UPDATED RESULTS FROM THE PHASE 1/2 MAJESTEC-1 STUDY OF TECLISTAMAB, A B-CELL MATURATION ANTIGEN X CD3 BISPECIFIC ANTIBODY, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Teclistamab (JN-64007957) is a bispecific antibody that binds to both B-cell maturation antigen (BCMA) and CD3 receptors to induce T cell-mediated cytotoxicity of BCMA-expressing myeloma cells. Results from phase 1 of the Majestec-1 study, an ongoing phase 1/2 study in heavily pretreated relapsed/refractory multiple myeloma (RRMM; NCT03145181), showed a tolerable safety profile at the recommended phase 2 dose (RP2D) and encouraging efficacy. Here we report initial data from the phase 2 portion of Majestec-1 (NCT04557098) as well as updated results from phase 1.

Patients (pts; ≥18 y) had MM per International Myeloma Working Group (IMWG) criteria, measurable disease, and were exposed to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody. In phase 1, pts were relapsed, refractory, or intolerant to established therapies. In phase 2, pts received ≥3 prior lines of therapy (LOT). The primary objectives were to identify the RP2D and to characterize safety and tolerability of teclistamab at the RP2D in phase 1, and to evaluate the efficacy at the RP2D (primary endpoint: ORR) in phase 2. The RP2D was weekly subcutaneous teclistamab 1500 μg/kg following step-down doses of 600 and 300 μg/kg. Responses were assessed by the investigator per IMWG criteria. Adverse events (AEs) were graded per CTCAE v4.03. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT criteria.

As of June 14, 2021, 159 pts (median age 64.0 y; range 33–84; 15% ≥75 y; 59% male) were treated at the RP2D (phase 1: 40 pts; phase 2: 119 pts). Pts received a median of 5 prior LOT (range 2–15); 100% were triple-class exposed, 69% were penta-drug exposed, 77% were tri-class refractory, and 29% were penta-drug refractory. In 159 pts, the most common nonhematologic AEs at the RP2D were CRS (any grade: 67%; grade 3 occurred in 1 pt, no grade 4 or 5), injection site erythema (23%; all grade 1/2), and fatigue (22%; grade 3/4: 45%). Anemia (41%; grade 3/4: 27%), and thrombocytopenia (2%). Of the hematologic AEs, most common were neutropenia (53%; grade 3/4: 45%), anemia (41%; grade 3/4: 27%), and thrombocytopenia (33%; grade 3/4: 18%). Four pts (2.5%) developed ICANS (all grade 1/2; all resolved). No new safety signals were identified in phase 2. Phase 2 pharmacokinetic and pharmacodynamic data supported those reported in phase 1. At the RP2D, teclistamab exposure was sustained across the dosing interval and exceeded target exposure levels. Across both phases, induction of proinflammatory cytokines and T cell activation were observed at the RP2D.

Phase 2 efficacy data are immature. At 8.2-mo median follow-up (range 1.2–15.2), responses in the phase 1 pts at the RP2D (n=40) were consistent with previous reports (ORR: 65% [95% CI 48–79]; ≥VGPR: 60% [95% CI 42–77]; median DOR: 60 mo [95% CI 25–77]; RR at 6 mo of response: 26% [95% CI 12–52]; RR at 12 mo of response: 27% [95% CI 14–43]; RR at 24 mo of response: 22% [95% CI 11–39]). Response rates deepened over time, and with longer follow-up of responders compared with previously presented data (median follow-up of 9.5 mo vs 7.1 mo), remained durable (Figure). 85% (22/26) of responders are continuing on treatment, including 1 pt with 15.2 mo of follow-up. Median duration of response (DOR) was not reached, with 6-month DOR rate of 90% (95% CI 63–97).

The safety of teclistamab is supported by data from 159 pts treated at the RP2D. Teclistamab continues to show deep and durable responses with a manageable safety profile in heavily-pretreated pts with RRMM.

Figure: Duration of Response

P07 RESULTS FROM THE CC-220-MM-001 DOSE EXPANSION PHASE OF IBERDOMIDE PLUS DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Iberdomide (IBER), a potent oral cereblon E3 ligase modulator (CELMoD®) agent with enhanced tumoricidal and immune-stimulatory effects versus immunomodulatory (IMiD®) agents, has shown marked synergy with dexamethasone (DEX) and other standard myeloma treatments in preclinical models. IBER is being evaluated with various treatment combinations in patients (pts) with relapsed/refractory multiple myeloma (RRMM) in the phase 1/2 study CC-220-MM-001 (NCT02773930). Results from the dose expansion of IBER-DEX in pts with heavily pretreated, triple-class exposed ≥1 IMiD agent, ≥1 proteasome inhibitor [PI], and ≥1 CD38 monoclonal antibody [mAb] RRMM are reported here.

Key eligibility criteria were: RRMM; ≥3 prior lines of therapy, including lenalidomide, pomalidomide, a PI, a glucocorticoid, and a CD38 mAb; progressive disease (PD) within 60 days of last myeloma therapy; and refractoriness to an IMiD agent, a PI, a glucocorticoid, and a CD38 mAb. Pts who had received prior anti-B cell therapy were included in a separate cohort. Oral IBER (at the recommended phase 2 dose of 1.6 mg)
P08 CARTITUDE-2 UPDATE: CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN-DIRECTED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN LENALIDOMIDE-REFRACTORY PATIENTS WITH PROGRESSIVE MULTIPLE MYELOMA AFTER 1-3 PRIOR LINES OF THERAPY

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Introduction: Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor T-cell (CAR-T) therapy expressing two B-cell maturation antigen (BCMA)-targeting, single-domain antibodies. The multicohort, open-label, phase 2 CARTITUDE-2 study (NCT04133636) is assessing cilta-cel in patients (pts) with multiple myeloma (MM) under various clinical settings and evaluating the suitability of outpatient management. Updated results of CARTITUDE-2 cohort A are presented here.

Methods: Cohort A pts had progressive MM after 1–3 prior lines of therapy (LOT; included proteasome inhibitor [PI] and immunomodulatory drug [IMiD]), were lenalidomide-refractory, and had no previous exposure to BCMA-targeting agents. A single cilta-cel infusion at a target dose of 0.75×10^6 CAR+ viable T cells/kg was given 5–7 d after starting fludarabine (30 mg/m2 for 3 d). The primary endpoint was minimal residual disease (MRD) negativity at 10^-5 at any time point. Secondary endpoints were overall response rate (ORR), duration of response (DOR), time and duration of MRD negativity, and incidence and severity of adverse events (AEs). Response was assessed per International Myeloma Working Group criteria and AEs were graded by Common Terminology Criteria for Adverse Events version 5.0 (cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]) by American Society for Transplantation and Cellular Therapy.

Results: As of April 15, 2021 (median follow-up of 9.7 mo), 20 pts (63% male; median age 60 y [range 38–75]) received cilta-cel, with 1 pt treated in an outpatient setting. Pts had a median of 2 prior LOT (range 1–3); 60% had 1–2 prior LOT and 40% had 3 prior LOT. All pts were exposed to a PI, IMiD, and dexamethasone; 95% were exposed to alkylating agents and 65% to daratumumab. 95% of pts were refractory to last LOT; 40% were triple-class refractory. ORR was 95% (95% CI 75.1–99.9); 85% (95% CI 62.1–96.8) had ≥complete response (CR), and 95% (95% CI 75.1–99.9) had ≥very good partial response (VGPR). Median time to first response was 1.0 mo (range 0.7–3.3) and median time to ≥CR was 2.6 mo (range 0.9–7.9). Median DOR was not reached; progression-free survival (PFS) at 6 mo was 90% (95% CI 65.6–97.4). Of 13 MRD-acceptable pts, 92.3% (95% CI 64.0–99.8) were MRD-negative at 10^-5. Hematologic AEs ≥20% of pts were neutropenia (95%; grade [gr] 3/4: 95%), thrombocytopenia (80%; gr 3/4: 35%), anemia (75%; gr 3/4: 45%), lymphopenia (65%; gr 3/4: 60%) and leukopenia (55%; gr 3/4: 55%). 95% of pts had CRS (gr 3/4: 10%; median time to onset was 7 d [range 5–9] and median duration was 4 d [range 2–11]). Four pts (20%) had CAR-T neurotoxicity (all gr 1/2). Three pts (15%) had ICANS (all gr 1/2); median time to onset was 8 d (range 7–10) and median duration was 3 d (range 1–3). One pt had facial paralysis (gr 2) with time to onset of 29 d and duration of 51 d. No movement and neurocognitive treatment-emergent adverse events (AEs) were reported. One death due to COVID-19 was assessed as treatment-related. Safety was manageable in the pt treated in an outpatient setting.

Conclusions: A single cilta-cel infusion led to early and deep responses in pts with MM who had 1–3 prior LOT and were lenalidomide-refractory. No movement and neurocognitive AEs were reported, suggesting successful implementation of monitoring and pt management strategies across phase 2/3 studies in the CARTITUDE program.

Figure: Overall response rate

P09 ATTRITION RATES IN MULTIPLE MYELOMA UNDER REAL WORLD CONDITIONS – AN ANALYSIS FROM THE AUSTRIAN MYELOMA REGISTRY

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Myeloma (MM) is characterised by frequent disease relapse with the need to introduce further lines of therapy (LoTs). How often all these theoretical options (Dimopoulos et al, 2021) are actually used in “Real World (RW)” settings is considered controversial. In recent studies MM patients were found to have attrition rates (ARs) of up to 57% from LoT-1 to LoT-2. (Yang et al, 2016; Fonseca et al, 2020). We aim to assess ARs across the Austrian Multiple Myeloma Registry and verify treatment patterns in the RW.

Methods: Patients with an index diagnosis made between JAN 2009 and AUG 2021 were eligible. Baseline data and treatment patterns were collected. Attrition was defined as being either deceased, progressive without receiving a further LoT, or being lost to follow up for 5 years or more.

Results: 571 pts. (n) were identified, of whom 57.1% were men. Median age at FD was 72 years (SD 12.7 y) with a median follow-up of 50.8 months (SD 44.1 m). 507 patients (88.1%) received the first LoT. In 1st LoT 43.2 % (n 219) received stem cell transplantation (SCT), 39.4% (n 200) received maintenance therapy (55.9 % of transplanted patients).

The most common treatment in both transplanted and non-transplanted patients was VRD with 20.3 %. AR was nearly constant across all LoTs, ranging from 50.2% in LoT 1-4. A further LoT was instituted in 37.7-48.6 % of pts. in LoT 1-4. Treatment with SCT was 36% (n 98) compared to 27.7% in the SCT cohort (65). A further LoT was instituted in 37.7-48.6 % of pts. in LoT 1-4. Treatment duration (DoT) decreased with a mean of 12.4months in LoT-1 (SD 15.8) to 8 months (SD 44.1 m). 507 patients (88.1%) received the first LOT. In 1st FD was 72 years (SD 12.7 y) with a median follow-up of 50.8 months (SD 44.1 m). 507 patients (88.1%) received the first LOT. In 1st LoT 43.2 % (n 219) received stem cell transplantation (SCT), 39.4% (n 200) received maintenance therapy (55.9 % of transplanted patients).

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The risk of attrition decreases by 32.1% in SCT pts. (CI95% 0.47- 0.99; p=0.045), and follow-up time becomes significantly longer at 53.8 months versus 47.2 months (p=0.007). Patients defined as being victims of attrition were significantly older at 73 years (SD 10.52months, p=0.003). Both factors influence each other, since patients with SCT are significantly younger (64 years, p=0.003). Frontline regimens with a PI and DEX alone increased the risk of falling into AR by 80% (95%CI 1.80:1.09-1.99; p=0.022) compared to triplet and quadruplet inductions. This might mirror the difference between fixed duration vs continuous therapies. Maintenance (nearly uniformly with LEN) in frontline regimens reduces the risk of attrition by 51.5% (95%CI 0.48:0.33-0.75; p<0.001).

Conclusions: Overall, our analyses demonstrated ARs significantly lower than that previously reported (Yang et al, 2016; Fonseca et al, 2020). This indicates that issues like drug access and reimbursement might also play major roles with respect to long term results in MM. Our results confirm a negative impact of doublet 1st treatments vs. more intensive ones. The positive impact of SCT on long term prognosis was also confirmed in the RW, in line with multiple clinical trials. The influence of antibody-based therapies was also identified. A high proportion of patients was enrolled in randomized trials across all LoTs. A further LoT was instituted in 37.7-48.6 % of pts. in LoT 1-4. Treatment duration (DoT) decreased with a mean of 12.4months in LoT-1 (SD 15.8) to 8 months (SD 44.1 m). 507 patients (88.1%) received the first LOT. In 1st FD was 72 years (SD 12.7 y) with a median follow-up of 50.8 months (SD 44.1 m). 507 patients (88.1%) received the first LOT.
evaluation of talquetamab as monotherapy (phase 2; NCT04634552) and in combination with other therapies in patients with RRMM is underway.

P11 IXAZOMIB WITH CYCLOPHOSPHAMIDE AND Dexamethasone in Relapsed or Refractory Multiple Myeloma: Mukeight Phase II Randomised Controlled Trial Results

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In the past two decades, treatment options for multiple myeloma (MM) have increased dramatically. While these developments hold great promise, many of the new treatment approaches will, for the foreseeable future, be inaccessible to large numbers of MM patients globally as they are costly and complex to deliver. The all-oral combination of ixazomib, cyclophosphamide, and dexamethasone (ICD) is well tolerated and effective in newly diagnosed and relapsed/refractory multiple myeloma (RRMM), and it is economically competitive. We carried out Mukeight, a randomised, controlled, open, parallel group, multi-centre phase II trial in patients with RRMM after prior treatment with thalidomide, lenalidomide, and a proteasome inhibitor (ISRCTN58227268), with the primary objective to test whether ICD has improved clinical activity compared to cyclophosphamide and dexamethasone (CD) in terms of progression-free survival (PFS). Between January 2016 and December 2018, 112 participants were randomised between ICD (n=58) and CD (n=54) in 33 UK centres. Baseline characteristics were generally well balanced between the arms, with a median age of 70 years (range 46-82). In the entire study population, 73.6% (81/112) participants had a Charlson Comorbidity Index score of 0-2. More participants in the ICD arm had ECOG PS 1 or 2 (78.9% vs. 66.0%), and more were classed as frail (80.7% vs. 66.0%) by the modified IMWG frailty score. Overall, participants had a median of 4 (range 1-5+) prior lines of therapy, and median time from diagnosis to trial entry was 6.8 years (range 1.8-21.0). Median PFS in the ICD arm was 5.6 months, compared to 6.7 months with CD (hazard ratio (HR)=1.21, 80% CI 0.9-1.6, p=0.3634). Response rates were not significantly different between ICD and CD, with 24/57 participants (42.1%, 80% CI 33.2-51.5) in the ICD arm, and 21/53 (39.6%, 80% CI 30.5-49.4) in the CD arm, achieving at least PR. Median PFS in the ICD arm was 5.6 months (80% CI 4.1-7.2), compared to 6.7 months (80% CI 4.7-7.3) with CD (hazard ratio (HR)=1.21, 80% CI 0.9-1.6, p=0.3634). Overall survival (OS) was not significantly different between the arms, with a median OS of 14.1 months for ICD compared to 19.1 months for CD (HR=1.52, 80% CI 1.06-2.18, p=0.1346) Dose modifications or omissions, and serious adverse events (SAEs), occurred more often in the ICD arm. Of the 34 patients who discontinued CD due to disease progression, 20 crossed over to and received ICD. Median PFS from day 1 cycle 1 of crossover treatment was 4.6 months (80% CI 4.1-5.0). 5/20 participants (25.0%) achieved at least PR, including 3 VGPRs, with 10/20 (50.0%) participants achieving stable disease as their maximum response. In summary, the addition of ixazomib to cyclophosphamide and dexamethasone did not improve key outcomes in the comparatively frail, old, and heavily pre-treated RRMM patients enrolled in the Mukeight trial. The results also suggest that the inexpensive and all-oral combination of CD can be associated with satisfactory responses, a finding that is particularly relevant for MM patients who do not have access to costly or complex novel drug combinations, or those with impaired access to healthcare facilities for reasons such as geographical remoteness, frailty, or public health concerns.

P12 Treatments in Patients with Relapsed/Refractory Multiple Myeloma: Retrospective Chart Review of Real-world Outcomes for Standard of Care

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Introduction: The prognosis of patients with multiple myeloma has improved considerably with the introduction of immunomodulatory agents (IMiDs), proteasome inhibitors (Pis), and anti-CD38 monoclonal antibodies (mAbs). However, most patients relapse and require further therapy, with no clear standard of care (SOC). Data on how patients with relapsed/refractory multiple myeloma (RRMM) are treated in clinical practice and outcomes to these treatments in the real-world setting are lacking. This study aimed to evaluate the outcomes of patients with triple-class (IMiD, Pi, and anti-CD38 mAb) and triple-line exposed RRMM using real-world data from patients in Belgium.

Methods: This multicenter (7 non-academic and academic Belgian centers), observational study was conducted based on a retrospective chart review of adult patients with RRMM who had received ≥3 lines (IMiD, Pi, anti-CD38-directed) of therapies (tri-exposed) and started subsequent treatment from March 2017 through May 2021. In patients meeting eligibility criteria, all treatment lines utilized were considered for analysis (as separate observations for patients who met the eligibility criteria more than once during the follow-up), with date of treatment initiation as specific baseline for each treatment line. Prognostic value with overall survival (OS), progression-free survival (PFS), and time-to-next therapy (TTNT) was evaluated using Cox proportional hazards models.

Results: A total of 112 patients with 237 eligible treatment-lines were included; median follow-up was 16.6 months. In 45% of initiated treatment lines, patients were refractory to 4 or 5 therapies, 62% had ≥5 prior lines, 22% had extramedullary disease; in 48% of observations, time-to-progression (TTP) in prior line was <4 months. After patients were tri-exposed, >50 unique regimens were initiated, with the most common being carfilzomib + dexamethasone (14%), pomalidomide + dexamethasone + chemotherapy (8%), and ixazomib + lenalidomide + dexamethasone (6%). Among included observations, 4% were exposed to anti-BCMA agents. The most frequently initiated therapies were: PI only (19%), PI + IMiD combinations (17%), and regimens that included
P13 CAN PATIENT-REPORTED OCULAR SYMPTOMS GUIDE DOSE MODIFICATIONS IN PATIENTS WITH RELAPSED/ REFRACTORY MULTIPLE MYELOMA RECEIVING BELANTAMAB MAFODOTIN?

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Introduction: Belantamab mafodotin (belamaf) is a B-cell maturation antigen (BCMA)-targeting antibody-drug conjugate approved as a monotherapy for triple-class refractory adult patients with relapsed/refractory multiple myeloma (RRMM). This hypothesis-generating post hoc analysis of DREAMM-2 trial (NCT03525678) data examined relationships between corneal exam findings, best-corrected visual acuity (BCVA) changes and direct patient-reported ocular symptoms per the Ocular Surface Disease Index (OSDI) questionnaire. This approach may provide insight into relationships between corneal exam findings, BCVA, ocular symptoms, impact on quality of life to determine BCVA decline and symptoms can guide dosing. Surrogate marker identification for results from corneal exam findings would help providers determine if dosing adjustments are necessary.

Methods: Snellen chart BCVA assessment and corneal eye exams were performed on all patients receiving belamaf (2.5 mg/kg, q3w) by ECPs at baseline (BL) and before each dose. Corneal exam findings (keratopathy) and BCVA were assessed per protocol-defined criteria. Grade (GR) assessment, relative to BL, was based on the worst finding in the worse eye. Patient-reported ocular symptoms and vision-related functioning, as per the OSDI, were used to evaluate the impact of treatment-related ocular toxicity. The OSDI patient-reported outcome questionnaire assesses eye symptoms/effects on vision-related function and was performed in all patients before each belamaf dose. Items 1–9 address the frequency of eye-related symptoms and items 6–9 address functional limitation frequency. OSDI was considered positive, clinically meaningful and potentially treatment associated when at least one question 1–5 (sensitivity to light, gritty/painful eyes, blurred or poor vision) was reported as experienced “all of the time” and at least one question 6–9 (driving at night, reading, working with PC or watching TV) was reported as experienced “most of the time.”

Results: GR 3–4 (severe) keratopathy was observed 5% of the time in patients not reporting frequent ocular symptoms measured by the OSDI questionnaire (no items 1–9 ≥ “most of the time”). In patients who reported no items 1–5 “all of the time” AND no items 6–9 ≥ “most of the time” (OSDI negative), GR 3–4 keratopathy was observed 6.5% of the time (Table). In patients who reported “no deterioration from BL” for any OSDI eye-related symptoms or functional limitations, GR 3–4 keratopathy was observed ~3%–7% of the time and GR 0–2 (mild) keratopathy ~23%–34% of the time. Similar results were observed in patients with BL BCVA ≤20/30 who reported “no deterioration from BL” for any eye-related adverse events (AEs) or functional limitations (GR 3–4 keratopathy: ~2%–6% of the time; GR 0–2 keratopathy: ~19%–28% of the time); patients with worse BL visual acuity (BCVA >20/30) who reported “no deterioration” for items 1–9 had lower incidence of GR 3–4 (~0%–1%) and GR 0–2 keratopathy (~3%–8%).

Conclusions: These results suggest that hematologists/oncologists may be able to use ocular symptoms and the OSDI tool as potential surrogate markers for eye exam results to help determine whether dosing changes are needed. Validation with other belamaf dose regimens is ongoing.

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Encore statement: Previously presented as Poster 2746 at the American Society of Hematology Annual Meeting, 11–14 December 2021; submitted with permission and on behalf of the original authors.

| Table: Summary of Concordance and Discordance Between Corneal Exam Findings (Keratopathy) and OSDI Criteria* |
| Keratopathy and OSDI (Total Evaluations, N = 773) | Events, n (%) |
| GR 0–2 Keratopathy and OSDI Negative | GR 3–4 Keratopathy and OSDI Positive | GR 0–2 Keratopathy and OSDI Positive* |
| 268 (34.7) | 87 (11.3) | 152 (19.7) |
| GR 3–4 Keratopathy and OSDI Negative* | 50 (6.5) |

| Missing Values (n with no corresponding OSDI data) | 236 (27.9) |

*Questions 1–5—only. Items 1–5 address the frequency of the following eye-related problems during the course of the prior week (range: “all of the time” to “none of the time”): eyes that are sensitive to light; eyes that feel gritty, puffy or sore; eyes blurred or poor vision. Items 6–9—address the frequency of eye-related problems that last during the prior week: reading, driving at night, working with a computer or bank machine (ATM), and watching TV. All responses range from “all of the time” to “none of the time.”

**OSDI Negative: No items 1–9 “all of the time” AND no items 6–9 “most of the time.”

**OSDI Positive: At least one item 1–5 “all of the time” OR at least one item 6–9 “most of the time.”
P14 DREAMM-9: PHASE I STUDY OF BELANTAMAB MAFODOTIN PLUS STANDARD OF CARE IN PATIENTS WITH TRANSPLANT-INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA

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Background: The bortezomib, lenalidomide, and dexamethasone (VRd) regimen is a SoC for NDMM. Belafam, a B-cell maturation antigen (BCMA)–targeting antibody-drug conjugate, demonstrated durable responses in patients with relapsed/refractory multiple myeloma. Preclinical studies of belafam in combination with bortezomib/lenalidomide suggest enhanced antimyeloma activity. We report preliminary findings of belafam + VRd for patients with TI NDMM.

Materials and Methods: DREAMM-9 (NCT04091126) is an ongoing Phase I, open label, randomized, dose and schedule evaluation trial. Adults with TI NDMM and ECOG status 0–2 are eligible. VRd is administered Q3W for Cycle 1, followed by lenalidomide + dexamethasone (Rd) Q4W. Belafam + VRd is administered until Cycle 8, and with Rd thereafter. The currently evaluated belafam dose cohorts are: Cohort 1 (1.9 mg/kg Q3/4W), Cohort 2 (1.4 mg/kg Q6/8W), Cohort 3 (1.9 mg/kg Q6/8W), Cohort 4 (1.0 mg/kg Q3/4W), and Cohort 5 (1.4 mg/kg Q3/4W). Primary endpoint is safety. Secondary endpoints include efficacy, tolerability, and pharmacokinetics (PK).

Results: Overall 36 patients were treated across the 5 cohorts. The median (range) age was 74.0 (63–80) years; 56% patients were male, 17 (47%) had stage 2 disease, 3 (8%) had extramedullary disease, 6 (17%) patients had high-risk cytogenetic abnormalities; the median number of belafam cycles ranged from 1–9. No new safety signals were observed. Across Cohorts 1–5, all patients experienced AEIs related to study treatment in Cohort 1 died due to COVID-19 infection. The most common AEs leading to dose modification were thrombocytopenia, neutropenia, and coneval events. Patients in Cohort 2 and 3 had the lowest number of Grade ≥3 coneval events (3 and 2 events, respectively).

All 12 patients in Cohort 1, all 6 in Cohorts 3 and 5/6 patients in Cohorts 2 and 4 have responded to the treatment; 17 patients in each cohort achieved very good partial response or better. As of data cut-off, 3/12 patients in Cohort 1, 2/6 in Cohort 4, and 1/6 patients each in Cohorts 3 and 5 remained in complete response. Belafam PK profile was similar to that observed in patients with RRMM taking into consideration baseline patient characteristics.

Conclusions: Preliminary data suggest addition of belafam to VRd did not reveal new safety signals and demonstrates high response rates, albeit with short follow-up. The trial is ongoing to confirm safety and evaluate the efficacy of belafam + VRd.

Funding: GSK (Study Number 209664); drug linker technology licensed from Seagen Inc; mAb produced using POTENTIAL Technology licensed from BioWets.

Encore statement: Previously presented as Poster 2738 at the American Society of Hematology Annual Meeting, 11-14 December 2021; submitted with permission and on behalf of the original authors.

P15 EVOLUTION OF MULTIPLE MYELOMA TREATMENT PATTERNS FROM 2015 THROUGH 2019: REAL-WORLD EVIDENCE FROM A EUROPEAN DATABASE STUDY

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Novel treatment options in multiple myeloma (MM) have resulted in a dynamic and heterogeneous treatment landscape. To describe real-world treatment patterns across five European countries from 2015–2019. Using the MM Oncology Advantage database (IQVIA Ltd), this retrospective observational study analyzed data on patients receiving an ongoing treatment in any line from July 2015 through December 2019. Triplets accounted for almost two-thirds of all first-line (1L) therapies and 51% of second-line (2L) regimens in 2019, but monotherapyp-doublet therapies were still mainly used in third line or later (3L+: 86% in 2015–2016; 62% in 2019) with a gradual increase of triplets during the period. In 2019, most common 1L therapies were bortezomib (V)-based regimen with no immunomodulatory drug (IMiD) (37%), lenalidomide (R)-based without proteasome inhibitor (PI) (22%), and V and thalidomide (V+T) based (19%) regimens. Since 2015-16, V-based without IMiD, and Chemo+T regimens have decreased, and R-based regimens have increased over time (Table). V-based without IMiD (DE 51%; UK 38%; ES 35%; FR 30%; IT 29%) and R-based only (FR 30%; DE 24%, IT 27%; ES 23%) were most common in all countries in 1L except in UK and IT where V+T was the most common (42% and 35%, respectively). For 2L in 2019, approximately half of patients were treated with a novel regimen and the remaining received mainly R-based only (34%) or V-based without IMiD (11%). From 2015 to 2019, use of V-based without IMiD and R-based only regimens nearly halved (Table). In 2019, R-based only was most common in ES (50%) FR (41%) and IT (35%); daratumumab (D)+R was most common in DE (34%) and V-based without IMiD common in UK (27%). For 3L+ in 2019, nearly half of patients received a novel regimen. About a third of patients received a pomalidomide (P)-based regimen consistently in 2019 and other years. Since 2015-16, overall use of R-based only, V-based without IMiD, and Chemo+T regimens have decreased from 64% to 18% in 2019 (Table). In 2019, P-based regimens were commonly used across all countries (FR 54%; IT 31%; DE 28%; ES 20%) except the UK where R-based only (37%) and other R regimens (42%) were used in almost all patients.

Since 2015, V use has increased three-fold in 1L accounting for 34% of regimens in 2019. Despite fluctuations in combinations, R use has remained constant at around 70% in 2L and around 35% in 3L+. Treatment sequence in 616 patients receiving 3L in 2019 was described using 7 treatment classes: IMiD, monoclonal antibody (mAb) only, mAb+IMiD, mAb+PI, PI without IMiD, PI+IMiD, and other. There were 86 different sequence permutations, with the top 10 sequences comprising 58% of patients. Focusing on prior/current IMiD use, 65% didn’t receive an IMiD in 1L (n=400), 26% received T (n=138) and 10% R (n=58). Of patients without 1L IMiD (n=400), 81% received R in 2L, and 64% of them had another IMiD in 3L. Among 1L R patients (n=58), 83% had no IMiD in 2L, of whom 56% received an IMiD in 3L (35% P; 21% R). Re-treatment with R occurred infrequently with 12% of all patients with re-treatment occurring at any time.

In conclusion, the uptake of novel agents since 2017 and the increased use of triplets (including R-based in 1L) continue to drive a changing MM treatment landscape with decreasing use of older combinations and increasing treatment options at all lines of therapy. Differences in access to novel treatments might have influenced further heterogeneity between countries.
P17 DARATUMUMAB MONOTHERAPY HAS A FAVORABLE EFFECT ON BONE METABOLISM IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: RESULTS OF THE PHASE 2 REBUILD STUDY

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Introduction: Non-invasive biomarkers of bone metabolism are indicative of bone dynamics during anti-myeloma treatment. Daratumumab (dara) inhibits in vitro osteoclastogenesis and bone resorption. We assessed the impact of dara monotherapy on bone remodeling in patients (pts) with relapsed/refractory multiple myeloma (RRMM).

Methods: REBUILD was a prospective, open-label, phase 2 study conducted in six centers in Greece. Eligible pts were adults with RRMM. The study aim was to assess the impact of dara monotherapy on bone remodeling in patients with RRMM, and to evaluate the impact on related toxicity. Eligible pts were adults with RRMM, regardless of age, comorbidities, impaired kidney function and reduced bone marrow reserve. Our cohort represents a patients population closer to real world clinical practice.

Patients: The median age at diagnosis was 66 years (32-83). The median age at the start of DRd was 70.2 years (41-85). The median time to the start of DRd from diagnosis was 3 years (0-19). The median therapy lines received were 1 (1-4). 49 patients (38.6%) had previously undergone single or tandem ASCT. The last treatment received before the D-based regimen was VMP (35%) or VTd (32%). 93 patients (73.2%) had relapsed MM and 34 (26.8%) patients had refractory MM. 80.3% of MM relapsed patients had been previously exposed to only one therapy.

Results: After a median follow-up of 28 months from the start of DRd, 34 (26.8%) patients had experienced disease progression (DPL: 34.8%), 14 (11.2%) of PFS, and non-haematological toxicities (renal failure 6%, gastrointestinal toxicity 6%, skin rash 5%, musculoskeletal toxicity 4%, thrombotic events 3%), while a delay before subsequent course administration was recorded because of neutropenia (18%), infections (15%), diarrhoea (5%) and thrombotic events (2%). 20.6% of patients discontinued treatment because of relapse, and 3.2% for haematological toxicities. After a median follow-up of 12 months from the start of study treatment, grade 3/4 neutropenia (36%) was the most common haematological toxicity. After a median follow-up of 28 months from the start of treatment, grade 3/4 neutropenia (37.7%) continues to be the most common haematological adverse event. As regards non-haematological adverse
P18 DARATUMUMAB (D) PLUS BORTEZOMIB (V) AND DEXAMETHASONE (D) AS SALVAGE THERAPY FOR PATIENTS WITH REFRACTORY/RELAPSED MULTIPLE MYELOMA (RRMM): INITIAL FOLLOW-UP OF AN ITALIAN MULTICENTER RETROSPECTIVE CLINICAL EXPERIENCE BY “RETETE EMATOLOGICA PUGLIESE”

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Introduction: Real-life reports of experiences with D-based combination therapies in RRMM are very limited. We report herein a multicenter retrospective analysis of 65 consecutive patients (M 59.4%, F 40.6%) with symptomatic RRMM, from January 2018 to December 2020, treated with Dvd as salvage therapy at 9 haematological centers in Puglia.

Patients: The median age at diagnosis was 62.5 years (range 36-81). The median age at the start of Dvd from diagnosis was 68.1 years (range 40-81). The median time to the start of Dvd from diagnosis was 4 years (range 0-16). The median therapy lines received were 3 (range 1-6). 38 patients (58%) had previously undergone single or tandem ASCT. The patients were previously exposed to V (93%) and carfilzomib (32%), in addition to a prior exposure to IMIDs (Len 78%, Thal 41%, Pom 8%). The last treatment received before the Dvd regimen was KRd (29%) or Rd (26%). 52 (80%) patients had relapsed MM, while 13 (20%) patients had refractory MM. 73.9% of MM relapsed patients had been heavily treated.

Results: After a median follow-up of 28 months from the start of study treatment, the median number of cycles administered was 8 (range 1-34). 7% of patients required dose reduction/adjustment (V to 1 mg/m2) for peripheral neuropathies (5%) and thrombocytopenia (2%), respectively, while 25% of patients were shifted to a weekly schedule of V and d for haematological toxicities (14% thrombocytopenia, 11% neutropenia), and 5% for constipation. 35.4% of patients discontinued treatment due to relapse. The ORR was 72.6% (CR 8.1%, VGPR 19.3%, PR 45.2%). Median TTR was 1.5 months (range 1-9). Best response was achieved at a median number of 5 cycles. Median TTP was 10.8 months (95%-CI: 7.1-13.8). Median OS was not reached (1-year OS: 70.2%; 2-years OS: 53.8%). OS was significantly affected both by “the high-quality response” (p = 6.15E-06) and “number of prior lines of treatment” (p = 0.02), while TTP was significantly affected only by the “high-quality response” (p = 0.001). “Baseline disease status” and “age at starting treatment” did not affect either OS or TTP. We evaluated haematological and non-haematological toxicities after a median follow-up of 12 and 28 months.

After a median follow-up of 12 months from the start of treatment, grade 3-4 thrombocytopenia (26%) was the most common haematological adverse event. After a median follow-up of 28 months, FUO/infections (15%) continue to be the most common non-haematological adverse event, although the incidence rate has reduced by half, and constipation occurred in 7.6% of patients.

Conclusions: The ORR, in our experience, was lower than what was previously reported in the POLLUX trial (ORR 86.5% vs 93%). The lower ORR observed could be related to a less selected population. In fact, in our survey, no exclusion criteria were applied. In addition, unfortunately, the interference of D with immunofixation and serum protein electrophoresis assays may lead to an underestimation of CR.

P19 BASELINE CORRELATES OF COMPLETE RESPONSE TO IDECABTAGENEC VICLEUCEL (Idec-Cel, BB2121), A BCMA-DIRECTED CAR T CELL THERAPY IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA: SUBANALYSIS OF THE KARMMA TRIAL

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Introduction: In the pivotal phase 2 KarMMa trial (NCT03361748), in heavily pretreated RRMM, 33% of patients (pts) who received ide-cel, a B-cell maturation antigen (BCMA)-directed CAR T cell therapy, had complete response (CR) or stringent CR (sCR), with a median duration of response of 21.5 months (Anderson et al. ASCO 2021, Poster 8016). This subanalysis aimed to identify baseline correlates of pts attaining CR/sCR in KarMMa.

Methods: Pts with ≥3 prior lines of therapy (including an immunomodulatory agent, proteasome inhibitor, and anti-CD38 antibody), and MM refractory to last regimen per IMWG criteria received ide-cel infusion (target doses 150–450 x 10^6 CAR+ T cells) after lymphodepletion. Bridging therapy was optional. Endpoints included overall response rate (primary) and CR/sCR rate (key secondary). Baseline characteristics were collected prior to lymphodepletion and for select biomarkers on day of infusion. Univariate and multivariate logistic regression models were used to identify baseline characteristics correlating with the likelihood of achieving CR/sCR.

Results: Of 128 pts who received ide-cel (data cutoff Dec 21, 2020), 42 pts achieved CR/sCR and 86 had non-CR/sCR (very good partial response, partial response, or no response). In pts with CR/sCR, 32 (76%) were negative for minimal residual disease (MRD) (sensitivity level of ≤10^{-4}), and 19 maintained MRD negativity at 12-mo follow-up. Baseline characteristics were generally balanced between pts with CR/sCR and non-CR/sCR; notable exceptions included revised International Staging System (ISS) stage III disease, IgG chain type, CD138+ plasma cell percentage, and β-2-microglobulin levels (Table). Univariate analysis of CR/sCR by baseline characteristics showed that IgG heavy chain versus other heavy chain types (odds ratio [OR]: 0.162, P = 0.0001), high sBCMA (OR: 0.646, P = 0.0007), β-2-microglobulin (≥5.5 vs <3.5 mg/L; OR: 0.201, P = 0.0072), and presence of extramedullary disease (OR: 0.428, P = 0.0394) were negatively associated with CR/sCR, whereas high vector copy number in drug product was positively associated with CR/sCR (OR: 1.290, P = 0.0287).

Multivariate analysis of CR/sCR identified IgG heavy chain versus other heavy chain types (odds ratio [OR]: 0.162, P = 0.0001), high sBCMA (OR: 0.637, P = 0.0110), and elevated prothrombin time-ininternational normalized test (PT-INR) (OR: 0.005, P = 0.0365) as negative correlates of CR/sCR, and high vector copy number in drug product (OR: 1.486, P = 0.0168) as a positive correlate of CR/sCR. Descriptive analysis demonstrated lower median (range) sBCMA levels at baseline in pts with CR/sCR (191 ng/mL [11–909]) versus non-CR/sCR (340 ng/mL [19–2731]) across both groups, sBCMA levels had increased from screening (CR/sCR, 161 ng/mL [27–689]; non-CR/sCR, 302 ng/mL [24–1490]).

Conclusions: In this subanalysis of KarMMa, multivariate analysis identified IgG, sBCMA, and PT-INR as negative correlates of CR/sCR, and vector copy number in drug product a positive correlate. As sBCMA is a tumor burden indicator and can affect BCMA-targeted therapies...

April 6-9, 2022 Virtual Meeting
P20 POLYCENTRIC “REAL LIFE” STUDY OF BELANTAMAB MAFODOTIN FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Background: Despite recent therapeutic advances, multiple myeloma (MM) remains an incurable disease. Particularly poor outcomes were described for “triple-refractory” patients, who are refractory to at least one proteasome inhibitor, immunomodulatory agent and anti-CD38 antibody. In this setting, we need further therapeutic options, and the DREAMM-2 study has shown interesting responses with Belantamab Mafodotin (BM). However, real-life studies are still lacking.

Methods: We performed a real-life analysis in two Italian centers (AOU Federico II and AORN Cardarelli, both in Naples). Unselected triple refractory patients received BM monotherapy as part of a compassionate use program. Whole sample (WS) included patients who received at least 1 dose of BM; evaluable population (EP) included only patients receiving not less than 2 BM cycles. Primary endpoint was overall response rate (ORR, i.e rate of patients with partial response -PR- very good partial response -VGPR- or complete response -CR-). Secondary outcomes included median progression free survival (mPFS), median overall survival (mOS), clinical benefit rate (CBR, i.e. rate of patients achieving stable disease -SD- or better), duration of response (DoR), time to response (TTR), time to best response (TTBR) and toxicity.

Results: Among responsive patients (RP), 2 patients received successfully consolidation with a second ASCT; 3 patients are to date still on treatment and 1 patient experienced PD after 3 months of PR. In the EP, mPFS and mOS were 4 months (r.:1-18) and 11 months (r.:2-18), respectively. Among RP, DoR, mPFS and mOS were not reached, TTR was 2 months (r.: 2-8) and TTBR was 6 months (r.: 2-8). Thrombocytopenia (57%) and keratopathy (21%) were the most frequent adverse reactions. Two patients with grade 3 eye toxicity discontinued the therapy and eye damage resolved.

Conclusions: Our analysis confirms the efficacy of BM and compares favorably with DREAMM-2 study (ORR: 43% vs 32%, mPFS: 4 vs 2.8 months, mOS: 11 vs 13.7 months, respectively). Moreover, we found less corneal toxicities (21% vs 72%), more thrombocytopenia (57% vs 38%) and no infusion-related reactions (0% vs 21%). In conclusion, BM shows meaningful anti-MM activity and a manageable toxicity profile even outside controlled clinical trials, proving to be an effective novel strategy in advanced MM.

P21 SUBSEQUENT ANTI-MYELOMA THERAPY AFTER IDECABTAGENE VICLEUCEL (IDEC-CEL, BB2121) TREATMENT IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA FROM THE KARMMA STUDY

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Introduction: Ide-cel, a novel B-cell maturation antigen (BCMA)-directed CAR T cell therapy, showed frequent, deep, and durable responses in triple-class-exposed patients (pts) with RRMM in the phase 2 KarMMa study (NCT03361748; Munshi et al. N Engl J Med 2021). The difference between median progression-free survival (PFS; 8.6 mo) and overall survival (OS; 24.8 mo; Anderson et al. ASCO 2021; poster 8016) prompted analyses examining additional outcomes for pts enrolled in KarMMa, including time to second disease progression (PFS2), type and duration of subsequent anti-myeloma therapy (sAMT), and OS in pts who received sAMT.

Methods: Pts with MM, ≥ 3 prior lines of therapy (including an immunomodulatory agent, proteasome inhibitor [PI], and anti-CD38 antibody), and disease refractory to their last regimen per IMWG criteria received ide-cel infusion (target dose range 150–450 x 10⁶ CAR+ T cells) after lymphodepletion (fludarabine 30 mg/m²/day + cyclophosphamide 300 mg/m²/day for 3 days). After ide-cel treatment, pts who relapsed could receive sAMT immediately or following ide-cel re-treatment (R-ide-cel).

Results: At a median follow-up of 24.8 mo among surviving pts, 104/128 (81%) pts who received ide-cel had progressive disease or had died. After ide-cel treatment, 68 pts received sAMT alone or with R-ide-cel (11/68 received subsequent anti-BCMA therapy). Fifty-two pts did not receive sAMT or R-ide-cel; of these, 33 relapsed after, or did not respond to, ide-cel and did not receive sAMT; and 19 were not included in this analysis because they were continuing in remission at time of analysis (n = 18) or discontinued without progressive disease or death (n = 1). Eight patients received R-ide-cel alone and were excluded from the analysis. Baseline demographics and clinical characteristics of pts receiving sAMT, anti-BCMA, and no sAMT/R-ide-cel were similar; however, more pts with no sAMT/R-ide-cel had revised International Staging System III disease compared with pts who had sAMT or anti-BCMA therapy (33%, 9%, 9%, respectively). The most frequent sAMT classes were corticosteroids (n = 58) and Ps (n = 47); the most frequent sAMT agents were dexamethasone (n = 56) and carfilzomib (n = 32). Anti-BCMA agents included belantamab mafodotin (GSK2857916; n = 10) and teclistamab (JNJ64007957; n = 1). In pts who received sAMT, median PFS and OS after ide-cel were 6.1 and 24.8 mo (Table). Median duration of first sAMT was 44 d and duration of all sAMT was 215 d, with a PFS2 of 13.6 mo inclusive of time on ide-cel. Among pts who received anti-BCMA therapy, median PFS and OS to ide-cel were 12.1 and 31.0 mo; median duration of first sAMT was 48 d and PFS2 was 15.5 mo.

Conclusions: In this descriptive subgroup analysis of the KarMMa trial, the majority of patients who relapsed after ide-cel were able to receive...
sAMT successfully with a PFS2 intermediate between PFS to initial ide-cel and OS. The PFS2 in this subgroup supports that disease control can be achieved by sequencing of sAMT after relapse from anti-BCMA CAR T therapy. Various classes of anti-myeloma drugs were used as sAMT. Studies are ongoing to define tumor phenotypes prior to and after ide-cel that may correlate with these clinical observations.

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**P22 A NON-INTERVENTIONAL, PROSPECTIVE, OBSERVATIONAL STUDY OF RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS TREATED WITH IAXOMIB IN REAL-WORLD SETTINGS IN GREECE; INTERIM RESULTS OF THE ‘OL-ORAL’ STUDY**

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**Background:** Iaxomib (IAX) combined with lenalidomide (LEN) and dexamethasone (DEX) (IRd) is approved for adults with multiple myeloma (MM) after ≥1 prior therapy. Real world data on IRd use in Greece are limited.

**Aims:** The objective of this study is to generate data on progression-free (PFS) and overall survival (OS) rates, as well as on medication adherence in IRd-treated MM patients.

**Methods:** Relapsed/refractory (RR) MM patients prescribed IRd for the first time, after ≥1 prior therapies, per the approved label, were eligible to consent and consecutively enrolled. Patients refractory to bortezomib (Bor), pre-treated with IAX, and having received >1 IRd cycles, are excluded. Data were collected by routine assessments, patient self-report, and medical chart review. We present the interim analysis results with cut-off at 24 months after first patient’s enrollment.

**Results:** Forty eligible patients (57.5% (23/40) males; median (interquartile range, IQR) age: 71.7 (64.8-77.3) years) were enrolled from Sep-2018 to Sep-2020 by 14 hospitals. Prior to IRd, 80.0% (32/40) of patients had received proteasome inhibitors [77.5% BOR; 7.5% carfilzomib], 65.0% (26/40) immunomodulatory drugs [57.5% LEN; 10.0% thalidomide; 2.5% pomalidomide], and 30.0% (12/40) autologous stem cell transplantation. At IRd initiation, the median (IQR) time since MM diagnosis was 3.5 (1.7-5.5) years. Of the patients, 85.0% (34/40) had ECOC PS 0-1, while 55.0% (22/40) had relapsed, 37.5% (15/40) relapsed and refractory, and 7.5% (3/40) refractory MM; 42.5% (17/40) were refractory to LEN.

IRd was initiated as 2nd, 3rd and 4th line in 67.5% (27/40), 22.5% (9/40) and 10.0% (4/40) of patients, respectively, at the recommended dose in 40.0% (16/40); IAX, LEN and DEX were started at a lower dose in 12.5%, 42.5%, and 50% of patients, respectively. Patient characteristics are shown in Table 1. Over a median (IQR) observation period of 6.9 (4.4-15.5) months, a median (IQR) of 7.5 (4.5-12.5) IRd cycles were received. Overall confirmed response rate [partial response (PR)] in the response-evaluable patients was 56.7% (17/30) [61.1% in 2nd and 50% in ≥3rd line]. Mean (SD) time to first documented response was 12.2 (1.3) months. Kaplan-Meier estimated 12-month PFS and OS rates were 58.0% (95% CI: 37.8-73.7) and 82.9% (95% CI: 65.6-92.0) (Figure 1). Adherence to IAX was high (median ratio of capsules taken/prescribed: 1). IRd discontinuation rate was 59.0% (23/39), due to disease progression (12/23), adverse event (AE) (8/23), death (2/23; unrelated to IAX in both cases), and lack of efficacy (1/23). IAX-related AE rate was 42.5% (17/40); serious AE rate: 17.5% (7/40).

**Conclusions:** These results provide preliminary insight on patient and disease characteristics and clinical outcomes in MM patients treated with IRd in 2nd to 4th line in Greek routine settings. The final results are awaited to complement these findings in a larger patient cohort.

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**P23 RELAPSED/REFRACTORY MULTIPLE MYELOMA PATIENTS. A MULTICENTER RETROSPECTIVE ANALYSIS OF ELIGIBILITY CRITERIA FOR CAR-T CELL THERAPY.**

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The overall survival (OS) of multiple myeloma (MM) patients (pts) has improved over the last years due to the introduction of several novel drugs, such as proteosome inhibitors (PI), immunomodulatory drugs (IMiDs) and anti-CD38 monoclonal antibodies (moAb). The majority of pts continue to relapse, and MM remains an incurable disease. No standard of care has been established for relapsed/refractory (RR) MM pts who have been exposed to the main anti-myeloma drugs. These pts have a limited number of treatment options and represent an unmet medical need. The outcome of pts failing standard of care regimen is poor, with a median progression free survival (PFS) of 3-4 months (mo) and OS of 8-9 mo. Immunotherapy represents the emerging therapeutic strategy for this subset of pts. Chimeric antigen receptor (CAR)-modified T cells are a promising new therapy approach for triple refractory RRMM. Specific CAR-T targets are being studied, but BCMA-directed CAR-T cells have so far provided the most convincing evidence of activity, with one product (idecabtagene vicleucel) recently approved by FDA and EMA.
The primary endpoint of this study was to define the clinical characteristics and outcome of a cohort of RRMM pts potentially eligible to CAR-T cell treatment according to the KarMMa trial criteria. Secondary endpoints were aimed at defining specific factors influencing CAR-T cell therapy eligibility and at identifying a real-life estimate of RRMM pts truly eligible for CAR-T cells.

This is a cohort analysis on RRMM pts managed between January 2018 and July 2021 at 4 Italian Centers of the Multiple Myeloma Lazio Group. At the time of data collection, 47 RRMM pts had undergone at least 3 prior therapy regimens; they had received a previous PI, IMiDs and a moAb and were considered refractory to the last regimen. The clinical characteristics are listed in Table 1. Median age was 68 years, 27 pts were >65 years; 27 were male. Of 47 pts, 33 were ECOG 0-1; 21 pts were ISS III. The majority of pts, 28, had undergone an autologous stem cell transplantation; 31 pts had received 3 prior lines of therapy and 16 >3 prior lines of therapy. Thirty-seven were triple-refractory and 8 were penta-refractory. Based on the KarMMa trial criteria, 22 pts would be defined as eligible and 25 not eligible for CAR-T cell therapy. Specifically, 14 pts were not eligible because of an ECOG 3-2, 24 had an organ dysfunction such as impaired renal function, anemia and thrombocytopenia. Of the 23 pts considered ineligible for CAR-T cell therapy, 17 presented ≥2 ineligibility criteria.

After a median follow-up of 34.7 mo (0.5-38.8), the median OS for the entire cohort was 21.7 mo, the median OS in eligible pts was 33.6 mo and in non-eligible pts was 16.8 mo (p=0.002). The median PFS of the eligible cohort was 7.6 mo and the median PFS was 7.8 mo in eligible pts vs 6.5 mo (p=0.513) in non-eligible pts. Despite the limits of a retrospective cohort, our real-life data shows that heavily treated pts are not excluded from CAR-T cell therapy. Considering the emergent role of quadruplet combined approaches for first-line therapy and the therapeutic relevance of CAR-T cells for refractory patients, a real-life estimate of RRMM pts truly eligible for CAR-T cells was reported.

Table 1. Characteristics of a real-life cohort of RRMM pts potentially eligible for CAR-T cell therapy (N=47).

| Characteristics | Patients (N=47) | % |
|-----------------|----------------|---|
| Gender          |                |   |
| Male            | 27             | 57 |
| Female          | 20             | 43 |
| Age (years)     |                |   |
| Median (range)  | 68 (43-86)     |   |
| Age >65         | 27             | 61 |
| ECOG I          |                |   |
| I               | 18             | 38 |
| II              | 15             | 33 |
| III             | 10             | 22 |
| IV              | 4              | 8.7 |
| Timing of diagnosis, median (years) | 5.40 (1.09-30) |
| ISS             |                |   |
| I               | 15             | 31 |
| II              | 11             | 23 |
| III             | 21             | 44 |
| Salmon factor   |                |   |
| I               | 9              | 19 |
| II              | 12             | 25 |
| III             | 26             | 55 |
| Durian factor A |                |   |
| A               | 35             | 74 |
| B               | 12             | 25 |
| ASCT yes/no     |                |   |
| Yes             | 28             | 59 |
| No              | 19             | 40 |
| HCV/HBV/HIV serology |         |
| Negative/positive | 47/53 | 100 |
| Lines of previous therapy |          |
| 0               | 31             | 66 |
| >0              | 16             | 34 |
| Refractory Triple-refractory Penta-refractory | |
| Refractory      | 37             | 78 |
| Triple-refractory |              |
| Penta-refractory |              |
| Organ functions, median (range) |         |
| Ht  | 10.7 (7.5-13)  |
| Ht/g  | 2517 (1025-7735) |
| Neutrophils, mm³ | 77 | 2517 (1025-7735) |
| Pts, mm³ | 172 (16-393)  |
| eSR, ml/m² | 68 (7-177)  |
| Bone marrow plasmacytoma infiltration FIV | 48 (10-98) |
| 60 (50-70)  |

Background: First-line usage of lenalidomide (LEN) is prevalent and increasing with the availability of lower cost generic LEN but also leads to resistance to therapies in later lines as patients become LEN-refractory. LEN-sparing regimens available and utilised at the time of this study in October 2020, predominantly doublet regimens and the triplet combination therapy of daratumumab (D) with bortezomib (V) plus dexamethasone (d), had limited efficacy compared to LEN-based regimens. This raises the need for highly effective LEN-sparing regimens to treat relapsed/refractory multiple myeloma (RRMM).

Objective: To understand the unmet need of RRMM patients as perceived by physicians with the goal of providing insights and reaching consensus relating to patients receiving LEN-sparing regimens in RRMM.

Methods: To capture physician perspectives of unmet need and treatment patterns in RRMM across Europe, a web-based, double-blind observational survey was designed and completed by physicians who treated ≥20 patients with RRMM in the preceding 3 months to September 2020. The output of this physician survey was discussed by a panel of 8 European experts (who are authors) via an abbreviated virtual Delphi panel process in October 2020.

Results: In total, 51 physicians across Belgium, France, Italy, The Netherlands and Spain completed the survey. Forty-seven percent and 63% of their patients with RRMM were reported to be LEN-refractory in the second- and third-line settings, respectively. According to the physicians’ experience, patients receiving LEN-sparing regimens available at the time of the study experienced poorer clinical outcomes than those who received LEN-based regimens in terms of overall survival, progression-free survival, response rate, and duration of treatment. There were minimal perceived differences in real-world effectiveness amongst the LEN-sparing regimens at the time of the survey/panel including Vd, Dvd, pomalidomide (Pom)/d, and carfilzomib (K)d. The survey results indicated no clear differences in patient characteristics between RRMM patients treated with LEN-based or LEN-sparing regimens (Table). Treatment choices appeared to be patient-specific; there were no clear relationships between prior treatments or comorbidities driving the choice of LEN-sparing regimens. Over half of survey physicians (53%) reported their dissatisfaction regarding the typical LEN-sparing regimens utilised at the time of the survey and a greater proportion (75%) perceived the need for more LEN-sparing combinations. Collectively, experts strongly agreed with the physician survey findings and noted that LEN-refractory patients universally experience poor outcomes with the LEN-sparing regimens available at the time of this survey. Approximately 90% of patients requiring a LEN-sparing regimen are those becoming refractory to LEN used as maintenance or continuous therapy, and LEN-refractory patients are particularly difficult to treat. Therefore, high use of LEN in early treatment lines drives the difficulty to treat in subsequent lines.

Conclusion: Since October 2020, the RRMM treatment landscape has evolved rapidly with the availability of novel anti-CD38-containing regimens such as Kd, Isatuximab (Isa)Kd and DPomd which have the potential to overcome this need. The development of novel LEN-sparing treatment options is still a relevant and important treatment innovation in RRMM given the use of LEN-based regimens in front-line persistents.
Venous thromboembolic (VTE) risk in Multiple Myeloma (MM) patients treated with novel agents can be very high, particularly with lenalidomide combined with high dose steroid. Guidelines do not recommend a validated Risk Assessment Model (RAM) to precisely identify patients with high VTE risk, in order to personalize the thromboprophylactic strategy. The IMWG score, that is widely used, is not actually performing well, as VTE events continue to occur in about 15% of MM patients. We aim to test IMPED-VTE score, which seems to be the most effective RAM in MM, in our real life MM population, trying to eventually implement it with emergent new risk factors.

**Patients and methods:** In our database, we prospectively collected data from 393 MM patients, treated from 2010 to 2021. One-hundred-thirteen (29%) patients were >75 years old, 45% were frail according to the simplified Frailty Score, 17% had abnormal LDH level, 19% had renal failure and 4% had a BMI ≥35. ISS stage 3 was scored in 27% of patients and 31% of patients had high-risk cytogenetics. Sixty-six percent of patients received Immunomodulatory (IMiDs)-based therapy (lenalidomide in 32% of patients). Monoclonal antibodies (MoAbs) were used in 8% of patients (MoAbs associated to lenalidomide in 75%) and carfilzomib in 10% of patients (carfilzomib associated to lenalidomide in 51%). Patients were stratified per IMPED-VTE score: high, intermediate and low risk were formed by 10%, 41% and 49% of patients, respectively. Eleven percent of patients had a central venous catheter (CVC), and thromboprophylaxis was chosen according to the IMWG criteria (ASA or none 74%), anticoagulants 26%. We have finally analysed the impact of therapeutic risk factors on thromboembolic events’ incidence.

**Results:** VTE events’ rate in our MM population was 16%, the major risk factors associated with VTE were high dose steroid, lenalidomide and carfilzomib treatments. None of patient-related risk factors (age, CCI, Frailty Score, LDH value), nor disease-related risk factors (ISS, cytogenetics, renal failure), except for bone disease, was significant in univariate analysis for increasing VTE risk. On the contrary, CVC, IMPDE-VTE score, lenalidomide and carfilzomib treatments retained statistical significance. Analysing therapy-related risk factors for VTE risk, we have found only a trend between the group treated with IMiDs-based (thalidomide, lenalidomide, pomalidomide) and that with non-IMiDs-based therapy (p=0.095). Nevertheless, patients treated with lenalidomide had higher VTE risk compared with patients treated without lenalidomide (13% vs 7% at 6 months; p=0.001). MoAbs-based therapy concurred to increase VTE risk, but only when associated to lenalidomide (p=0.001). On the contrary, carfilzomib monotherapy significantly increased VTE risk (p=0.001), regardless the association with lenalidomide. Stepwise Cox regression analysis selected IMPDE-VTE score (LR-R vs HR: 7% vs 16% at 6 months; p=0.032) and carfilzomib treatment (24% vs 7% at 6 months; p= 0.001) as independent significant risk factors for VTE.

**Conclusions:** Despite our analysis being retrospective, we confirmed IMPDE-VTE as a predictive score of VTE risk in a real life MM population. However, our analysis found carfilzomib-based therapy an independent risk factor from IMPDE-VTE score. We attempted to prospectively study the “carfilzomib-based therapy” parameter in order to implement IMPDE-VTE score, aiming to better stratify VTE risk in MM patients.

**P25 CARFILZOMIB-BASED TREATMENTS COULD BE ADDED TO IMPIDE-VTE SCORE TO BETTER PREDICT VENOUS THROMBOEMBOLIC RISK IN MM PATIENTS**

**P26 EXTREMEDULARY MULTIPLE MYELOMA: A MONOCENTRIC RETROSPECTIVE OBSERVATIONAL STUDY**

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Extramedullary Multiple Myeloma (EMM) is a distinctive sub-entity of Multiple Myeloma, characterized by clonal plasma-cells proliferation outside the bone marrow; it can be diagnosed either as a tissue growing in contiguity with bone marrow (paraskeletal) or in distant organs (extra- medullary). This subset of patients, especially the latter ones, have a poor prognosis, and there are not EMM-specific therapy schedules. The aim of our observational study was to describe patients that presented both type of EMM in order to report which common therapeutic approaches were used and to identify which disease characteristics mostly affected overall survival. We retrospectively analyzed 111 patients (pts) with EMM disease referred to the Hematology Department of Sapienza University of Rome between 2004 and 2021: 64 presented EMM at the onset of disease and 37 at relapse. Sixty-one pts were male and 50 were female (55% vs 45%); 60 pts (54.1%) were ISS III, while the most common isotype was IgG (62.2%), followed by IgA (22.5%) and light chain myeloma (11.7%). Cytogenetics data were available for 37 patients: among them, 8 patients showed a high-risk cytogenetics profile: the most frequent findings were del13q (40.5%), amp/gain1q (24.3%) and t(4;14) (13.5%). Out of these 37 pts, 11 (30%) presented ≥ 2 more cytogenetics alterations, while 4 pts (11%) presented a complex karyotype. Ninety-eight pts (88%) presented a paraskeletal localization, while 13 pts (12%) showed extramedullary localizations: the most frequent organs involved were soft tissues (5/13), followed by nervous central system, lymph nodes and orbit (2/13). Regarding the therapeutic approaches, 47% of pts with EMM at diagnosis received regimens containing a proteasome inhibitor (PI) and immunomodulatory drugs (IMiDs); 38% of pts underwent autologous stem cell transplantation (ASCT). At relapse, the most used regimens (30% of pts) were combinations containing monoclonal antibodies or IMiDs monotherapy. In both groups, one-third of patients underwent radiotherapy to reduce the local symptoms. After a median follow-up of 52 months for pts with EMM at diagnosis and 20 months for pts at relapse, the median OS was 147 months (mo) in first group and 32 mo in the second group (p<0.001). Among pts with EMM at diagnosis, pts who underwent ASCT showed a better median OS compared to other pts (NR vs 87.6 mo, p=0.004). Analyzing the type of EMM, we showed that pts with EMM had a worse outcome compared to pts with paraskeletal disease (median OS 43.4 vs 147 months, p=0.011). Despite the limit of our cohort, pts with EMM at diagnosis and high-risk cytogenetics had a worse outcome compared to those with standard-risk cytogenetics (median OS: 33.2 months vs NR, p=0.041). Multivariate analysis showed that the ASCT and obtaining at least a very good partial response after therapy were independent factors associated with better progression free survival (PFS). Regarding OS, obtaining at least a partial response and a previous therapy with a PI were independent factors associated with better OS. Despite the limits of the retrospective study, our data demonstrated that specific therapy based on PIs and ASCT could overcome the poor prognostic factor of EMM, according to the previous published data. Further studies are warranted to assess the optimal strategies for pts with extramedullary EMM, whose prognosis is still poor.
Background: SARS-CoV-2 anti-Spike IgG response following mRNA vaccination (BNT162b2) is suboptimal and highly variable in MM patients.

Patients and Methods: We report here a single-institution retrospective analysis of 127 consecutive patients with symptomatic MM (71 males, 56 females), [median age 69.5 years (range 45-85)], 63 patients with untreated MM and 64 patients with MM refractory to one or more previous treatment lines. Myeloma therapies included PI+IMiD combos, IMiD-based regimens, PI-based regimens, anti-CD38 mAb-based therapies, antibody-drug conjugates (Belantamab Mafodotin monotherapy), dexamethasone and high-dose melphalan. Anti-Spike IgG antibody were detected also in 50 healthy volunteers. Patients with symptomatic MM and healthy controls received two doses of COVID-19 mRNA vaccine (Pfizer BioNTech) on days 1 and 21 between 29 April and 15 May 2021. Patients with prior history of SARS-CoV-2 were excluded from analysis. Quantitative determination of anti-spike S1/S2 IgG antibody was performed at 4 weeks from vaccina- tion completion (LIAISON® SARS-COV-2 S1/S2 IgG, LIAISON®). It was previously established a threshold >15 AU/ml of anti-Spike IgG which was related to neutralizing activity of anti-SARS-CoV-2 antibodies.

Results: Sixty-five out of 127 patients were evaluable for response. Anti-Spike IgG antibody were detected in 50/65 (76.9%) MM patients, defined as responders [177 AU/ml (range 26.4 – 1430)], 23.1% of MM patients, defined as non-responders, failed to respond to two doses of COVID-19 mRNA vaccine [3.8 AU/ml (range 0.65 – 9.33)]. Seroprotection rate at cut-off of 15 AU/ml was 100% in controls [249 AU/ml (range 104 – 2430)]. No statistically significant differences were found between the two subgroups of patients for myeloma disease phase (relapse/refractory MM vs. untreated symptomatic MM), LDH, residual gammaglobulin levels, WBC, ANC, lymphocytic response, age and sex (Tab. 2). Conversely, plasmacytosis level and HbG concentration was significantly higher in non-responders compared to responders (10.8 ± 2.0 vs. 28.2 ± 18.8 mean ± SD; p < 0.001) (Tab. 2). There was a trend to increase in Covid infection related to neutralizing activity of anti-SARS-CoV-2 antibodies.

Conclusion: Among 110 MM patients, the mortality rate is less than the one reported by IMS during the beginning of the pandemic. In our experience COVID-19 infection severity and mortality decreases with anti-Covid vaccination, response to vaccine, after a median follow-up of 7 months from second dose of COVID-19 mRNA vaccine, no cases of COVID-19 occurred.

P28 RESPONSE AND VACCINATION STATUS OR LACK OF IMMUNOPARESIS ARE ASSOCIATED WITH BETTER OUTCOME FOLLOWING COVID-19 INFECTION AMONG PATIENTS DIAGNOSED WITH MULTIPLE MYELOMA: A SINGLE CENTER EXPERIENCE ON 110 PATIENTS

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Introduction: Patients with multiple myeloma (MM) have an inherently compromised humoral and cellular immunity predisposing to Covid-19 infection. Factors associated with increased risk of adverse COVID-19 outcome is unclear. The aim of our retrospective analysis was to evaluate COVID-19 infection outcome among our myeloma patients and define the possible prognostic parameters.

Patients And Methods: Between March 2020 - February 2022, 10 myeloma patients were diagnosed with COVID infection confirmed by PCR test and computer tomography (CT). The severity of SARS-CoV-2 infection was classified according to WHO definition as: mild: symptomatic without pneumonia or hypoxia; moderate: with or without signs of pneumonia with SpO2 <90% on room air; severe disease: with symptoms of pneumonia and respiratory rate> 30/min, severe respiratory distress or SpO2 <90% on room air. Critical disease: with acute respiratory distress syndrome (ARDS), sepsis and septic shock. In addition, CALL (comorbidity-age-lymphocyte count-lactate dehydrogenase) score was used. All patients were given supportive care including heparin and 0.4 gr/kg/day intravenous immunoglobulin for those presenting with immunoparesis regardless of IgG treshold of 4.0 gr/L. Convalescent or monochonal plasma was not used. All anti-myeloma treatments were discontinued until full recovery.

Results: Baseline characteristics of our patients are summarized in Table 1. The median age at onset of COVID-19 was 62 years. Three patients were therapy naive, two newly diagnosed MM and one with smoldering MM. At the time point of COVID-19 diagnosis, eight patients were being followed without treatment. Twenty patients were followed out-patient without any treatment and with full recovery. Eighteen (16%) patients were admitted to ICU and 13 (12%) required invasive mechanic ventilation. Two patients received hydroxychloroquine, 68 received favipiravir, one patient received anakira and two patients received tocilizumab. Full recovery from COVID-19 infection with regression of clinic symptoms and achievement of PCR negativity of COVID-19 was observed in 93 (84.5%) patients and 17 (15.5%) patients died due to severe COVID-19 pneumonia with respiratory and multi-organ failure. No death due to thromboembolic event was observed. As expected, high CALL risk score (HR:0.17 (95% CI: 0.06-0.48) and higher COVID severity grade (HR:0.26 (95% CI: 0.07-0.97) were detrimental. Age did not have an impact. However response to vaccine, after a median follow-up of 7 months from second dose of COVID-19 mRNA vaccine [3.8 AU/ml (range 0.65 – 9.33)]. Seroprotection rate at cut-off of 15 AU/ml was 100% in controls [249 AU/ml (range 104 – 2430)]. There was a trend to increase in Covid infection incidence recently due to the Omicron variant.

Conclusion: Among 110 MM patients, the mortality rate is less than the one reported by IMS during the beginning of the pandemic. In our experience COVID-19 infection severity and mortality decreases with anti-Covid vaccination, response to vaccine, after a median follow-up of 7 months from second dose of COVID-19 mRNA vaccine, no cases of COVID-19 occurred.
Haematologica. 2022). In that study, we found that these subjects neither have an increased risk of contracting SARS-CoV-2, nor show poorer COVID-19 outcomes with respect to controls. Aiming to specifically address the clinical effects of vaccines, we compared incidence and outcome of SARS-CoV-2 infection of 1,454 previously described, not vaccinated MGUS patients (91 of whom were SARS-CoV-2 positive), with those observed in a similar population during the national vaccination campaign. So far, we have obtained retrospective information from 41 individuals found to be SARS-CoV-2 positive among 765 MGUS patients analyzed after at least two doses of anti-SARS-CoV-2 vaccine received between April 2021, and January, 2022. The mean age of this group was 64.1 +/-14.1 years (range 31-90); 16 patients were female (39%), and 25 were male (61%). About MGUS-subtypes, the most frequent one was IgG-lambda (n=20; 48.8%), followed by IgG-kappa (n=14; 34.1%), IgA-kappa (n=3; 7.3%), IgA-lambda (n=2; 4.9%) and IgM-kappa (n=2; 4.9%). Most of patients (39/41, 95%) were at low or low-intermediate risk, according to Mayo Clinic prognostic model. Twenty-one (51.2%) patients developed SARS-CoV-2 infection after two doses (5, 15 and 1 patients receiving ChAdOx1-S, BNT162b2 mRNA and mRNA-1273 vaccines, respectively), twenty (48.8%) after three doses (BNT162b2 mRNA or mRNA-1273 as “booster” dose, respectively). The mean number of days between last dose of vaccine and SARS-CoV-2 infection was 98.8 +/-77.8 (range 2-240). The two populations of SARS-CoV2 positive MGUS patients (before and after vaccination) were comparable for age, sex and presence of co-morbidities (data not shown). Overall, rates of symptoms (59.3% vs 31.8%), hospitalization (20.9% vs 0%), and hospitalization in Intensive Care Unit (11% vs 0%) were significantly higher in still not vaccinated MGUS patients than in those who had received vaccines (Table 1). A strong trend toward a higher rate of deaths (8.8% vs 0%) was also observed in not vaccinated patients, although it did not reach statistical significance, probably due to the small number of evaluated patients. Interestingly, incidence of SARS-CoV-2 detection in vaccinated patients was not significantly different from that of patients analyzed before vaccination (5.4% vs 6.2%, respectively) (p=0.402). Our data indicate that the possibility to be infected by SARS-CoV-2 is probably not significantly reduced by vaccination (even after three doses), likely also because of the higher diffusion capacity of the recently recognized Omicron viral variants. However, as observed in normal population and in other hematological contexts, the clinical outcome of COVID-19 may be significantly improved after vaccination in MGUS patients, with less of one third of patients who were symptomatic and no case of hospitalization or death in our series. These observation reinforces the need to proceed with an active vaccination program in these patients.

|                          | Pre-vaccination² | Post-vaccination | P-value |
|--------------------------|------------------|------------------|--------|
| Total SARS-CoV-2 positive MGUS, n. (%) | 91/1,454 (6.2)   | 41/763 (5.4)    | 0.402  |
| COVID-19 outcome         |                  |                  |        |
| Presence of symptoms, n. (%) | 20 (59.3)        | 13 (31.8)        | <0.05  |
| Hospitalization, n. (%)  | 19 (51.3)        | 0 (0)            | <0.05  |
| Hospitalization in ICU, n. (%) | 10 (11.0)    | 0 (0)            | <0.05  |
| Death due to COVID-19, n. (%) | 8 (8.8)          | 0 (0)            | 0.057  |

Table 1. Characteristics of COVID-19 in patients with MGUS, before and during anti-SARS-CoV-2 vaccination campaign.

Abbreviations: ICU: Intensive care unit; SD: standard deviation. * Sgherza N et al. Haematologica. 2022 Feb 1;107(2):555-557.
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