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ABSTRACT BOOK

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Author Information

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EHA EUROPEAN HEMATOLOGY ASSOCIATION

4th European Myeloma Network Meeting, Amsterdam, Beurs van Berlage, April 20-22, 2023

MAIN PROGRAM

MGRS: DIAGNOSIS AND TREATMENT

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Monoclonal gammopathy of renal significance (MGRS) refers to the association of a small, otherwise indolent B-cell clone, with renal disease induced by the secreted monoclonal Ig (MIg). Renal lesions, independent of the tumor burden, are governed by the physico-chemical characteristics of the MIg and involve either direct (MIg deposition or precipitation) or indirect (autoantibody activity, complement activation) mechanisms. The spectrum of MGRS-associated renal disorders is wide, encompassing tubulo-interstitial disorders (Fanconi syndrome, crystal storing histiocytosis) and glomerular disorders. The latter are classified into 3 categories according to the composition and ultrastructural appearance of glomerular deposits: 1) glomerulopathies (GP) with organized MIg deposits (immunoglobulinic [AL and AH} amyloidosis, cryoglobulinic GP, immunotactoid GP, light chain crystalline podocytopathy); 2) GP with non-organized deposits (monoclonal Ig deposition disease [LCDD, HCDD, LHCDD], proliferative glomerulonephritis with MIg deposits [PGNMID]); 3) GP without Ig deposits (MIg-associated C3GP and thrombotic microangiopathy). The diagnosis of each specific MGRS-related renal disease is suggested by the analysis of renal symptoms, particularly proteinuria, and by the presence of suggestive extra-renal manifestations. Kidney biopsy with light, immunofluorescence and electron microscopy studies, sometimes completed with proteomic analysis, is needed for diagnostic confirmation in most cases. Detailed hematologic workup is warranted for the identification and quantification of the pathogenic MIg (SPEP, UPEP, serum and urine immunofixation, serum free light chains) and for the characterization of the underlying clone (bone marrow flow cytometry, cytogenetics). Sensitive techniques such as RNA-based Ig repertoire sequencing may be useful for the detection of subtle clones. Early diagnosis and rapid achievement of deep hematological response through clone-targeted chemotherapy are the main factors influencing long-term renal and patient outcomes. Treatment of plasma cell clones mostly relies on bortezomib and anti-CD38 monoclonal antibody-based regimens, which do not require dose adaptation and have a favorable efficacy/toxicity ratio in patients with renal impairment. Renal transplantation is a valuable option in selected patients with end-stage kidney disease, providing that a deep and stable hematologic response (≥ VGPR) has been achieved prior to the procedure.

MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

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Aside from the risk to evolve to MM or WM, or to be associated with AL amyloidosis or POEMS syndrome, the M-protein in persons with MGUS can cause "per se" the so-called "monoclonal gammopathies of clinical significance –MGCS" resulting in neurologic, skin, ocular, bleeding or other disorders. The monoclonal gammopathy of renal significance (MGRS), coined to highlight renal damage, different from cast nephropathy or amyloid deposition, linked to the M-protein is not discussed here. In patients with MGUS and peripheral neuropathy (PN), and no evidence of AL amyloidosis or POEMS, a causal relationship must be considered. In the IgM type, a gammopathy-associated PN is likely (50% are MAG positive) while in the IgG and IgA types a CIDP with coincidental MGUS is the most likely diagnosis. The main skin conditions related to M-proteins are: 1) cryoglobulin (IgG/IgM) vasculatis with petechiae, purpura or ulcers, 2) Schnitzler syndrome (IgM, chronic urticaria, fever, artralgia), 3) pyoderma gangrenosum (IgA, ulcers with central necrosis), 4) necrobiotic xanthogranuloma (IgG, yellow papules, nodules, plaques), 5) escleromixedema (IgG-lambda, mucine dermal deposition with occasional systemic involvement –cardiomyopathy, pulmonary fibrosis or reduced esophageal motility-) or 6) acquired generalized cutis laxa (lambda, elastolysis of the skin –premature ageing-, occasionally associated with kidney –fibrillar glomerulopathy-, heart or lung involvement). The most frequent ocular M-protein related condition is crystalline keratopathy (Ig deposition, corneal thickening, photophobia, visual loss). Bleeding can result from acquired von Willebrand deficiency or by impaired platelet aggregation induced by the M-protein. In summary, The M-protein in MGUS can cause relevant clinical conditions. If a causal relationship is proven or highly suspected, therapy against the plasma cell clone (rituximab-based in IgM-types and bortezomib-based, even including ASCT, in non-IgM) must be timely initiated.

AL AMYLOIDOSIS UPFRONT TREATMENT AND CURRENT AND FUTURE STUDIES

Kastritis E.

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The treatment of AL amyloidosis is based on the elimination of the plasma cell clone. Today, approved therapies include combinations of the anti-CD38 monoclonal antibody daratumumab with bortezomib, cyclophosphamide and dexamethasone (D-VCd); this combination is effective with about 50%-60% of the patients achieving complete hematologic response and about 80% achieving at least a very good partial hematologic response. However, there are still several unmet needs: patients with very advanced cardiac amyloidosis, such as those stage 3B disease, have been excluded from the clinical trials, and they still have a very poor outcome. Second, at least 50% of patients with AL amyloidosis still fails to achieve a clinically significant organ function improvement. Finally, for patients failing to achieve hematologic or organ response or those who relapse after initial response, there is a need for new treatments and novel strategies. Although most treatments for patients with AL amyloidosis come from the myeloma field, not every therapy given for myeloma is suitable for patients with AL amyloidosis. Targeted therapies, such as those targeting BCL2, can be quite effective, since about 50% of AL patients harbor t(11;14). Anti-BCMA targeting therapies are also promising but they need to be further explored in the setting of AL amyloidosis. Experience with cellular therapies and T-cell redirecting therapies is still limited in AL amyloidosis; such therapies could be quite effective in eliminating the small but toxic amyloidogenic plasma cell clone but their toxicity should be explored specifically in patients with AL amyloidosis. An urgent need remains for the treatment of patients with very advanced cardiac involvement, for which even a deep hematologic remission may not be enough. For these patients, regimens with low toxicity and high efficacy should be prioritized and combined with potentially active amyloid targeting therapies. Combinations of non-cardiotoxic, non-nephrotoxic and non-neurotoxic agents should be prioritized, preferably in fixed duration regimens.

EARLY DETECTION AND SCREENING FOR MULTIPLE MYELOMA PRECURSORS

Thorsteinsdottir S.

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Monoclonal gammopaty of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic precursors of multiple myeloma (MM). Emerging data from clinical trials indicate that initiation of treatment at the stage of high-risk SMM can improve outcomes in MM. Currently there is no established screening for MM precursors and most MM patients are therefore diagnosed after the development of symptomatic end-organ damage. The Iceland screens, treats, or prevents multiple myeloma (iStopMM) study (ClinicalTrials.gov #NCT03327597) is a nationwide screening study investigating the benefits and harms of screening for MM precursor conditions. All individuals residing in Iceland over 40 years of age (n = 148,711) were offered participation with 75,422 (51%) were screened using serum protein electrophoresis (SPEP) and free light chain (FLC) analysis. The 3,725 with abnormal screening were randomized to one of the three arms of the study, and bone marrow sampling was performed in over 1,600 individuals.

The iStopMM study started in 2016 and is still ongoing. First results from the screening show that the prevalence of MGUS is 4.5% and the prevalence of SMM is 0.5% in individuals over 40 years old, both conditions are more common in men than women and the prevalence increases with age. Around one third of the SMM patients have intermediate- to high-risk SMM according to the Mayo Clinic 20/2/20 risk stratification model, and could potentially be candidates for early treatment. Furthermore, initial results from the randomized clinical trial show that active screening identified significantly higher number of individuals with full-blown malignancy (MM and related disorders) than in the control arm. These first results show that screening is feasible, however, until the final results from the iStopMM study become available, including overall survival data, data on MM related organ damage and quality of life, we advise against systematic MGUS screening in healthy individuals.

MASS SPECTROMETRY AS A TOOL FOR MINIMAL RESIDUAL DISEASE DETECTION IN THE BLOOD OF MYELOMA PATIENTS

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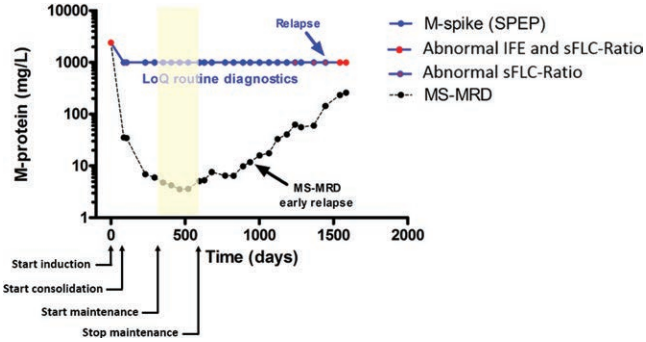
M-protein detection and quantification are integral parts of the diagnosis and monitoring of multiple myeloma. Novel treatment modalities impose new challenges on the traditional electrophoretic and immunochemical methods that are routinely used for M-protein diagnostics, most importantly the need for increased sensitivity to measure minimal residual disease (MRD).

In the past two decades flow cytometric and next generation sequencing methods have been developed to assess MRD in bone marrow aspirates of patients with multiple myeloma. MRD-status is an important independent prognostic marker and its potential as surrogate endpoint for progression-free survival is currently studied. In addition to that, numerous clinical trials are investigating the added clinical value of MRD-guided therapy decisions in individual patients. Because of these novel clinical applications, repeated MRD-evaluation is becoming common practice, also in regular management of patients outside clinical trials. A disadvantage of MRD-evaluation on bone marrow aspirates is the risk of sampling-error, resulting from heterogenous dispersion of myeloma cells and/or extramedullary myeloma outgrowth. In addition, invasive bone marrow biopsies are a burden to patients.

Recently, advances have been made in ultra-sensitive detection and quantitation of serum M-proteins using mass spectrometry (MS-MRD), which represents an attractive minimally invasive alternative to bone marrow-based MRD-evaluation. Several studies have shown that MS-MRD blood-testing is feasible in all patients with multiple myeloma and that it has similar sensitivity and prognostic value compared to NGS-MRD evaluation performed on bone marrow. The MS-MRD blood-test paves the way for dynamic MRD monitoring to allow detection of early disease relapse (see Figure) and may proof to be a crucial factor to facilitate future clinical implementation of MRD-guided therapy.

Figure. Early relapse detection with dynamic MS-MRD monitoring.



MS-MRD blood monitoring on 26 sera of one patient with multiple myeloma treated in the IFM2009 clinical trial. The increased sensitivity of MS-MRD (black) compared to routine M-protein diagnostics (blue) allows early detection of disease relapse.

DEBATE UPFRONT VS DELAYED TRANSPLANT

Gay F.

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Standard treatment approach for newly diagnosed patients eligible for high-dose chemotherapy consists of a multiagent induction treatment (including, based on local availability and approval, anti CD38 Monoclonal antibody, proteasome inhibitor, immunomodulatory agent and dexamethasone) followed by stem cell collection and then high dose chemotherapy (Melphalan 200 mg/sqm, Mel200) and autologous stem cell transplantation (ASCT).

Several trials consistently showed a progression free survival benefit for Mel200-ASCT upfront vs novel agent based chemotherapy, including bortezomib-lenalidomide-dexamethasone and carfilzomib lenalidomide dexamethasone.

Stem cell collections is now adequate in the majority of the patients, and rarely patients who are intended for ASCT have to be excluded from this therapeutic approach. With the current supportive measures, Mel200-ASCT became a well tolerated procedures, with a mortality rate <1% and manageable and predictable toxicities (mainly hematological, infections and gastrointestinal toxicities). In many countries, patients can be also managed in the outpatient setting.

Despite improvement in progression free survival, no benefit in terms of OS has been proven so far in randomized studies were ASCT is compared with combinations of proteasome inhibitors and immunomodulatory agents. This might be related to the general improvement in survival for myeloma patients, and as a consequence a very long follow-up is needed to show OS benefit. Another reason could be that now, with improvement in supportive cares, many patients can indeed be able to receive ASCT at first relapse.

Indeed, prolonged remission after first line, even with so far no improvement in OS, is of importance since outcome after first line is generally the longest in the patient journey, and a proportion of patients who relapse might not be able to get to second line therapy.

TREATMENT OF TRIPLE-CLASS REFRACTORY DISEASE: BEYOND IMMUNOTHERAPY

Gavriatopoulou M.

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Proteasome inhibitors (PIs),immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies (MoAbs) are the cornerstone of multiple myeloma (MM) therapeutics. After the incorporation of novel agents the clinical outcomes of patients with MM have improved significantly, however prognosis of patients refractory to three drug classes (triple-class refractory [TCR]) is extremely poor. Observational data indicate an overall response rate of approximately 30% and overall survival less than 1 year. Novel agents with different mechanisms of action have been studied and have demonstrated significant activity in TCR MM, including anti-B-cell maturation antigen (BCMA) chimeric antigen receptor T cells, anti-BCMA antibody-drug conjugates and exportin 1 (XPO1) inhibitors.

Selinexor is a first-in-class, selective exportin-1 inhibitor. Selinexor in combination with dexamethasone has emerged as an important therapeutic approach for heavily pretreated TCR patients with safe and manageable toxicity. Melflufen in combination with dexamethasone was granted accelerated approval by FDA in February 2021 for RRMM in patients who have previously failed at least four lines of therapy. However, examination of OS data from this trial found a higher death rate (48% vs. 43%) in the melflufen group, leading the FDA in October 2021 to withdraw this approval. The drug is approved in the EU. Several other small molecule cereblon E3 ligase modulators (CELMoDs) have been developed for treatment of MM the past few years. This group includes iberdomide (CC-220), which binds to cereblon with an affinity that is twenty times higher than that of either lenalidomide or pomalidomide, leading to more efficient degradation of Ikaros and Aiolos. The combination of iberdomide with dexamethasone in heavily pretreated MM patients yielded ORRs of 26%-32% with serious adverse events noted in 53%. Avadomide (CC-122) is another glutarimide-based cereblon modulator that has broader activity than lenalidomide, possibly due to deeper and faster kinetics of Aiolos degradation. Mezigdomide (CC-92480), another promising drug, showed significant antimyeloma activity in cell lines, including those resistant to pomalidomide and lenalidomide. In addition, venetoclax has demonstrated significant activity in t(11;14) MM patients and represents another therapeutic option. The most appropriate sequencing of existing therapies and the most potent treatment combination still remains unanswered.

ANTIBODY DRUG CONJUGATES (ADCS)

Terpos E.

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BCMA (B-cell maturation antigen) is a and member of the tumor necrosis factor receptors superfamily, which is primarily expressed in late-stage B-lineage cells, normal and malignant plasma cells, and B-lymphocytes, with very low expression on nonhematologic cells. Belantamab Mafodotin (belamaf) is the first approved anti-BCMA ADC for the treatment of relapsed/refractory multiple myeloma (RRMM). This afucosylated, humanized, IgG1 monoclonal antibody is conjugated to monomethyl auristatin F, an inhibitor of tubulin polymerization, through a protease-resistant maleimidocaproyl linker. Following binding to the plasma cell surface, belamaf is internalized, and the active cytotoxic drug is released following enzymatic cleavage leading to cell death. Mechanisms of action include also NK-cell mediated ADCC and ADCP. DREAMM-2 trial explored the safety and activity of belamaf in MM patients who were refractory to PI, IMiD and an anti-CD38 mAb alone or in combination. Patients were randomized 1:1 to receive 2.5 mg/kg (n = 97) or 3.4 mg/kg (n = 99) belamaf, iv, every three weeks until disease progression or unacceptable toxicity. After a median follow up of 9 months, the median PFS was 2.8 and 3.9 months in the two cohorts, respectively, with one year OS probability of 53%. ORR was similar among the group of patients with 3–6
(34%) and seven or more (30%) prior lines of therapy. Two post hoc analyses demonstrate the efficacy of belamaf in the subgroups of patients with high-risk cytogenetics and impaired renal function (EGFR 30 ml/min). Regarding AEs, this study confirmed the frequent occurrence of corneal events; 72% of patients developed keratopathy of any grade, while 31% developed keratopathy grade 3–4. Keratopathy was attributed to the MMAF and was reversible after temporary discontinuation of the drug. Other frequent adverse events grade 3–4 were anemia (21%) and thrombocytopenia (22%). Based on this study belamaf was giver provisional approval by EMA for use in triple-class refractory RRMM at a dose of 2.5 mg/kg every 3 weeks.
Currently, the role of belamaf is being evaluated in earlier RRMM settings. Three-phase III studies evaluate the safety and efficacy of belamaf in combination with pomalidomide (NCT04162210; DREAMM-3), daratumumab plus bortezomib (NCT04246047; DREAMM-7), or pomalidomide plus bortezomib (NCT04484623: DREAMM-8). The results are eagerly awaited.
MEDI2228 is another antibody-drug conjugate (ADC) composed of fully human monoclonal antibody, conjugated to a dimeric cross-linking pyrrolobenzodiazepine dimer via a protease-cleavable dipeptide linker8/42. MEDI2228 has shown potent antitumor activity in preclinical models, including cell lines resistant to lenalidomide. Phase 1 data in heavily pretreated patients were encouraging.

BONE DISEASE

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Osteolytic bone disease is the most common complication of multiple myeloma. Both diagnosis and follow up of bone disease during anti-myeloma therapy require modern imaging. 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, a landmark analysis at 15 months showed a superiority of denosumab in terms of SREs.
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;
Newly-diagnosed patients at high risk for developing skeletal-related events should be considered for an early intervention in addition to the administration of bone-targeting agents. 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.

HOW TO HARNESS NEW IMMUNOTHERAPIES WITH COMBINATION STRATEGIES?

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Abstract
Immunotherapy includes all treatment approaches that use components or mechanisms of the immune system to fight malignant cells. These therapeutic approaches include e.g. bispecific antibodies and CAR-T cell therapy. By adding immune checkpoints, anti-CD38 Abs, IMiDs, CelMODs and tyrosine kinase inhibitors their effectiveness can be increased. Preclinical data as well as data from clinical trials using this combination approach will be presented.

Bispecific Antibodies

Another approach to fighting cancer in the field of immunotherapy is bispecific antibodies, which were clinically developed at the University Hospital in Würzburg and are now called bispecific T cell engagers. These antibodies contain the binding parts of two different monoclonal antibodies and can thus recognize two different surface structures and bind them together. Accordingly, cancer cells can be bound to highly active T cells of the immune system via bispecific antibodies. This reprograms the immune cell and induces tumor cell killing.

CAR T cell therapy

In CAR T cell therapy functional autologous T cells are removed from the patient's blood. These are genetically modified in such a way that they form a receptor on their cell surfaces that recognizes the cancer cells. These CAR-T cells are then multiplied and given to the patient following a lymphodepleting therapy to optimize CAR T cell expansion and activation. Once established in the body, CAR-T cells are able to kill cancer cells.

BEST ABSTRACTS - ORAL PRESENTATIONS

B01 VENETOCLAX TARGETED THERAPY IN AL AMYLOIDOSIS PATIENTS: A RETROSPECTIVE ANALYSIS FROM THE FRENCH AMYLOIDOSIS NETWORK

Roussel M.[1]; Pirotte M.[2]; Gounot R.[3]; Queru K.[1]; Rizzo O.[4]; Royer B.[5]; Harel S.[5]; Desport E.[6]; Huart A.[7]; Niault M.[8]; Karlin L.[9]; Decaux O.[10]; Chalopin T.[11]; Carpentier B.[12]; Macro M.[13]; Vignon M.[14]; Chalayer E.[15]; Stoppa AM.[16]; Bridoux F.[6]; Jaccard A.[1]

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Background: BCL-2 inhibition represents a promising therapeutic approach in multiple myeloma (MM). Venetoclax (VEN) is an oral BCL-2-selective BH3 mimetic and is currently approved in CLL. VEN has shown activity in MM cell lines with t(11;14), in part because there may be greater BCL-2 co-dependence in such clones. VEN is safe in MM patients (pts) with encouraging clinical activity. VEN should provide a novel targeted therapy in AL amyloidosis as most of the pts harbored a t(11;14). Various retrospective cohorts are now reported with VEN alone or in combination with bortezomib (BOR) and/or daratumumab (DARA), with rapid and deep hem. responses. We report here on efficacy of VEN based regimen in AL amyloidosis pts in a real-life setting.
Patients: This retrospective study included 51 pts with AL amyloidosis, from the French Amyloidosis Network, who received at least one cycle of VEN as part of their regimen. Individual data were prospectively and retrospectively collected. Responses were reviewed using current criteria for CR (serum/urine negative immunofixation and normal involved FLC) and for VGPR (differential FLC<40 mg/l). Median age was 62 years (54-70); 34 pts had >=2 organs involved with heart in 70.5% and kidney in 57.0%, MAYO stage 3/4 in 25 pts and median NT-proBNP and troponin levels of 1706 ng/l (IQR: 339-4275), 59 pg/ml (19-88), respectively. Median dFLC was 314 mg/l (IQR:133-565) and 32 pts had a dFLC>180 at diagnosis. Of note, 72.5% of pts were FLC only. Median plasma cells infiltration was 8% (IQR: 5-14). All except 3 pts had a t(11;14).
Results: Median time from diagnosis to VEN therapy was 24 months (IQR:9-60). VEN (100-800 mg/day) was given alone (n=25), or with dexamethasone/DEXA (n=5), BOR (n=12), DARA (n=3), or all (n=6). Twelve pts received frontline VEN to deepen or restore response, and 39 received VEN at relapse with a median of 2 prior lines of therapy (min/max: 1–6); 37 pts were DARA exposed and 7 were DARA "refractory". Overall, 45% of pts never achieved >=VGPR with their previous line of therapy. Median dFLC was 74 (IQR: 45-133) at time of VEN. Median time on therapy was 9 mos (IQR:6-14): 34 pts discontinued VEN because of CR/VGPR (n=21), disease progression (n=7), toxicities (n=8) and/or death (n=6). The hematologic response rate was 90% with 61% CR, 14% VGPR, and 10% PR, 3 pts are not evaluable. Only 1/3 pt with no t(11;14) achieved CR. Responses were fast and median time to best response was 2.75 mos (IQR:1.05-3.00). Median DOR is 12.7 mos (IQR:7.0-18.9). For VEN monotherapy, 72% achieved >=VGPR and 56% CR; with the addition of DEX, BOR, DARA or both, CR was 60, and 67%, respectively for the last 3. In frontline pts, all except 3 achieved CR with the addition of VEN. In relapsed pts, 56.5% achieved CR and 18% VGPR. Considering DARA exposed/relapsed pts, 14/25 (56%) achieved CR, and 4 (16%) VGPR; considering the 7 R/R pts, 71% reached CR. With median FU of 17.2 mos, median PFS is 40 mos, and estimated 3-year OS 68.2% (SD 10.3); 10 pts died. VEN was well tolerated with no unexpected adverse events (AEs). Eighteen pts reported AEs, mainly diarrhea/nausea, neutropenia, infections and fatigue.
Conclusion: Venetoclax in AL amyloidosis is a promising targeted therapy. With CR of >55% with VEN alone or VEN-based regimen, these results confirm the efficacy of VEN in pts with t(11;14) AL and support randomized clinical trials, even in daratumumab and/or bortezomib-exposed pts (and somehow refractory).

B02 CARFILZOMIB AND LENALIDOMIDE-BASED THERAPY FOR THE TREATMENT OF PRIMARY PLASMA CELL LEUKEMIA: RESULTS OF THE FINAL ANALYSIS OF THE PROSPECTIVE PHASE 2 EMN12/HOVON-129 STUDY FOR PATIENTS AGED 18-65 YEARS

van de Donk N.[1]; Minnema M.C.[2]; van der Holt B.[3]; Schjesvold F.[4]; Wu K.L.[5]; Capra A.[6]; Broyl A.[7]; Roeloffzen W.W.H.[8]; Gadisseur A.P.A.[9]; Pietrantuono G.[10]; Pour L.[11]; van der Velden V.[12]; Lund T.[13]; Offidani M.[14]; Grasso M.[15]; Giaccone L.[16]; Cavo M.[17]; Silkjaer T.[18]; Caers J.[19]; Zweegman S.[1]; Hajek R.[20]; Benjamin R.[21]; Vangsted A.[22]; Boccadoro M.[16]; Gay F.[16]; Sonneveld P.[7]; Musto P.[23]

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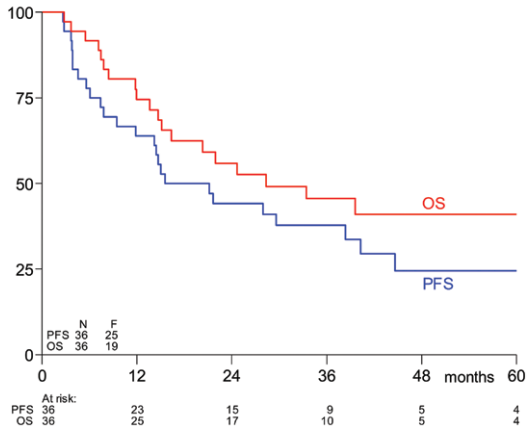
Introduction: Primary plasma cell leukemia (pPCL) is a rare, aggressive plasma cell disorder with poor prognosis. Median PFS for transplant-eligible pts is approx. 9 months. The EMN12/HOVON129 study assessed carfilzomib and lenalidomide in induction, consolidation, and maintenance for pPCL pts. Pts ≥18 years were enrolled, with different treatment for those 18-65 and ≥66 years. Here we report the results for pts 18-65 years.
Methods: Inclusion criteria were newly diagnosed pPCL (>2x10^9/L circulating monoclonal plasma cells or plasmacytosis >20% of the differential white cell count) and WHO performance status 0-3. Main exclusion criteria were severe cardiac or pulmonary dysfunction; and creatinine clearance of <15 ml/min. There were no restrictions based on blood counts.
Pts aged 18-65 years received four 28-day induction cycles of carfilzomib-lenalidomide-dexamethasone (KRd; K: 20/36 mg/m^2 days 1,2,8,9,15,16; R: 25 mg days 1-21; d: 20 mg days 1,2,8,9,15,16,22,23), tandem ASCT, 4 KRd consolidation cycles, and KR maintenance (K: 27 mg/m^2 on days 1,2,15,16; R: 10 mg on days 1-21/28 days) until progression. Pts eligible for allo-SCT could also receive one ASCT, followed by 2 KRd consolidation cycles, reduced-intensity conditioning allo-SCT and KR maintenance.
The primary endpoint was PFS, and secondary endpoints were response rate, OS, and toxicity.
Results: From Oct 2015 to Aug 2021, we enrolled 36 pts with pPCL aged ≤65 years. Median age was 60 years; 67% had bone disease; WHO performance status was ≥2 in 33% of pts. Pts had a high tumor burden with a median plasma cell percentage in BM of 80%. The median peripheral blood plasma cell count was 4.1x10^9/L (range 1.6-60.0); median platelet count was 111x10^9/L (range 20-517); and median eGFR was 54.0 ml/min (range 15.0-123). Pts had high-risk disease: 58% had elevated LDH, and 47% del(17p), 9% t(4;14), 19% t(14;16), 61% gain/ampl(1q); ≥2 high-risk cytogenetic abnormalities were present in 38%; 26% had t(11;14); 17% had extramedullary plasmacytomas; 64% had ISS 3 and 50% revised ISS 3. Response to induction was ≥PR in 72%, ≥VGPR in 64%, and ≥CR in 14%. 24 pts (67%) received HDM/ASCT; 12 pts (33%) underwent second HDM/ASCT; 5 (14%) received allo-SCT after first HDM/ASCT. 18 pts (50%) received maintenance. Best response on protocol was ≥PR in 83%, ≥VGPR in 81% and ≥CR in 50%; 10 (28%) pts achieved MRD-negative (10^{-5}) CR. With a median follow-up of 40.8 months (range 8-2-74.5), median PFS was 15.5 months (95% CI 9.4-38.4); median OS was 28.4 months (95% CI 15.1-not reached – 19 deaths: 14 for disease progression, 4 infections, and 1

cardiac disorder). In exploratory analyses, pts with elevated LDH, t(14;16), and del(17p) had inferior PFS and OS. For pts who underwent first HDM/ASCT, median PFS and OS were 32.9 and 34.1 months from date of ASCT. ≥G3 toxicity rate was 67%, including infections (25%) and cardiovascular disorders (14%). One patient developed a SPM (MDS). As of July 24, 2022, 25 pts (69%) discontinued treatment mainly because of progression, none for treatment-related toxicity.

Conclusions: KRd induction provides efficient and rapid disease control, which allows two-thirds of pts to undergo a first course of HDM/ASCT. Toxicity occurred mainly during the first cycle of induction and was manageable. However, median PFS and OS remain low in pPCL compared to MM.

Figure. Median PFS and OS



B03 CARFILZOMIB AND LENALIDOMIDE FOR PRIMARY PLASMA CELL LEUKEMIA: FINAL RESULTS OF THE PROSPECTIVE PHASE 2 EMN12/HOVON-129 STUDY FOR PATIENTS AGED ≥66 YEARS

Musto P.[1]; Minnema M.C.[2]; Roeloffzen W.W.H.[3]; Capra A.[4]; van der Holt B.[5]; Juul Vangsted A.[6]; Broyl A.[7]; Schjesvold F.[8]; Lund T.[9]; Silkjaer T.[10]; Benjamin R.[11]; Grasso M.[12]; Lung Wu K.[13]; Caers J.[14]; Cavo M.[15]; Hájek R.[16]; Bruno B.[17]; Gadisseur A.[18]; Pietrantuono G.[19]; Offidani M.[20]; Pour L.[21]; Sonneveld P.[22]; Boccadoro M.[4]; van de Donk N.[23]

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Introduction: Primary plasma cell leukemia (pPCL) is a rare and aggressive plasma cell disorder with poor prognosis. The EMN12/ HOVON-129 study assessed carfilzomib and lenalidomide as first-line therapy in pPCL. Pts ≥18 years were enrolled, with different treatment for those 18-65 and ≥66 years. Here we report the results for pts ≥66 years.

Methods: Inclusion criteria were newly diagnosed pPCL (>2x10^9/L circulating monoclonal plasma cells and/or plasmacytosis >20% of the differential white cell count) and WHO performance status 0-3. Main exclusion criteria were severe cardiac or pulmonary dysfunction and creatinine clearance <15 ml/min. There were no restrictions based on blood counts.

Pts ≥66 years received eight 28-day induction cycles of carfilzomib-lenalidomide-dexamethasone (KRd; K: 20/36 mg/m^2 days 1,2,8,9,15,16; R: 25 mg days 1-21; d: 20 mg days 1,2,8,9,15,16,22,23), followed by maintenance with KR (K: 27 mg/m^2 days 1,2,15,16 for the first 12 cycles; then 56 mg/m2 days 1,15; R: 10 mg days 1-21/28 days) until progression.

The primary endpoint was progression-free survival (PFS); secondary endpoints were response rate, overall survival (OS), and toxicity.

Results: From Oct 2015 to Aug 2021, we enrolled 61 pts with pPCL: 36 were ≤65 years and 25 ≥66 years. Among pts ≥66 years, median age was 71 years (range 66-84); 68% had bone disease; WHO performance status was 2 in 24% and 3 in 16% of pts. Median plasma cell percentage in bone marrow biopsy was 80% (10-100). Median peripheral blood plasma cell count was 3.8x10^9/L (range 2.0-52); median platelet count was 142x10^9/L (range 13-384); median GFR was 56 ml/min (range 24-95). Most of pts had high-risk disease features: 52% had elevated LDH; 20% del(17p), 4% t(4;14), 4% t(14;16), and 48% gain/amp(1q); 12% of pts had extramedullary plasmacytomas; 68% had ISS III and 40% Revised ISS III.

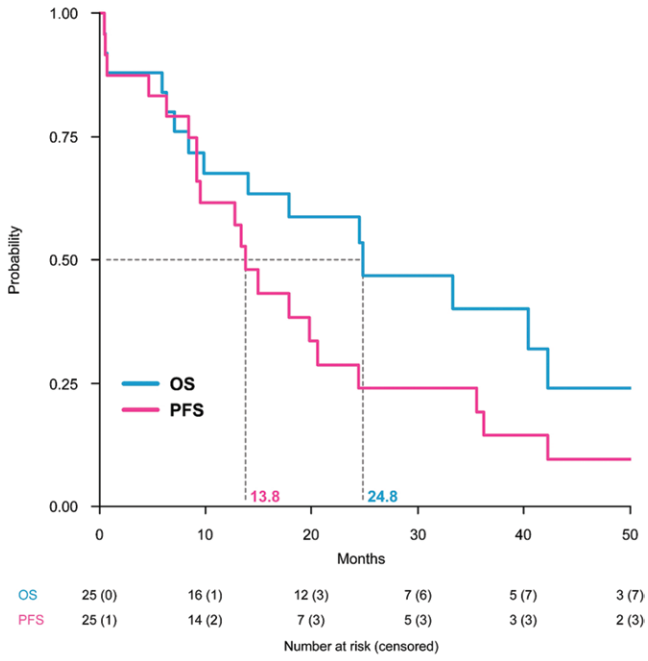
At the data cut-off (July 1, 2022), among the 25 pts, 17 (68%) received the planned 8 cycles of induction treatment, achieving ≥ PR in 80%, ≥VGPR in 68%, and ≥CR in 32%; 16 pts (64%) received maintenance treatment. Best response on protocol was ≥PR in 80%, ≥VGPR in 68% and ≥CR in 36%; 3 out of 4 pts in CR who could be evaluated for minimal residual disease (MRD) achieved MRD negativity (10^{-5}) by flow cytometry.

With a median follow-up of 24.6 months (range 7.9-59.6), median PFS was 13.8 months (95% CI 9.2-35.5); median OS was 24.8 months (95% CI 14-NR - 16 deaths: 8 disease progression, 2 unknown, 1 pneumonia, 1 sepsis, 1 systemic aspergillus infection, 1 small intestinal SPM, 1 disseminated intravascular coagulation, 1 respiratory failure due to COPD exacerbation).

Toxicity rate was 36% both for G3 and for G4 events. G3 and G4 hematologic toxicity rates were 8% and 12%. Infections (20% and 16%) and respiratory events (16% and 4%) were the most common G3 and G4 non-hematologic toxicities. Twenty-two pts (88%) discontinued treatment, mainly because of progression (13 pts, 59%).

Conclusions: KRd is a potent strategy to control pPCL in pts ≥66, with not negligible, but generally manageable, treatment-related toxicities. Besides a significant PFS improvement, median OS substantially doubled compared to what has been reported in recent retrospective studies (see the only other prospective trial with Rd) in transplant ineligible, elderly pts with pPCL (Musto P et al. Leukemia. 2014).

Figure. Overall survival and progression-free survival



Abbreviations. OS, overall survival; PFS, progression-free survival.

B04 IMPLEMENTING M-PROTEIN DIAGNOSTICS IN MULTIPLE MYELOMA PATIENTS USING ULTRA-SENSITIVE TARGETED MASS SPECTROMETRY DATA AND AN OFF-THE-SHELF CALIBRATOR

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Introduction: Minimal residual disease (MRD) detection in Multiple Myeloma (MM) patients currently relies on bone marrow samples. These tests provide important information, but are invasive and not suitable for frequent monitoring. However, current blood-based diagnostics, lack the sensitivity to detect MRD. Our group has published a targeted mass spectrometry-based MRD blood-test (MS-MRD) that detects clonotypic peptides originating from the variable region of the M-protein. This assay provides a patient-specific test solution that is more sensitive compared to currently used M-protein detection methods. For quantification of the M-protein Stable Isotope Labeled (SIL) peptides are synthesized. SIL peptides are heavy labeled, synthetic copies of the clonotypic peptide and currently the gold standard for MS-MRD quantification as these standards offer the best possible reference for clonotypic peptides. However, SIL peptides are patient specific and require the synthesis of new peptides for each new patient. To this end, an alternative, generic quantification method was explored using a heavy labeled monoclonal antibody (SILuMAB).
Methods: In the new MS-MRD assay, both SILuMAB and clonotypic peptides were targeted. M-protein concentrations were determined by calibration on a sample with a known M-protein concentration quantified by SPE. The resulting M-protein concentration for each clonotypic peptide within a sample was averaged. Validation of MS-MRD using the off-the-shelf SILuMAB calibrator was performed using serum samples from patients participating in the IFM2009 trial.
Results: Sensitivity and dynamic range of the SILuMAB-based MS-MRD assay was determined in two separate dilution series of two patient sera, serially diluted in control serum. We observed a linear signal until respectively 0.003 g/L (R2=0.994) and 0.001 g/L (R2= 0.995), indicating that the lower limit of quantification for SILuMAB-based MS-MRD is approximately between 0.003 g/L and 0.001 g/L. Overall, we observed a 1000-fold improved sensitivity for MS-MRD compared to SPE.
Generating reproducible results is indispensable for quantitative clinical tests used for disease monitoring. To this end we have assessed the intra-assay variation, the inter-assay variation and the variation between laboratories. For both intra- and inter-assay variation, all observed CVs were below 20%, indicating a stable instrumental setup and sample preparation protocol. The variation between laboratories was tested by preparing and acquiring 16 longitudinal patient series (320 samples in total) by two different laboratories using different LC-MS/MS platforms. All M-protein concentrations were quantified using SILuMAB and results show an R^2 of 0.9087 and a slope of 1.03. Combined data from the reproducibility experiments indicate great robustness of the SILuMAB-based MS-MRD assay. Concordance between SILuMAB quantified data and SIL quantified data was assessed by preparing all available longitudinal samples from 3 patients with both SILuMAB and SIL. This experiment was performed by both the Radboudumc and Erasmus MC. Both sites reported R^2s of >0.99 were, indicating great concordance between both SILuMAB and SIL quantified MS-MRD.
Conclusion: MS-MRD was simplified by using an off-the-shelf calibrator. This reduces time and money spent on synthesis of personalized SIL and will allow robust M-protein quantification and leads to improved harmonization of MS-MRD analysis in the clinic.

B05 PLASMA CELL LEUKEMIA-LIKE STATUS HAS INDEPENDENT PROGNOSTIC VALUE IN THE CONTEXT OF THE SECOND REVISION OF THE INTERNATIONAL STAGING SYSTEM

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Introduction: Even though the majority of newly diagnosed multiple myeloma (NDMM) patients has benefited significantly from the introduction of novel agents, it remains an unmet need to identify the best upfront treatment strategy for high-risk disease. Risk-adapted trial designs (e.g., the OPTIMUM/MUKnine trial, NCT03188172, and the GMMG-CONCEPT trial, NCT03104842) aim to answer this question, which in turn drive research efforts to improve risk assessment in NDMM.
Recently, our group has published two novel prognostic tools for NDMM:
(I) The Second Revision of the International Staging System (R2-ISS), which identifies four different risk categories by combining conventional prognostic markers (*D'Agostino et al. – J Clin Oncol 2022*).
(II) Plasma Cell Leukemia-like (PCL-like) status, which identifies high-risk disease by combining tumor transcriptomic data of 54 genes reflecting high levels of circulating tumor cells (*Hofste op Bruinink et al. – J Clin Oncol 2022*).
Since both tools may detect different types of aggressive disease, we hypothesized that combining PCL-like status with the R2-ISS classification would improve prognostic accuracy in NDMM.
Methods: Baseline characteristics including serum markers and high-risk cytogenetic aberrations were collected from NDMM patients enrolled in the HOVON-65/GMMG-HD4 (EudraCT 2004-000944-26), HOVON-87/NMSG-18 (EudraCT 2007-004007-34), EMN02/HO95 (EudraCT 2009-017903-28) and MMRF CoMMpass studies (NCT01454297) and used to determine the R2-ISS classification. PCL-like status was calculated from transcriptomic profiles of CD138-enriched bone marrow tumor cells. Hazard ratios (HRs) for PCL-like status, R2-ISS classification or a combination thereof were estimated using a Cox proportional hazards model stratified by study cohort and corrected for age ≤ 65 years.
Results: For 865 NDMM patients of known age, both the R2-ISS classification and PCL-like status could be determined, with a median follow-up time of 55 months. 18% were classified as R2-ISS low (R2-ISS I), 30% as R2-ISS low-intermediate (R2-ISS II), 43% as R2-ISS intermediate-high (R2-ISS III) and 9% as R2-ISS high (R2-ISS IV); 10% as PCL-like MM and 90% as intramedullary MM (i-MM).
In univariate analyses, PCL-like status was associated with both an inferior PFS (HR, 1.8; 95% confidence interval (CI), 1.4 to 2.3; $P < 0.0001$) and OS (HR, 2.4; 95% CI, 1.8 to 3.3; $P < 0.0001$). This also applied to the R2-ISS classification when comparing R2-ISS IV to R2-ISS I, II and III (HR for PFS, 2.0; 95% CI, 1.5 to 2.6; $P < 0.0001$ and HR for OS, 3.0; 95% CI, 2.2 to 4.2; $P < 0.0001$). PCL-like status retained its prognostic significance in a multivariate model when combined with the R2-ISS classification, both in terms of PFS (HR, 1.6; 95% CI, 1.2 to 2.1; $P = 0.0004$) and OS (HR, 2.1; 95% CI, 1.6 to 2.9; $P < 0.0001$). Of note, 2% of patients classified both as PCL-like MM and R2-ISS IV, translating into a median PFS of 12 months and a median OS of 15 months. Patients with PCL-like MM and R2-ISS III (5%) had a comparable median OS to those with i-MM and R2-ISS IV (7%) (47 and 38 months, respectively). Validation is planned in other European Myeloma Network trial cohorts.
Conclusions: 1. PCL-like status combined with the R2-ISS classification improves prognostic accuracy in NDMM.
2. The presence of both PCL-like MM and R2-ISS IV may confer exceptionally high risk.
3. Patients with PCL-like MM and R2-ISS III have a comparable OS to those with i-MM and R2-ISS IV.

B06 HIGH LEVELS OF CIRCULATING PLASMA CELLS AT DIAGNOSIS ARE PREDICTIVE FOR WORSE PROGNOSIS IN BOTH TRANSPLANT-ELIGIBLE AND -INELIGIBLE PATIENTS WITH MULTIPLE MYELOMA

Malandrakis P.[1]; Ntanasis-Stathopoulos I.[1]; Kostopoulos I.V.[2]; Roussakis P.[2]; Eleutherakis-Papaiakovou E.[1]; Panteli C.[2]; Angelis N.[2]; Spiliopoulou V.[1]; Orologas-Stavrou N.[2]; Theodorakakou F.[1]; Fotiou D.[1]; Migkou M.[1]; Gavriatopoulou M.[1]; Kastritis E.[1]; Tsitsilonis O.E.[2]; Dimopoulos M.A.[1]; Terpos E.[1]

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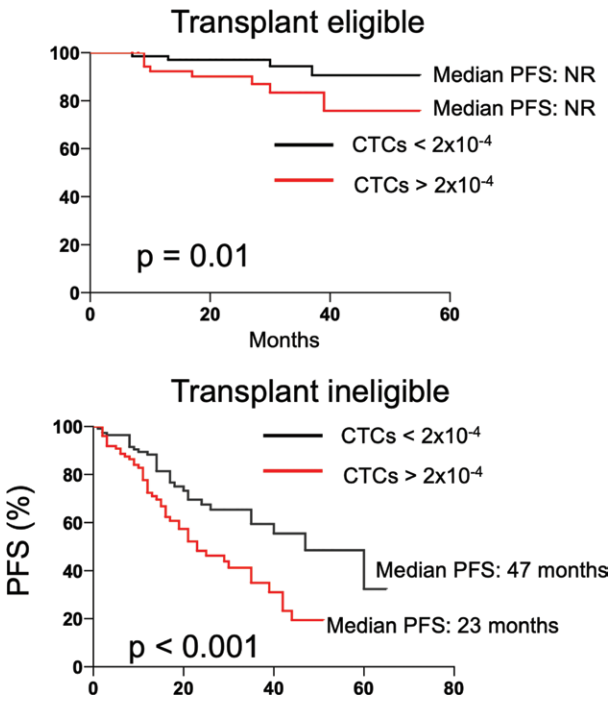
The presence of circulating tumor cells (CTCs) has long been suggested as a valuable prognostic biomarker in Multiple Myeloma (MM). Quantification of plasma cells (PCs) continues to be performed in BM since the clinical translation of circulating tumor cells (CTCs) remains challenging because of their low frequency in PB. However, evaluation of PCs in peripheral blood (PB) may outperform quantification of BM PCs. Early studies using standard flow cytometry showed that elevated numbers of CTCs predicted inferior survival. The detection of ≥0.01% CTCs could be a new risk factor in novel staging systems for patients with transplant-eligible MM.

The aim of the study was to define the clinical significance of CTCs and optimal cutoffs using NGF cytometry, in a large series of patients with newly diagnosed MM in a single center. At diagnosis, assessment of CTCs in PB and in BM aspirates collected in EDTA was performed using the EuroFlow NGF methodology for surface membrane and cytoplasmic staining after bulk lysis.

Overall, 525 patients with newly diagnosed MM were included in this study (patients with primary plasma cell leukemia were excluded). Out of these patients, 193 were transplant eligible (36.7%) and 332 were transplant ineligible (63.2%). The median follow-up for all the pts was 42 months (range:3-66 months). CTCs were detected in 468/525 samples (89.1%) and the median CTC value was 0.014%. CTCs did not correlate with the type of response to induction therapy, but their levels were associated CTCs≥2x10-4 at baseline were associated with reduced median PFS (39 vs 60 months). Transplant eligible patients with CTCs≥2x10-4 had inferior PFS compared to patients with CTCs<2x10-4 (p=0.01). Transplant-ineligible patients with CTCs≥2x10-4 had a worse PFS compared to those with CTCs<2x10-4 (median PFS= 47 vs 23 months, p<0.001). Moreover, high CTCs levels ≥2x10-4 may identify patients with adverse prognosis within each ISS stage (median PFS 60 months vs not reached for ISS 1 p=0.1, p=0.01 for ISS 2, 39 months vs 17 months for ISS 3, p=0.04).

Our large number of matched samples allowed for a phenotypic comparison between BM clonal cells and CTCs. The majority of patients with detectable CTCs (86%) showed a matched phenotypic profile of aberrant plasma cell in the two sites. However, 66 patients showed phenotypic discrepancies based on one of the following patterns: i) all phenotypic subsets were present in both BM and PB but with significantly altered ratios (≥20% of relative prevalence) for at least two concomitant subsets; ii) presence of ≥ 1 phenotypic subsets (with a minimum relative prevalence of 20% of all clonal cells) only in the BM; and iii) presence of ≥1 phenotypic subsets only in the PB. Remarkably, patients with phenotypic discrepancies had significantly higher CTC levels than those with a phenotypic agreement on the two sites (P<0.001), together with signs of a more diffuse disease pattern on imaging.

The detection of CTCs is possible in 90% of NDMM patients; CTCs levels equal to or more than 0.02% is an adverse prognostic factor in patients who are treated outside of clinical trials, irrespective of their transplant status. Since the liquid biopsy is a better representative of the entire tumor load than a tissue biopsy sample, the analysis of CTCs may serve as the new hallmark for the real-time evaluation of a patient's disease and immune status.



B07 HIGH EXPRESSION OF NUCLEAR CEREBLON IS ASSOCIATED WITH LONGER SURVIVAL IN PATIENTS WITH MULTIPLE MYELOMA TREATED WITH IMIDS

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Patients with multiple myeloma (MM) demonstrate variable outcomes with treatment. With increasing treatment options, predictive factors for response and outcome are relevant to inform treatment choices. Immunomodulating agents (IMiDs) represent the cornerstone of MM treatment and act through binding to Cereblon (CRBN), affecting downstream targets of this E3 ubiquitin ligase. We hypothesized differential expression of effector or target proteins from the CRBN pathway to predict outcome in patients treated with IMiDs. Bone marrow (BM) biopsies were obtained from 148 newly diagnosed, transplant non-eligible patients with MM. Per HOVON-87/NMSG-18 trial protocol, these patients were treated with thalidomide or lenalidomide combined with melphalan and prednisone followed by thalidomide/lenalidomide maintenance (i.e. MPT-T or MPR-R). Immunohistochemistry was performed for CRBN, its neosubstrates Ikaros and Aiolos and the downstream targets interferon regulatory factor 4 (IRF-4) and cellular myelocytomatosis oncogene (c-MYC). Patients with response of VGPR or better have higher nuclear CRBN expression compared to patients with PR or worse (≥VGPR: median CRBN H-score=185 (interquartile range (IQR), 147-211) vs ≤PR median CRBN H-score=159 (IQR 129-193); p=0.02). Higher nuclear CRBN expression was associated with a longer progression-free survival (PFS) and overall survival (OS). For PFS a hazard ratio (HR) of 0.53 was found (95% confidence interval (CI) =0.37-0.77; p<0.001); for OS: HR = 0.59 (95% CI=0.38-0.90; p=0.02). The association between CRBN and OS varied with IRF-4 levels. In patients with IRF-4 levels above the median, a hazard ratio of 0.22 was found (95% CI=0.10-0.49; p=0.0002); in contrast, patients with IRF-4 levels below the median, had a hazard ratio of 0.82 (95% CI=0.44-1.53; p=0.5). For Ikaros, Aiolos and c-MYC no correlation with survival was found, either alone or in combination with CRBN. In conclusion, higher expression of nuclear CRBN was associated with a superior PFS and OS upon MPT or MPR treatment. Levels of nuclear CRBN protein, possibly in combination with IRF-4, may represent a biomarker for predicting treatment outcome in patients treated with IMiDs.

B08 IDECABTAGENE VICLEUCEL VERSUS STANDARD REGIMENS IN PATIENTS WITH TRIPLE-CLASS–EXPOSED RELAPSED AND REFRACTORY MULTIPLE MYELOMA: KARMMA-3 A PHASE 3 RANDOMIZED CONTROLLED TRIAL

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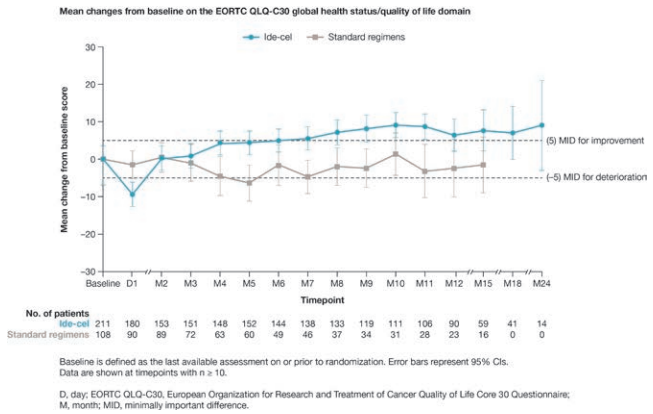
Background: Survival outcomes are poor in patients with relapsed and refractory multiple myeloma (RRMM) who are triple-class–exposed (TCE) to immunomodulatory (IMiD®) agents, proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies. As patients become TCE in earlier lines of therapy, treatment options are limited. Idecabtagene vicleucel (ide-cel) demonstrated deep durable responses in heavily pretreated TCE RRMM.
Methods: KarMMa-3 (NCT03651128), an international, open-label, randomized controlled trial, enrolled patients with RRMM who received 2–4 prior regimens, including an IMiD agent, PI, and daratumumab, and refractory to the last regimen. Patients were randomized 2:1 to ide-cel or a standard regimen (investigator choice of daratumumab + pomalidomide + dexamethasone, daratumumab + bortezomib + dexamethasone, ixazomib + lenalidomide + dexamethasone, carfilzomib + dexamethasone, or elotuzumab + pomalidomide + dexamethasone based on prior regimen). Ide-cel was infused at a target dose of 150–450×10^6 chimeric antigen receptor-positive (CAR+) T cells (≤540×10^6 cells allowed). Primary endpoint: progression-free survival (PFS) assessed by Independent Response Committee (IRC). Key secondary endpoints: IRC-assessed overall response rate (ORR) and overall survival. Other secondary endpoints: duration of response (DOR), health-related quality of life (QoL), pharmacokinetics, and safety. Efficacy assessed per ITT.
Results: Of 386 patients (ide-cel n=254, standard regimens n=132), 225 received ide-cel (median dose 445×10^6 CAR+ T cells [range 175–529×10^6]) and 126 received standard regimens. Baseline characteristics, including median age (63 years), median time since diagnosis (4.1 years), median prior therapies (n=3), triple-class (66%) and daratumumab (95%) refractoriness, and high-risk cytogenetics (44%), were generally balanced. Median follow-up from randomization to data cutoff was 18.6 months. Ide-cel significantly improved PFS versus standard regimens (median 13.3 vs 4.4 months, HR 0.49, *P*<0.0001). Ide-cel significantly improved ORR versus standard regimens (71% vs 42%, *P*<0.0001), with deeper (complete response 39% vs 5%), more durable responses (median DOR 14.8 vs 9.7 months). PFS and ORR benefit of ide-cel was consistent across multiple patient subgroups. Post–ide-cel infusion, CAR+ T cells underwent rapid multi-log expansion (median 11 days to maximum expansion). In the treated population, grade 3/4 adverse events (AEs) occurred in 93% and 75% of patients in the ide-cel and standard regimen arms, respectively, and grade 5 AEs in 14% and 6%; grade 5 treatment-related AEs in 3% and 1%. In ide-cel-treated patients any grade cytokine release syndrome occurred in 88%; grade 3/4 in 4%. Any grade investigator-identified neurotoxicity occurred in 15% of patients; grade 3/4 in 3%. Ide-cel demonstrated clinically meaningful improvements on patient-reported outcomes, including symptoms, functioning, and QoL versus standard regimens (**Figure**).
Conclusions: Ide-cel treatment resulted in a significant improvement in PFS and ORR, with deeper and more durable responses versus standard regimens. Ide-cel benefit was consistent across difficult-to-treat subgroups. The toxicity profile of ide-cel was consistent with prior studies. These results support the use of ide-cel in patients with early relapse TCE RRMM, a population with poor survival outcomes.
This abstract is an encore previously submitted at ASTCT 2023.



Baseline is defined as the last available assessment on or prior to randomization. Error bars represent 95% CIs. Data are shown at timepoints with n ≥ 10.

D, day; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; M, month; MID, minimally important difference.

B09 CARTITUDE-2 COHORT B 18-MONTH FOLLOW-UP: CILTACABTAGENE AUTOLEUCEL (CILTA-CEL), A BCMA-DIRECTED CAR-T CELL THERAPY, IN PATIENTS WITH MULTIPLE MYELOMA (MM) AND EARLY RELAPSE AFTER INITIAL THERAPY

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Introduction: Cohort B of the multicohort phase 2 CARTITUDE-2 (NCT04133636) study is evaluating cilta-cel in patients with multiple myeloma (MM) and early relapse (≤12 months after autologous stem cell transplant [ASCT] or ≤12 months after start of initial treatment with anti-myeloma therapy). This patient population has functionally high-risk disease and represents an unmet medical need, as progression within 1 year of starting initial therapy is a poor prognostic factor, with overall survival <2 years in these patients. Here we present updated clinical results and cytokine analyses.
Methods: Patients with MM, 1 prior line of therapy (proteasome inhibitor and immunomodulatory drug required), early disease progression (≤12 months after ASCT or ≤12 months after start of anti-myeloma therapy for patients who did not undergo ASCT), and treatment-naive to CAR-T/anti-B-cell maturation antigen (BCMA) therapies were eligible. Bridging therapy was permitted between apheresis and CAR-T cell infusion. A single cilta-cel infusion (target dose 0.75×10^6 CAR+ viable T cells/kg) was administered post lymphodepletion. Safety and efficacy were evaluated. Primary endpoint was minimal residual disease (MRD) negativity by next generation sequencing at 10^{-5}. Management strategies were used to reduce risk of movement/neurocognitive treatment-emergent adverse events (MNTs)/parkinsonism. Pharmacokinetics, CAR-T cell phenotype, and cytokine profiles are also being evaluated.
Results: As of June 1, 2022, 19 patients received cilta-cel (median age 58 years [range 44–67]; 74% male; 16% high-risk cytogenetics, 63.2% standard risk, 21.1% unknown) and 16 remained on study. Median follow-up was 17.8 months (range 5.2–26.3). 79% of patients had prior ASCT. Overall response rate was 100% (100% very good partial response or better; 90% complete response or better) (Figure). Median time to first response was 0.95 months (range 0.9–9.7); median time to best response was 5.1 months (range 0.9–11.8). Of 15 MRD-evaluable patients, 14 (93%) achieved MRD 10^{-5} negativity during the study. Median duration of response was not reached. 12-month event-free rate was 84%; 12-month progression-free survival (PFS) rate was 90%. Most common treatment-emergent AEs (TEAEs) were hematologic (grade 3/4: neutropenia, 90%; lymphopenia, 42%; thrombocytopenia, 26%; leukopenia, 26%). Cytokine release syndrome (CRS) occurred in 16 (84.2%) patients (grade 4, n=1). Median time from cilta-cel infusion to onset of CRS was 8 days (range 5–11); CRS resolved in all patients. Immune effector cell-associated neurotoxicity syndrome (grade 1) occurred in 1 patient. Movement and neurocognitive TEAEs/parkinsonism (grade 3) occurred in 1 patient (previously reported). 3 patients died post cilta-cel at days 158, 417, and 451 due to progressive disease. Interleukin (IL)-6, interferon gamma, IL-2Rα, and IL-10 levels increased after infusion, peaking at days 7–14 and coincident with the timing of CRS, and returning to baseline levels within 2–3 months after infusion.
Conclusions: In this functionally high-risk patient population (all of whom relapsed within a year of receiving standard of care upfront therapy, including ASCT [79%]), 90% remained progression-free at 1 year after cilta-cel treatment. At this longer follow-up of 18 months, results show durability and deepening of response to cilta-cel and maintenance of PFS rate, representing a potentially significant advancement in a population with high unmet need.

POSTER

1. Biology and preclinical

P01 LACTATE TRAFFICKING INHIBITION RESTORES SENSITIVITY TO PROTEASOME INHIBITHORS AND ORCHESTRATES IMMUNOMICROENVIRONMENT IN MULTIPLE MYELOMA

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Even though the advantages in therapeutic strategies, multiple myeloma (MM) remains an incurable disease as patients eventually develop relapsed or refractory MM. Metabolic changes of malignant plasma cells (PCs) and adaptation to tumor microenvironment represent determinant players in tumor cell growth, adaptation and resistance to anti-cancer therapy. Metabolic features of tumor PCs are typical of the Warburg effect with increased lactate production, but at the same time, MM cells can use the reverse Warburg effect taking up lactate from tumor microenvironment by using monocarboxylate transporter 1 (MCT1). We previously showed that MM mesenchymal stromal cells are more glycolytic and produce more lactate than healthy counterpart. Hence, we aimed to explore the effect of lactate on PCs and tumor microenvironment.
Lactate concentration resulted increased in MM patient's sera compared to healthy donors. Exposing MM cells to high levels of lactate resulted in a significant increase of MCT1, MCT4 and the lactate receptor GPR81. Interestingly, we also found a significant reduction of the apoptotic effect of proteosome inhibitors (PIs). Given that the uptake of lactate by myeloma PCs decreased anti-myeloma efficacy of PIs, we next investigated whether MCT1 is differentially expressed in primary CD138+ cells from MM at diagnosis and resistant/refractory patients. Analyzing BM biopsy specimens by using immunofluorescence, we found a higher colocalization of MCT1 within CD138+ PCs in resistant/refractory MM compared to patients at diagnosis. To elucidate whether the protective effect of lactate was mediated by metabolic activity of lactate or through the activation of GPR81 signaling, PCs were cultured in medium supplemented with 20% sera from different MM patients and treated with PIs alone or in combination with AZD3965, a selective inhibitor of MCT1, or 3-OBA, an antagonist of GPR81. Only combination with AZD3965 increased PI-induced apoptosis. These findings led us to examine metabolic effects of lactate in PCs. A significant increase of oxidative phosphorylation-related genes and mitochondrial ROS were observed after exposure to high lactate concentration. The lactate-induced oxidative metabolism was then confirmed by the higher basal respiration and mitochondrial ATP production found in PCs after exposure to lactate. However, growing MM cells for 3 days in medium supplemented with lactate resulted in a gradual decrease in cell growth. Also the oxygen consumption (OCR) and extracellular acidification rate (ECAR) were reduced, but the OCR/ECAR ratio was increased in respect of control, suggesting a higher contribution of mitochondrial respiration versus glycolysis to energy generation. This metabolic switch, resulting from chronic exposure to lactate, is essential to limiting the anti-myeloma effect of PIs. Finally, we explored the effects of lactate in promoting immune escape mechanisms in myeloma microenvironment. Lactate exposure increased of the amount of myeloid derived suppressor cells and Treg percentages. A significant reduction of both subtypes was found after blocking MCT1 by AZD3965. These data were confirmed using MM sera and blocking circulating lactate by AZD3965.
Overall, these findings showed that targeting lactate trafficking in TME inhibits metabolic rewiring of tumor PCs and lactate-dependent immune evasion and thus improving therapy efficacy.

P02 ARGININE DEPRIVATION INDUCES ACQUISITION OF A SENESCENT PHENOTYPE AND FAVORS GENOMIC INSTABILITY IN MULTIPLE MYELOMA PLASMACELLS

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Multiple myeloma (MM) originates from a neoplastic clone of plasma cells which establish vicious interactions with the multicellular microenvironment, including myeloid derived suppressor cells that produce arginase leading to arginine (arg) deprivation.
Our previous work showed that in vivo the treatment with arginase inhibitor could reduce MM growth while increasing serum arg concentrations independently from the infiltrates of myeloid cells. Thus, we aimed to investigate how arg deprivation can contribute to MM progression.
We combined gene expression profiling with coupled metabolomic analysis performed by high performance liquid chromatography (HPLC), in three human myeloma cell lines (HMCLs, U266, NCI-H929 and OPM2). Cells were cultured for short (24h - 48h) and long term (10 days) in media with 50ug/ml of Arg (R low medium), which correspond to the concentration found in MM bone marrow, which is generally lower than in healthy and MGUS subjects, supplemented with 10% dialyzed fetal bovine serum. Progressive arg deprivation did not affect cell viability in vitro, but it was associated to proliferation slowing down and cell cycle arrest in G0-G1 phase, associated to reduced mitochondrial activity and a low-energy metabolic state, as detected by SeaHorse analysis.
Differently from other cell lines, in H929 autophagy induction and the engagement of uncharged t-RNA tyrosin kinase GCN2 lacked, due to unchanged amount of available intracellular arg, as detected by HPLC. Conversely, H929 upregulated the expression of the arginine-succinate synthase (ASS1) enzyme, which catalyzes the conversion of nitrogen from ammonia and aspartate from glutamine to form argininosuccinate, a metabolite required to synthesis of urea, nitric oxide synthesis, polyamine, creatine synthesis, and the de novo synthesis of arginine. We used multiplex immune fluorescence immunohistochemical analysis to evaluate ASS1 in trephine BM biopsies from patients with MM (n=25), MGUS (n=10) and SMM (n=10). MM but not MGUS biopsies showed a multifocal pattern of ASS1 positivity, with dense clusters of tumor cells observed in MM but not MGUS biopsies.
Combined flow cytometry and immunofluorescence microscopy analysis showed that γH2AX, a marker for DNA double-strand breaks, was increased and appeared as punctate spots in the cell nucleus and enriched in leaked DNAs, associated with genomic instability as showed by the increase of micronuclei percentage. Consistently, we also found the reduction of the Histone H3 lysine K4 (H3K4) and the increase of histone variant macro H2A1, recruited to DNA double-strand breaks to promote gene silencing and hampering DNA-repair mechanisms, as shown by a significant down-regulation of Fanconi Anemia (FA) pathway members BRCA2 and FANCI, master regulators of efficient replication DNA fork damage recovery. The acquisition of senescence-associated secretory phenotype was confirmed by the overexpression of of NLRP3, pro-Caspase 1, Caspase 1, interleukin-18 (IL-18) and cleaved IL-1□ as detected by WB analysis, associated to chromatin remodeling.
Taken together, our findings suggest that arginine deprivation, while inducing immune dysfunction, conveys a complex adaptive response which causes a chromatin remodeling that leads to the acquisition of a senescence phenotype to select the most fit clone and favors genomic instability, providing new insights to improve immunotherapy and induce synthetic lethality in MM.

P03 COMBINING SKY92 GENE EXPRESSION PROFILING AND IGH CLONALITY TO EVALUATE GENETIC RISK IN IRISH MULTIPLE MYELOMA PATIENTS

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Multiple myeloma (MM) is an incurable malignancy characterised by clonal proliferation of malignant plasma cells in bone marrow (BM). Currently, there are a lack of standardised approaches to determine patient prognosis and response to therapy.

The MMProfiler is a prognostic test based on the well validated SKY92 gene signature which can accurately identify high-risk (HR) patients at diagnosis with survival of less than 2 years. The achievement of minimal residual disease (MRD) negativity after therapy is considered a key goal of treatment. Recent evidence indicates that achievement of MRD negativity may improve the PFS of MM patients with HR cytogenetics but data supporting this in SKY92-defined HR are lacking. NGS approaches have aimed to standardise MRD testing by monitoring clonal, disease-driving IGH rearrangements. Through an ongoing national study, for the first time in Ireland we are combining two genomic approaches with the aim of improving baseline genetic risk-stratification as well as subsequent assessment of response to treatment based on MRD. Ultimately, we aim to determine how SKY92 risk impacts the ability to achieve MRD negativity in transplant eligible (TE) patients.

Diagnostic and follow-up BM samples were provided from TE MM patients across Ireland. Both a mononuclear cell (MNC) fraction and CD138+ fraction were isolated using SepMate tubes and the EasySep CD138+ selection kit respectively. Briefly, RNA from CD138+ plasma cells at diagnosis was used for SKY92 classification using MMProfiler (Affymetrix arrays). Invivoscribe LymphoTrack PCR-based IGH-FR1 assay and sequencing using the Illumina MiSeq platform were used to identify clonal DNA rearrangements at diagnosis. Clonality is defined as ≥2.5% of the total reads of that sample and greater than two times the third-ranked top sequence. This clonal sequence identified will be used for MRD monitoring using DNA from MNCs post-ASCT.

Preliminary results show that 11/33 (33.3%) patients were classified as SKY92 HR. In addition, t(4;14) was detected in 27.2% patients, t(11;14) in 12.1%, t(14;16)/t(14;20) in 6.1% and gain(1q) in 45.5%. There was an association between SKY92 HR signature and t(4;14) (63% HR vs 9.1% SR, p<0.01), and a higher proportion also had gain(1q) (63.6% HR vs 36.4% SR). Both t(4;14) and gain(1q) are often considered as independent HR markers. Interestingly, the prevalence of SR cytogenetic marker t(11;14) was similar (9.1% HR vs 13.6% SR).

LymphoTrack IGH-FR1 assay detected clonality in 16/19 patients (84.2%). Remaining patients will be sequenced using additional LymphoTrack IGH assays until a clonal sequence is determined. At follow-up, we will determine if these clonal sequences remain present post-ASCT using the appropriate targeted assay. Optimisation of DNA input and sequencing depth will define the sensitivity of MRD negativity.

We successfully identified clonal IGH rearrangements in the majority of newly diagnosed MM patients, and expect this to reach >95% in combination with additional IGH-targeting assays. These clonal sequences will be used to monitor MRD. A significant proportion of MM patients in Ireland present with HR disease as defined by both SKY92 and cytogenetic profile. Future work will aim to evaluate the achievement of MRD negativity based on SKY92 status, and whether this impacts survival. We will continue to profile Irish patients and ultimately, we hope this could lead to a more risk-stratified treatment approach.

P04 MULTIPARAMETRIC FLOW CYTOMETRY REFINES RISK STRATIFICATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

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The European Myeloma Network has underlined the clinical utility of multiparametric flow-cytometry (MFC) analysis in the work-up and follow-up of multiple myeloma (MM) patients. The prerequisite of MFC in MM is to discriminate within the whole PC compartment between normal and aberrant clonal PCs.

Clonal PCs show a heterogeneous expression of CD19, CD45lo and CD56–/lo, together with high amounts of CD38, CD138 and cVS38. Their identification is favored by the concomitant expression of other surface antigens, such as CD28, CD20, CD33, CD13, CD117, CD56. The definition of clonal PCs is established due to the variable association of these antigens together with cytoplasmic immunoglobulin k or λ chain staining. Between 2018 and 2022, we prospectively analyzed by flow cytometry BM samples from 84 consecutive newly diagnosed MM patients managed at the Hematology Center of the Sapienza University of Rome to assess the immunophenotypic characteristics of clonal PCs and to investigate the possible correlation between the aberrant phenotype, the clinical characteristics of the disease and cytogenetic abnormalities

Table 1a

Patient's baseline characteristics

	N=84 (%)
Median age, years (range)	61.3 (27.9 – 88.2)
<65/≥65	54/30
Gender	
Male, n(%)	52 (62)
Female, n(%)	32 (38)
Type of MM	
Classic	76 (91)
Micromolecular	6 (7)
Non secreting	2 (2)
Type of heavy chain	
G	51 (61)
Non G	32 (38)
No monoclonal component	1 (1)
Type of light chain	
k	60 (69)
λ	22 (26)
k + λ	2 (2)
NA*	2 (2)
CRAB	
Ca^{++} ≥12 mg/dl	5 (6)
Cr >2 mg/dl	7 (8)
Hb <10 g/dl	27 (32)
Osteolytic bone lesions	69 (82)
Bone marrow plasma cells infiltration, median % (range)	30 (10-90)
ISS, n (%)	
I	32 (38)
II	20 (24)
III	26 (31)
NA	8 (9)
High-risk FISH cytogenetics, n (%)	
No	67 (85)
Yes	12 (15)
NA	5 (6)
High-risk FISH cytogenetics ± ampl/gain1q, n (%)	
No	45 (57)
Yes	34 (43)
NA	5 (6)
R-ISS, n (%)	
I	22 (26)
II	39 (46)
III	16 (19)
NA	13 (15)
ASCT eligible	
Yes, n (%)	71 (85)
No, n(%)	13 (15)
Overall response rate (ORR)	70 (85)

*NA: not available

Table 1b

Patient's baseline induction therapy

Transplant eligible patients	N=71 (84%)
Induction therapy	
VTd	59 (90)
D-VRd	3 (5)
VRr	3 (5)
ASCT	
Single	37 (52)
Tandem	11 (15)
No ASCT*	23 (32)
Maintenance	
Lenalidomide	43 (61)
Lenalidomide plus anti-CD38	3 (4)
No therapy**	25 (35)
Toxicity	
Hematological	3 (4)
-Anemia	1 (1)
-Thrombocytopenia	2 (3)
Non-hematological	21 (46)
-Neuropathy	10 (15)
-Infections	3 (4)
-Thromboembolic events	2 (3)
-Allergic reactions	1 (1)
-Others	4 (6)
Transplant ineligible patients	**N=13 (16%)**
Induction therapy	
VMP	7 (54)
Rd	2 (15)
Kd	2 (15)
VRd	1 (8)
Toxicity	
Hematological	2 (15)
-Anemia	2 (15)
Non-hematological	2 (15)
-Infections	2 (15)

*No ASCT: 9 pts waiting for ASCT

**No therapy: waiting to start maintenance therapy

Fifty-two pts were males and the median age was 61 years (28-88). Thirty-eight % of patients were ISS I and 46% were R-ISS II. Fifteen % of patients showed high-risk cytogenetic abnormalities.

Eighty-five % of patients were considered eligible for ASCT. The main therapeutic regimens used were bortezomib-based combinations, such as VTd in transplant eligible patients and VMP in transplant ineligible patients. The baseline clinical characteristics and the frontline induction treatments are summarized in Table 1a and 1b, respectively.

BM clonal PCs from a minority of patients of our cohort presented early B-cell maturation antigen expression, such as CD19 (2%), while CD20 and CD45 were detected in 17% and 52% of the clonal PCs, respectively. In 69% of cases, BM PCs showed a bright CD56 surface expression. Among the remaining patients, 1% showed a reduced reactivity for CD56 while CD56 was completely negative in the other cases (30%). CD117 was detected in 42% of clonal BM PCs, while CD28 and CD33 were detected in 15% and 5% of clonal PCs, respectively.

When considering unusual antigens on the surface of aberrant PCs (CD28, CD20 and CD45) we observed that the expression of CD28 was mutually exclusive compared to CD56 ($p<0.001$). The presence of CD20 was associated with the absence of CD28 ($p=0.048$). Expression of CD28 on clonal PCs was associated with a significantly lower median number of platelets at baseline ($p=0.005$) and with a significantly reduced percentage of MM patients achieving a complete response ($p=0.038$). Focusing on high-risk chromosomal aberrations, t(14;16) tended to associate with CD28 expression ($p=0.079$), while t(4;14) tended to associate with a lower median value of CD138 mean fluorescence intensity (MFI) ($p=0.06$). We also observed that CD20 expression on clonal PCs (18% of all patients) was associated with the type of secretory MM ($p=0.041$). Patients with CD2O expression showed a higher median level of serum monoclonal protein at baseline compared to patients lacking CD20 ($p=0.038$).

Despite the relatively limited sample size, these data confirm that the antigenic surface profile of MM PCs is highly variable, in line with the characteristic heterogeneity of the disease.

MFC represents a simple, reproducible, and cost-effective tool which could help to identify MM subsets at diagnosis and improve risk stratification.

P05 ACETYL SALICYLIC ACID INDUCES POLARIZATION OF MACROPHAGES AND CYTOTOXICITY ON MYELOMA CELLS IN VITRO

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Background and aim: As in many cancers, tumor microenvironment (TME) plays a vital role in progression in Multiple Myeloma (MM). Macrophages, which are members of TME, promote tumor progression by secreting various cytokines and can exist in two different forms as pro-tumorigenic (M2 macrophage) and anti-tumorigenic (M1 macrophage). M2 macrophages are inactive cells that cannot perform tumor cell phagocytosis, while M1 macrophages are active cells with high phagocytosis capabilities of tumor cells. It is known that the M1-M2 polarization observed in macrophages in the TME during myeloma progression is associated with poor prognosis. Therefore, reprogramming of macrophages can result in the formation of anti-tumorigenic TME. Acetyl Salicylic Acid (ASA) is used as an anti-thrombotic agent in MM and has been shown to effect the anti-tumorigenic polarization of macrophages in TME in breast and rectal cancer (Hsieh and Wang 2018; Farrugia, Long et al. 2021) Aim of this study is to investigate molecular effects of ASA on macrophage mediated phagocytosis in MM.

Methods: To demonstrate the cytotoxic effects of ASA on MM1S myeloma cells, MTT was performed by applying at different concentrations of ASA. IL10 and IL6 expression level from THP1 derived macrophages and MM1S cells was determined by qRT-PCR. In addition, CD80 gene (M1 marker) expression level was determined by qRT-PCR to monitor the effect of ASA on macrophage polarization from M2 to M1 in THP1 cells. According to MTT analysis results, 2.5mM was selected as the optimal dose of ASA and was applied to M1 and M2 macrophages for 48 hours. DiD-labeled macrophage cells and GFP+ MM1S cells were co-cultured and rates of macrophage-mediated phagocytosis were determined using flow cytometry and confocal microscopy. Statistical software GraphPad Prism6 was used for the assessment of the differences between all treated and control groups. Wilcoxon test and Two-way ANNOVA test are used to compare means of multiple samples.

Results: It was determined that ASA has a time (24h,48h,72h) and dose-dependent cytotoxic effect on MM1S cells in vitro (Figure 1). ASA had no effect on the viability of macrophages. It was shown that IL6 and IL10 expression were decreased in relation to cytotoxicity in MM1S cells treated with ASA ($p<0.05$, $p<0.0001$;). While ASA did not change CD80 expression in M1 macrophages, it caused an increase in CD80 expression in M2 macrophages ($p=0.0003$), indicating polarization from M2 to M1 phenotype (Figure 2). Finally, among M1 and M2 macrophages following ASA exposure, the baseline rate of phagocytosis of 63% and 26%, were found to be 69% and 70% confirming anti-tumorigenic effect of M1 and polarized M2 cells (Figure 3).

Conclusion: To our knowledge this is the first report on the effects of ASA effects on macrophage mediated phagocytosis and anti-myeloma cytotoxicity. At 2.5mM concentration which is equivalent to 45µg/dl and below the therapeutic range required in the clinic, ASA showed anti-tumorigenic effects by suppressing IL6 and IL10 expression, cytotoxicity in MM1S cells and M2 to M1 polarization mediated increase in phagocytosis. We conclude that ASA has a potential to induce direct and indirect effects targeting both MM cells and TME.

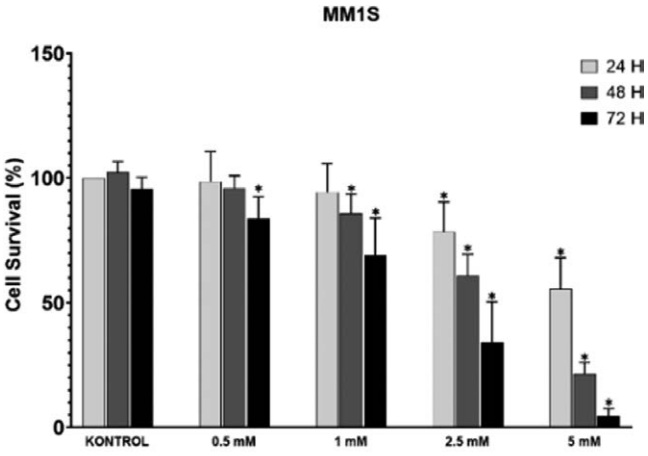

Figure 1. The effect of ASA treatment on MM1S cells viability.

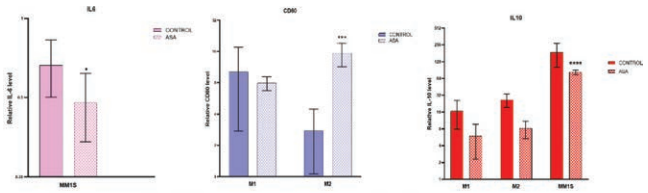

Figure 2. qRT-PCR Analysis of IL6, IL10 and CD80 expression on myeloma MM1s cells and M1 and M2 macrophages.

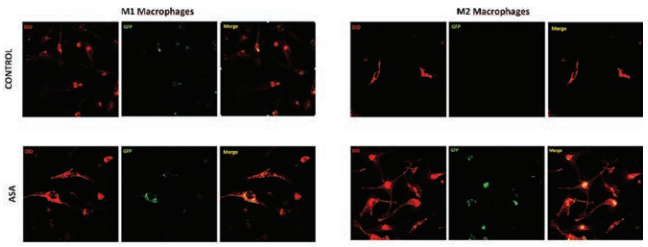

Figure 3. Phagocytosis Analysis by Confocal Microscope. After ASA treatment, while phagocytosis rate of M1 macrophages increased from 63% to 69%, the phagocytosis rate of M2 macrophages significantly increased from 26% to 70%.

DiD: M1 and M2 Macrophages

GFP: MM1S cells

P06 MODELING DYNAMIC EVOLUTION OF MULTIPLE MYELOMA STUDYING CELL POPULATIONS METABOLISM AND COMPETITION UNDER MAXIMUM POWER CONSTRAINTS: A SYSTEMS-THINKING BASED APPROACH

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Several groups are attempting to integrate clinical and biological variables arising from genomics, microenvironment and immune function in Multiple myeloma (MM) evolutionary path. However, it is hard to develop a taxonomy that could take in account the intra-patient heterogeneity of neoplastic plasma cells (PCs), their interaction with microenvironment and emerging cell-extrinsic factors to predict the disease evolution in each individual patient.

Ecological interactions between different cell stocks are recognized as fundamental at the mesoscale, addressing the possibility of a description that uses language and concepts of ecology to address their complex interaction dynamics. Nevertheless, a comprehensive biophysical framework encompassing growth, adaptation and survival of cell populations is still lacking to describe the dynamic evolution of MM.

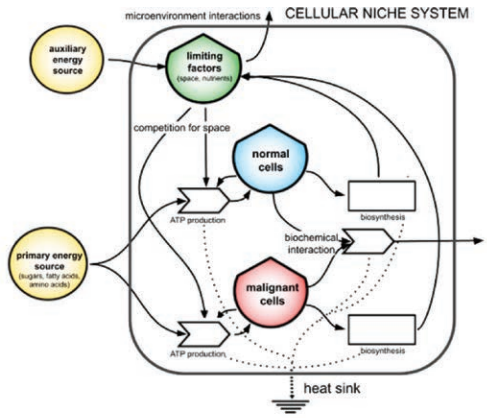
Taking advantage of mathematical modelling and system dynamics, we propose to describe the evolution of MGUS into MM as a unique complex system in dynamic balance. Dynamic models, where the temporal evolution of extensive variables can be simulated in the form of configurations, derive their initial conditions from available and assessed evidence. Varying the key system parameters, trajectories represent the possible evolutive (structural) patterns of the system at issue, becoming abstracted with respect to local specific attributes related to single case studies.

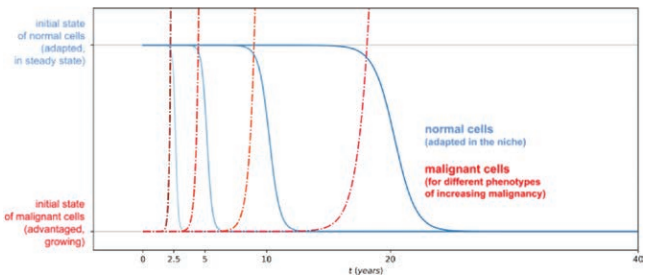
By a properly identified physical-based state space, we show a method to classify cell population growth regimes under limited resource availability from measures of ATP power generation and dissipation. The maximum power state naturally emerges as the thermodynamic limit for such constrained systems.

The competition for limited space between different phenotypes of antagonist populations exhibits a class of regime shifts to more stable and dissipative states for selective advantaged populations operating closer to the thermodynamic limit. The critical time for the transitions is controlled by the strength of the actual biochemical interaction.

At time of MM onset, the presence of several accountable variables confers a complex network of feedbacks leading to specific systemic configurations, which can evolve to maximize the persistence of neoplastic PCs, thus changing the system structure, output, and purpose (a pattern that we call in clinics Multiple Myeloma) or to be so resilient to co-evolve with neoplastic PCs (a pattern that we call in clinics MGUS or sMM). At any timepoint, under the pressure of external driver forces, which cannot be evaluated separately (e.g. new mutations, immune system dysregulation, inflammaging), the dynamic configurations could evolve to achieve a new stationary status in a pattern which identifies a new disease phase, which could still evolve in presence of additional external driver forces and so on.

Thus, our modeling approach is relevant for biophysical and biomedical research as it represents a novelty in the description of MM evolution, using systemic stock-flow diagrams that address feedback mechanisms and trade-offs operating at the cell population level.





2. Newly diagnosed multiple myeloma

P07 BORTEZOMIB-MELPHALAN-PREDNISONE (VMP) VS. LENALIDOMIDE-DEXAMETHASONE (RD) IN REAL-LIFE MULTIPLE MYELOMA PATIENTS INELIGIBLE FOR TRANSPLANT: UPDATED ANALYSIS OF THE RANDOMIZED PHASE IV REAL MM TRIAL

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Background: Until the recent introduction of daratumumab (Dara), bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd) have been standards of care for transplant-ineligible (NTE) newly diagnosed multiple myeloma (NDMM) patients (pts) in the frontline setting. Nonetheless, no prospective randomized trial has directly compared VMP with Rd, and only few data on real-life experiences in older NTE pts are available.

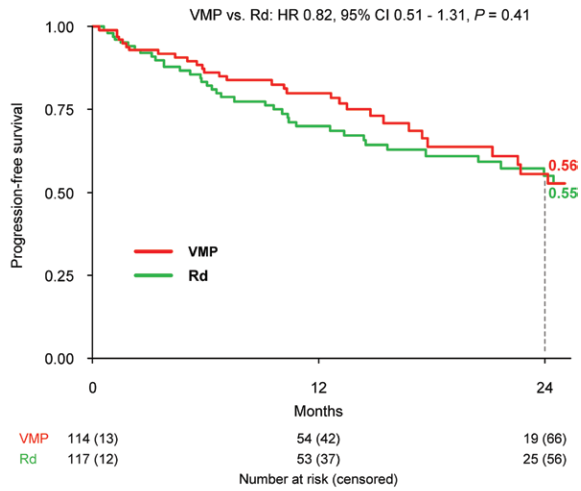
Methods: In this multicenter randomized phase IV trial (NCT03829371; funded by the Italian Medicines Agency AIFA - Independent Research), real-life NDMM pts ineligible for transplant due to comorbidities or age ≥65 years were randomized 1:1 to VMP (nine 42-day [dd] cycles [cc], V: 1.3 mg/m^2 dd 1,4,8,11,22,25,29,32 cc 1-4 and dd 1,8,22,29 cc 5-9; M: 9 mg/m^2 dd 1-4; P: 60 mg/m^2 dd 1-4) vs continuous Rd (28-day cc, R: 25 mg dd 1-21; d: 40 mg dd 1,8,15,22), according to standard practice. Upon written informed consent, pts were enrolled regardless of comorbidities, performance status, baseline laboratory values, or renal function. Stratification was performed according to the International Myeloma Working Group frailty score and to cytogenetic risk by fluorescence *in situ* hybridization [high risk with del(17p), t(14;16), or t(4;14)]. Progression-free survival (PFS) in the intention-to-treat (ITT) population was the primary endpoint. Overall survival (OS), response rates, and safety were key secondary endpoints.

Results: The data cut-off was July 4, 2022: 231 pts were randomly assigned to VMP (n=114) or Rd (n=117). Baseline characteristics were balanced in VMP vs Rd: median age 77 (IQR 73-80) and 76 years (IQR 73-79); frail pts 49% vs 50%; pts with high-risk cytogenetics 17% vs 19%. After a median follow-up of 19 months, median PFS in the ITT population was 29.6 vs 26.2 months with VMP vs Rd (hazard ratio [HR] 0.82, 95% CI 0.51-1.31, *P*=0.41; *Fig. 1A*). HR was 0.21 (95% CI 0.04-0.99) in pts with high-risk cytogenetics vs 1.24 (95% CI 0.70-2.18) in standard-risk pts (interaction *P*=0.036). No differences in terms of age or frailty status were observed. In the ITT population, 2-year OS was 89% with VMP vs 75% with Rd (HR 0.53, 95% CI 0.26-1.07, *P*=0.08; *Fig. 1B*). No safety concerns were reported. Thrombocytopenia (15%) and neuropathy (7%) were the most frequent grade 3-4 adverse events with VMP; neutropenia (23%), infections (12%), and dermatologic toxicities (9%) with Rd. At least 1 dose reduction (any drug) was reported in 66% of pts in the VMP and 59% in the Rd arms, including 35% of pts in the VMP arm switching to once-weekly V before cc 5.

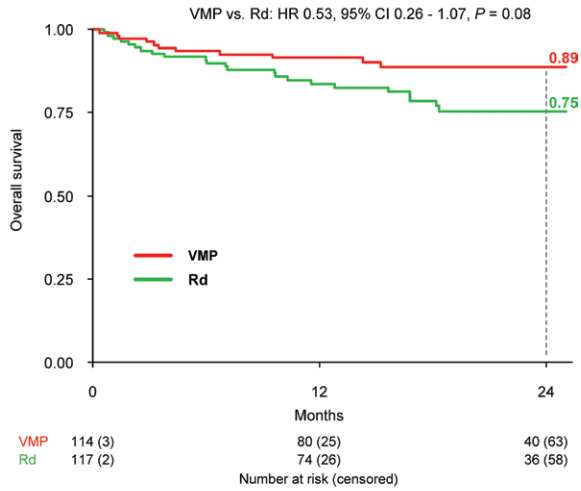
Conclusion: Overall, the advantage of Rd over VMP was lower than anticipated in this older real-life NTE NDMM population with 50% of frail patients. However, a strong effect modification by cytogenetic risk was found, with high-risk pts benefiting more from VMP vs Rd in terms of PFS (HR 0.21). Safety data were consistent with those previously reported. Of note, only 1/3 of real-life pts were able to receive full-dose VMP or Rd. Despite the limited follow-up, the poor outcomes in pts failing R-based treatment could explain the different OS rates in the two arms. As of July 2022, pts have been randomized to Dara-VMP vs Dara-Rd. With longer follow-up, an analysis of the addition of Dara will further improve decision-making.

Figure 1

A. Progression-free survival



B. Overall survival



Abbreviations. V, bortezomib; M, melphalan; P, prednisone; R, lenalidomide; d, dexamethasone; HR, hazard ratio; CI, confidence interval; *P*, p-value.

P08 TEMPORAL TRENDS IN PROGNOSIS OF PATIENTS WITH SMOLDERING MULTIPLE MYELOMA (SMM) WHO MEET CRITERIA FOR BIOMARKER-DEFINED EARLY MULTIPLE MYELOMA (SLIM CRAB POSITIVE MM)

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Background: Biomarker-defined pts with SMM were included in the diagnostic criteria of multiple myeloma (MM) in a 2014 update by the International Myeloma Working Group (IMWG). This category includes SMM pts with either ≥60% BMPC or a free light chain (FLC) ratio of

Published	Median time to progression (months) [CI]		Risk for progression at 2 years (%) [CI]	
	BMPCs ≥ 60 %	*BMPCs < 60 %*	*BMPCs ≥ 60 %*	*BMPCs < 60 %*
Early publications	9.20 [6.02-15.56]	101.47 [89.90-NA]	86.21 [65.74-94.45]	21.19 [18.15-24.12]
Recent publications	30.31 [18.71-62.93]	80.46 [70.97-115.48]	45.45 [20.12-62.75]	20.32 [15.18-25.14]
Combined data	15.48 [10.93-21.93]	96.73 [87.01-NA]	68.63 [52.92-79.09]	20.97 [18.37-23.48]
	FLCratio ≥ 100	*FLCratio < 100*	*FLCratio ≥ 100*	*FLCratio < 100*
Early publications	15.33 [9.38-19.10]	58.59 [52.78-65.80]	73.00 [62.39-80.62]	26.58 [22.89-30.09]
Recent publications	48.06 [40.51-64.91]	115.15 [105.96-118.81]	31.61 [25.30-37.39]	16.79 [14.91-18.64]
Combined data	30.40 [25.43-38.69]	93.19 [81.37-105.96]	43.82 [38.14-48.97]	19.45 [17.75-21.12]
	> 1 lesion	*≤1 lesion*	*> 1 lesion*	*≤1 lesion*
Early publications	15.07 [10.49-32.98]	102.42 [69.67-102.42]	67.30 [48.97-79.05]	16.14 [11.10-20.90]

≥100 and an involved FLC concentration of ≥100 mg/dl or > 1 MRI-defined ≥5mm focal lesion. The main reason for revising the diagnostic criteria was the data available at that time, which showed a very short time to progression (TTP) to CRAB positive MM (between 9.2 and 15.3 mos), leading to the recommendation to initiate anti-MM therapy in these pts.

Objective: To determine whether the prognosis (median time to progression □TTP□ and 2-year risk of progression) of biomarker-defined early MM or "SliM CRAB" positive MM pts has changed over the past decade compared with data previously available for the consensus group. Recent clinical experience suggests that a substantial proportion of pts meeting SliM CRAB MM criteria do not progress to MM within a short period of time.

Methods: We performed a comprehensive literature search and meta-analysis, including studies listed in Embase and PubMed (01/01/2010 - 01/11/2022) on SliM CRAB positive pts, including digitizable progression curves that would allow generation of individualized data. We used WebPlotDigitizerTM to digitize published TTP curves and then applied the algorithm described by Guyot et al (2012) in R to obtain individualized patient outcomes. We generated Kaplan-Meier curves and forest plots using random-effects models from the digitized and published data and compared median TTP, 2-year risk of progression, and odds ratios (ORs) for the comparison of 2-year risk of progression between data published before and after the publication of the IMWG consensus.

Results: We found 11 recent studies in addition to the six previously available studies with a total of 3482 pts. Our analysis showed longer TTP (median: 30.3 vs. 9.2 mos) and a reduction in 2-year risk of PD (45.5% vs. 86.2%) in pts with ≥60% BMPCs and in pts with a FLCratio ≥ 100 (48.1 vs. 15.3 mos and 31.6% vs. 73.0%, respectively) in more recent compared with earlier studies. Such analyses were not possible for pts with focal lesions defined by MRI because no further studies were published after 2014 (table 1).

A meta-analysis using ORs for the 2-year risk of progression in pts with ≥ 60% BMPC showed a significantly higher OR in the two earlier (OR: 27.01, 95% CI 4.49-162.34, p=0.0003) compared to a later report (OR: 3.27, 95% CI 1.37-7.99, p=0.009). Testing for heterogeneity revealed that the two time periods differed significantly in their ORs (I2 =78.6%, p=0.009). Similar results were obtained for pts with a FLCratio ≥100 compared to those with a FLCratio < 100 in early (OR: 7.03, 95% CI 4.34-11.37, p < 0.0001) and recent publications (OR: 2.69, 95% CI 1.77-4.09, p < 0.0001), I2 = 67.8%, p = 0.005.

Conclusions and Relevance: We found an approximately 3-fold longer TTP and 50% lower 2-year risk of progression in SMM patients with ≥60% BMPC or FLC ratio ≥ 100 in recent compared to earlier studies. This phenomenon is likely due to improved diagnostic workup with modern skeletal imaging and exclusion of patients with bone lesions. Therefore, routine treatment of patients meeting SliM criteria CRAB (BMPC or FLC ratio) should be initiated only after careful evaluation and documentation of signs of progression.

P09 DARATUMUMAB PLUS LENALIDOMIDE AND DEXAMETHASONE (D-RD) VERSUS LENALIDOMIDE AND DEXAMETHASONE (RD) ALONE IN TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM): UPDATED ANALYSIS OF THE PHASE 3 MAIA STUDY

Weisel K.[1]; Kumar S.[2]; Moreau P.[3]; Bahlis N.[4]; Facon T.[5]; Plesner T.[6]; Orlowski R.[7]; Basu S.[8]; Nahi H.[9]; Hulin C.[10]; Quach H.[11]; Goldschmidt H.[12]; O'Dwyer M.[13]; Perrot A.[14]; Venner C.[15]; Raje N.[17]; Tiab1 M.[8]; Macro M.[19]; Frenzel L.[20]; Leleu X.[21]; Pei H.[22]; Krevvata M[23]; Carson R[23]; Borgsten F.[24]; Usmani S.[25]

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Introduction: Daratumumab is a human IgGκ monoclonal antibody that is approved as monotherapy and in combination with standard-of-care regimens for relapsed/refractory multiple myeloma and in combination with standard-of-care regimens for NDMM. In the primary analysis of the phase 3 MAIA study (median follow-up, 28.0 months), D-Rd significantly improved progression-free survival (PFS) and the minimal residual disease (MRD)–negativity rate (10–5 sensitivity) versus Rd alone in transplant-ineligible patients with NDMM. With longer follow-up (median follow-up, 56.2 months), D-Rd significantly improved overall survival (OS) versus Rd. Here, we present an analysis of MAIA after a median follow-up of 64.5 months.

Patients and methods: Patients with NDMM ineligible for high-dose chemotherapy and autologous stem cell transplant were randomized 1:1 to Rd ± D. Randomization was stratified by International Staging System disease stage (I vs II vs III), region (North America vs other), and age (<75 vs ≥75 years). All patients received 28-day cycles of Rd (R: 25 mg PO on Days 121; d: 40 mg PO on Days 1, 8, 15, and 22). In the D-Rd arm, D (16 mg/kg IV) was given once weekly in Cycles 12, once every 2 weeks in Cycles 3-6, and once every 4 weeks thereafter. In both groups, patients were treated until disease progression or unacceptable toxicity. PFS was the primary endpoint; key secondary endpoints included MRDnegativity rate (10–5 sensitivity, clonoSEQ® version 2.0), overall response rate (ORR), OS, and safety.

Results: A total of 737 patients were randomized (D-Rd, n=368; Rd, n=369). At a median follow-up of 64.5 months, PFS was improved with D-Rd versus Rd (median, 61.9 vs 34.4 months; hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.45-0.67; P<0.0001). D-Rd reduced the risk of death by 34% versus Rd. Median OS was not reached with D-Rd versus 65.5 months with Rd (HR, 0.66; 95% CI, 0.53-0.83; P=0.0003), with estimated 60-month OS rates of 66.6% and 53.6%, respectively. ORR was higher for D-Rd versus Rd (92.9% vs 81.6%; P<0.0001), as were rates of MRD negativity (32.1% vs 11.1%; P<0.0001) and sustained MRD negativity lasting ≥12 months (18.8% vs 4.1%; P<0.0001). The most common (≥15% of patients in either arm) grade 3/4 treatment-emergent adverse events (TEAEs; D-Rd/Rd) were neutropenia (54.1%/37.0%), anemia (17.0%/21.6%), pneumonia (19.5%/10.7%), and lymphopenia (16.5%/11.2%); grade 3/4 infection rates were 42.6%/29.6%. Pneumonia was the most common serious

TEAE in both groups (18.7%/10.7%). Rates of treatment discontinuation due to TEAEs were lower with D-Rd (14.6%) versus Rd (23.8%).
Conclusions: In this analysis of MAIA after a median follow-up of >5 years, the addition of DARA to Rd continued to demonstrate PFS and OS benefits in transplant-ineligible patients with NDMM. D-Rd also achieved higher MRD-negativity and ≥12-month sustained MRD-negativity rates versus Rd alone. No new safety concerns were observed with longer follow-up. These results continue to support the frontline use of D-Rd in transplant-ineligible patients with NDMM. Additional OS results based on extended follow-up will be presented.

P10 AN ULTRA-SENSITIVE METHOD FOR SEQUENCING AND MONITORING OF M-PROTEIN IN PERIPHERAL BLOOD (M-INSIGHT)

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With the improvement of therapy (monoclonal antibody, CAR-T), detection of minimal residual disease (MRD) and early restart of therapy is of high importance to manage multiple myeloma disease (MM). Most sensitive MRD assays to date are based on quantification of clonal plasmocytes by next generation sequencing or flow cytometry in bone marrow aspirates. However, such methods have shown limitations such as being invasive with sample heterogeneity and lacking the possibility for frequent sampling. Frequent MM monitoring on blood at equivalent sensitivity than achieved with bone marrow could provide actionable information on disease activity and detect early signs of progression.
M-protein is a well-established biomarker used for MM diagnostic and monitoring. Mass spectrometry (MS) has been introduced as a possibility to monitor M-protein. Intact protein measurement by MS has the drawback of lacking in sensitivity with high interference from the polyclonal background. Clonotypic peptides originating from the variable region of the M-protein are unique for each patient. Their detection by MS, which circumvent interferences from other immunoglobulins, has been demonstrated to quantify M-protein at MRD level. Several studies from our group have been published showing the use of targeted mass spectrometry-based MRD blood-test (M-InSight) that detects clonotypic peptides.
In this study, M-InSight is used to sequence and select clonotypic peptides to allow highly specific and ultra-sensitive monitoring of the M-protein. Therapy response of 41 Multiple myeloma patients from the IFM-2009 clinical trial (NCT01191060) was used to evaluate the assay. M-InSight uses a novel de novo approach using Peaks Ab software to sequence the M-protein with mass spectrometry from serum that are further assembled into full length HC (Heavy Chain) and LC (Light chain) sequences. All 41 patients were sequenced by mass spectrometry, which was then compared to RNA sequencing data based on tala cDNA from all expressed genes. RNA assembly pipeline using Trust4 was used to construct clonotypes and to identify clonal molecular fingerprints and finally their clonotypic peptides based on transcriptomic datasets. Results showed a coverage of more than 90% of the entire LC and HC sequenced by mass spectrometry compared to the data obtain from RNA sequencing.
Once the M-protein sequence was obtained, several clonotypic peptides were further chosen with the use of an in-house bioinformatics algorithm to select the best candidate. Each peptide is chosen to be specific to the patients (CDR region) from both chains. Clonotypic peptides are used to quantitate M-protein in patients' serum after treatment. M-protein concentrations were determined by calibration on a sample with a known M-protein concentration quantified by an agarose gel electrophoresis system (Hydrasys 2, Sebia).
Results showed a very high sensitivity with M-protein still detectable by M-InSight despite a MRD negativity determined by next generation sequencing data on bone marrow aspirate. The best sensitivity achieved by M-InSight, detecting 0.2 mg/L of M-protein, was 1000- and 100-fold more sensitive compared to SPE and intact protein MS method, respectively.
In conclusion, the newly developed and validated M-InSight assay is presented as an ultra-sensitive fully blood based assay to sequence and monitor M-protein with the possibility for frequent non-invasive analysis.

P11 COMBINED DIFFUSION WEIGHTED WHOLE BODY MRI (DW-MRI) AND MULTIPARAMETRIC FLOW CYTOMETRY (MFC) EVALUATION FOR MINIMAL RESIDUAL DISEASE DETECTION IN MULTIPLE MYELOMA PATIENTS: CONCORDANCE ANALYSIS OF THE TWO TECHNIQUES AND PREDICTIVE ROLE AFTER TRANSPLANT

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Introduction: The increasing availability of functional imaging techniques has enabled the combined evaluation of MRD in MM within and outside bone marrow (BM). Diffusion-weighted whole-body MRI (DW-MRI) is increasingly used in the management of MM patients (pts) and criteria for Response Assessment Category (RAC) have been established by the Myeloma Response Assessment and Diagnosis System (MY-RADS), with a 5 point scale defining complete imaging response (i.e. RAC 1) or residual-progressive disease after treatment (i.e. RAC 2-5). We compared the results of MY-RADS with those of MRD assessment by flow cytometry (MFC) at different timepoints after autologous stem cell transplant (ASCT) in order to evaluate the agreement of the two techniques and to investigate the predictive role of a dual assessment of response on patients outcome.
Methods: we retrospectively assessed MRD in transplant eligible MM pts by performing combined evaluations of BM and DW-MRI at day +100 after ASCT and yearly thereafter. MY-RADS RAC criteria were applied for the evaluation of imaging residual disease, whereas 8-color MFC (sensitivity 10-5) was performed for BM MRD detection. The concordance between DW-MRI and MFC results was calculated and the level of agreement was expressed by Cohen's kappa statistics. The outcome according to the combined DW-MRI/MFC evaluation after ASCT was also investigated. Results: from 2016 to 2021 we performed 143 combined evaluations of DW-MRI and MFC in 79 pts. MFC was negative in 96 BM samples (67%); according to MY-RADS, a complete imaging response (RAC1) was observed in 107 cases (75%), whereas some residual disease was identified in 36 cases (25%) [RAC2: 24 (17%), RAC3: 6 (4%), RAC4: 3 (2%), RAC 5: 3 (2%) respectively]. The concordance between WB-MRI and BM MFC results was low (68.5%, kappa 0,067: 13% both positive, 55% both negative). MRD assessment at day +100 after ASCT (considering the second ASCT in case of double transplant) was available in 76 patients [27(35%) ISS-3, 29 (38%) high risk cytogenetics]. Pts were treated with the following induction regimens: VTD 56 (74%), DaraVCD 6 (8%), DaraVRD 6 (8%), VRD 6 (8%), KCD 1 (1%), KRD 1 (1%); 37 pts (49%) received double ASCT (MEL200). Response rates were sCR 25%, CR 45%, VGPR 21%, PR 9%. MFC was negative in 48 samples (63%), whereas RAC1 was observed in 52 (68%) pts.
Seventy pts (92%) received maintenance therapy with lenalidomide (58), daratumumab-lenalidomide (6), daratumumab-ixazomib (6). After a median follow up of 42 months, PFS was significantly better for patients with DW-MRI RAC1 and MFC negative after ASCT, compared to pts with RAC ≥2 and MFC positive results (PFS NR vs 22.3 months; p <0.0001, HR 0.10 - 95%CI: 0,02-0,43). Intermediate PFS was observed for pts with either imaging or BM positive results (PFS NR), with a significantly different outcome of the three subgroups (p <0.0001). A trend of different OS was also observed, although not statistically significant (3y OS: 95% for double negative pts, 89% for pts with either imaging or BM positive results, 60% for double positive pts, p 0.06). Conclusion: DW-MRI is a powerful tool to evaluate the prognosis of pts treated with ASCT; the low concordance between DW-MRI and MFC highlights the complementarity of the two techniques for the definition and monitoring of response in order to better refine the prognosis of pts achieving CR after ASCT

P12 HEALTH-RELATED QUALITY OF LIFE IN FRAIL AND INTERMEDIATE-FIT PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH DOSE-ADJUSTED MELPHALAN-PREDNISONE-BORTEZOMIB (MPV)

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Background: Frailty in non-transplant eligible (NTE) newly diagnosed multiple myeloma (NDMM) patients is associated with toxicity which can negatively affect physical functioning and quality of life (QoL). Older patients may prefer QoL and physical independence over length of life, highlighting the importance of taking health-related (HR) QoL assessment into account for treatment guidance.
Methods: The HOVON123 study (NTR4244) was a phase II trial in which 238 NTE-NDMM patients ≥75 years were treated with 9 dose-adjusted cycles MPV. Nine (3 functional; 6 symptom) subscales of two HRQoL instruments (EORTC QLQ-C30 and MY20) were obtained at baseline (T0), after 3 (T1) and 9 (T2) cycles of therapy, and 6 (T3) and 12 (T4) months after discontinuation of therapy in patients without progression. The presence of "tingling hands/feet" was used as a proxy for neuropathy.
Differences in baseline HRQoL were analysed with independent t-tests and changes over time with linear mixed models. HRQoL changes and/or differences were reported only when both statistically significant ($p<0.005$, adjusted for multiple testing) and clinically relevant (>MID).
Results: A total of 137 frail and 71 intermediate-fit patients were included in the HRQoL analysis, after exclusion of fit patients and patients whose frailty status or baseline HRQoL questionnaire was missing. Compliance was not materially different in both groups. Frail patients had an inferior HRQoL at baseline in the subscales global health status, physical functioning, fatigue and pain, compared with intermediate-fit patients. Both groups reported improvements in global health status and future perspective. In contrast to intermediate fit patients, frail patients improved in physical functioning, fatigue and pain over time. The improvements in global health status were reached earlier in frail patients (T1) compared with intermediate fit patients (T2), **Figure 1**. In both intermediate fit and frail patients there was an increase in neuropathy. All other subscales remained within MID ranges and/or were not statistically significant different from baseline.
The improvement in global health status sustained after treatment completion (T3-T4) both for frail and intermediate fit patients. This also accounted for future perspective at T3, however, at T4 for intermediate fit patients only. In contrast, the improvement in all other HRQoL domains during treatment, lost clinical relevance and/or statistical significant difference during the TFI. The deterioration in neuropathy remained until T4 in frail patients, but not for intermediate fit patients, reversing at T4, **Figure 1**.
Conclusion: HRQoL in frail patients is inferior as compared to intermediate fit patients at diagnosis. Importantly, treatment improved HRQoL, irrespective of frailty level, being more pronounced and occurring even faster in frail patients. Therefore, physicians should not withhold therapy in these patients because of their frailty status only.

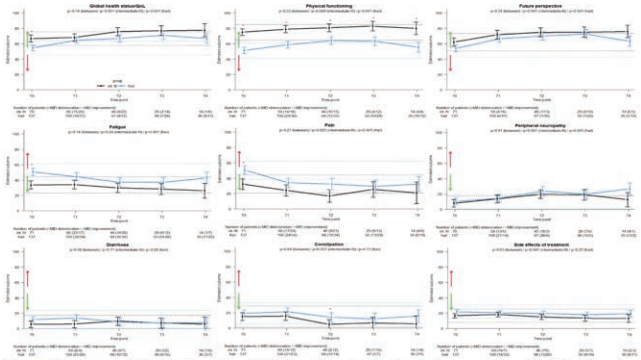

Figure 1 Estimated HRQoL for nine HRQoL subscales for both intermediate fit (black) and frail (blue) patients.
Green arrows point towards improvement, red arrows point towards deterioration. Dotted lines implicate threshold for clinically relevant change from baseline (MID), red asterisks indicate a MID (>5 points) *and statistically significant ($p<0.005$)* difference between intermediate fit and frail patients:

- Global health status, p-values over the entire course: p=0.14 (between groups), p<0.001 (frail) & p=0.001 (intermediate fit)
- Physical functioning, p-values over the entire course: p=0.33 (between groups), p<0.001 (frail) & p=0.086 (intermediate fit)
- Future perspective, p-values over the entire course: p=0.34 (between groups), p<0.001 (frail) & p<0.001 (intermediate fit)
- Fatigue, p-values over the entire course: p=0.14 (between groups), p<0.001 (frail) & p=0.24 (intermediate fit)
- Pain, p-values over the entire course: p=0.27 (between groups), p<0.001 (frail) & p=0.023 (intermediate fit)
- Peripheral neuropathy (PNP), p-values over the entire course: p=0.41 (between groups), p<0.001 (frail] & p=0.001 (intermediate fit)
- Diarrhoea, p-values over the entire course: p=0.38 (between groups), p=0.28 (frail) & p=0.71 (intermediate fit)
- Constipation, p-values over the entire course: p=0.84 (between groups), p=0.13 (frail) & p=0.007 (intermediate fit)
- Side effects of treatment, p-values over the entire course: p=0.63 (between groups), p=0.27 (frail) & p=0.081 (intermediate fit)

P13 IXAZOMIB, DARATUMUMAB AND LOW-DOSE DEXAMETHASONE IN INTERMEDIATE-FIT PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA; RESULTS OF THE INDUCTION AND MAINTENANCE TREATMENT OF THE PHASE II HOVON 143 STUDY

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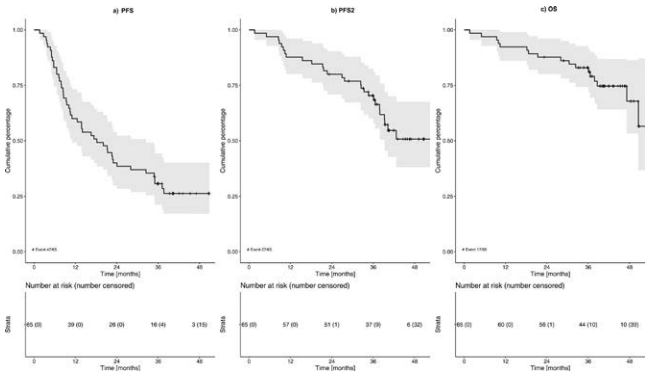
Introduction: Non-transplant eligible newly diagnosed multiple myeloma (NTE-NDMM) patients have a heterogeneous clinical outcome, depending of frailty level. The aim of this study was to prospectively investigate the efficacy and tolerability of Ixazomib-Daratumumab-low dose dexamethasone (IDd) in intermediate-fit NTE-NDMM patients.
Methods: In this phase II multicenter HOVON-143 study, IWMG-frailty index based intermediate-fit patients were treated with nine induction cycles of IDd, followed by maintenance with IDd for a maximum of two years. Health related quality of life (HRQoL) was investigated at baseline, after 3 and 9 induction cycles and after 6, 12 and 24 months of maintenance treatment.
Results: Sixty-five patients were included. The overall response rate during induction was 71% (95% confidence interval (CI) 63-73%). After a median follow-up of 41 months (range 28.9-53.8), median PFS was 18.2 months. Median PFS2 and OS were not reached, PFS2 at 2 years was 80% (95% CI 68-88%), OS at 3 years was 83% (95% CI 71-90%). (Figure 1) Thirty-five patients (54%) completed induction treatment and started maintenance therapy. During maintenance, 12/35 (34%) patients had an improvement of response.
Reasons for discontinuation of induction treatment were progressive disease (PD) (19/30; 63%), toxicity (4/30; 13%), incompliance (3/30; 10%), sudden death (1/30; 3%) and other (3/30; 10%). Of the 35 patients who started maintenance therapy, 15 (43%) patients completed the protocol and 20 patients discontinued treatment due to PD (13/20; 65%), refusal (2/20; 10%), toxicity (2/20; 10%), death (1/20; 5%) or other reasons (2/20; 10%).
Hematologic adverse events (AE) grade ≥3 during induction occurred in 12% of patients, of which neutropenia was most commonly reported (6%). During maintenance only 1 patients (1/35; 3%) experienced a grade 3 hematologic AE (thrombocytopenia). Non-hematologic AEs grade ≥3 during induction occurred in 51% of patients, of which most commonly gastro-intestinal AEs (14%) and central nervous system AEs (14%). All grade polyneuropathy (PNP) occurred in 42% of patients, including 5% grade 3 PNP. During the maintenance phase non-hematologic AEs grade ≥3 occurred in 46% of patients, which were most commonly gastro-intestinal AEs (11%) and infections (9%). There was no new onset of grade ≥3 PNP.
Dose modifications of ixazomib occurred in 24/65 (37%) patients during induction treatment and in 19/35 (54%) patients during maintenance. Eight/35 (23%) patients discontinued ixazomib treatment during the maintenance phase, while continuing with daratumumab once every eight weeks.
The global health status/quality of life improvement significantly during treatment and was clinically significant from the 9th induction cycle onwards.
Of the patients who experienced PD, second line treatment was started in 40 out of 42 patients (95%). The remaining 23 patients were still free of progression (18) or died before the occurrence of PD (5). Second line therapy was most commonly lenalidomide based (35/40; 88%).
Conclusion: IDd treatment in intermediate-fit patients with NDMM is safe and improves global quality of life. However, PFS is limited, partly explained by limited efficacy due to frequent dose modifications of ixazomib, mainly due to neurotoxicity. This underscores the need for more efficacious and tolerable regimens improving the outcome in non-fit patients.



P14 OCULAR TOXICITY IN TRANSPLANT INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH BELANTAMAB MAFODOTIN, LENALIDOMIDE AND DEXAMETHASONE IN A PHASE 1/2 TRIAL

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Introduction: Belantamab mafodotin (belamaf) is a B-cell maturation antigen-binding antibody-drug conjugate approved as a monotherapy in pretreated patients (pts) with relapsed/refractory multiple myeloma. Corneal examination findings (e.g., keratopathy) and visual acuity changes are common with belamaf, warranting belamaf dose modifications (dose reduction, dose holds) or treatment discontinuation. Here, we evaluate the ocular adverse effects of belamaf and their impact on daily functioning in pts participating in the phase 1/2 BelaRd study.
Methods: The ongoing, prospective, open-label, 2-part, phase 1/2 BelaRd study (NCT04808037) aims to enroll 66 adult pts with TI NDMM. In Part 1 of the study (dose selection), 18 pts are randomized (1:1:1) in 3 cohorts to receive belamaf 2.5, 1.9, or 1.4 mg/kg doses by intravenous infusion once every 8 weeks (Q8W) plus Rd and the safety/tolerability of the combination is evaluated for pts with ≥4 weeks of follow up. As a safety review found no unexpected findings, an additional 6 pts were enrolled in each dose cohort to select the belamaf recommended phase 2 dose (RP2D). Part 2 (dose expansion; not initiated) will further evaluate the safety and clinical activity of belamaf RP2D plus Rd. Ocular assessments include best corrected visual acuity (BCVA), using Snellen chart and manifest refraction, and corneal exam using slit lamp microscopy. Ocular symptoms are classified by Common Terminology Criteria for Adverse Events and dry eye disease severity and vision-related functioning is assessed with the patient-reported Ocular Surface Disease Index (OSDI). In Part 1 of the study, severity of corneal events is assessed with the Keratopathy Visual Acuity scale. This descriptive analysis included all Part 1 pts from the BelaRd study (data cut-off: 24 June 2022).
Results: Thirty-six pts were included in this analysis, who were followed up for a median of 9.5 months (range 3.2–15.4). At baseline (cycle 1 day 1), all pts had ocular comorbidities. During follow-up, the most common any grade (gr) ocular adverse events (OAEs) across cohorts were dry eye and visual acuity reduced (Table 1). Gr 3 OAEs were observed only for visual acuity reduced, visual impairment, and cataract; no Gr 4 OAEs were observed. Belamaf doses skipped due to OAEs per the total number of planned belamaf administrations were 23/68 (33.8%), 15/73 (20.5%), and 10/69 (14.5%) in cohorts 2.5, 1.9, and 1.4 mg/kg, respectively. For the entire pt population, median times to resolution of keratopathy and BCVA change from baseline were 2.1 months (range 0.7–11.1) and 2.0 months (range 0.3–6.9), respectively; across cohorts, numerically similar median times to resolution were observed for each OAE (Table 1). Low (<2.0%) proportions of OSDI assessments included 'all' or 'most of the time' impact of study treatment on activities of daily living (ADLs), while most assessments were 'some' or 'none of the time'.

Table 1

Most common ocular adverse events* by MedDRA preferred term and time to resolution

	Cohort 2.5 mg/kg	Cohort 1.9 mg/kg	Cohort 1.4 mg/kg
Patients, n	**12**	**12**	**12**
Most common OAEs†, n (%)			
Dry eye	11 (91.7)	12 (100.0)	12 (100.0)
Visual acuity reduced	10 (83.3)	12 (100.0)	12 (100.0)
Visual acuity reduced gr ≥3	4 (33.3)	2 (16.7)	6 (50.0)
Keratopathy	8 (66.7)	11 (91.7)	9 (75.0)
Visual impairment	8 (66.7)	9 (75.0)	10 (83.3)
Visual impairment gr ≥3	1 (8.3)	-	-
Vision blurred	7 (58.3)	7 (58.3)	7 (58.3)
Foreign body in eye	6 (50.0)	6 (50.0)	9 (75.0)

	Cohort 2.5 mg/kg	Cohort 1.9 mg/kg	Cohort 1.4 mg/kg
Time to resolution of OAEs†, months (median [range])^			
Keratopathy	1.9 (0.7–11.1)	2.0 (0.9–9.2)	2.1 (1.0–4.6)
Visual acuity reduced	2.1 (0.3–6.0)	2.1 (0.8–6.9)	1.8 (0.9–6.6)
Ocular symptoms§	1.7 (0.3–10.4)	1.1 (0.8–4.8)	1.1 (0.2–6.5)
Dry eye	2.2 (0.9–4.6)	1.0 (0.9–3.9)	1.1 (0.3–6.5)
Eye irritation	0.90 (0.8–1.0)	1.1 (1.0–1.1)	1.0 (0.3–1.8)
Eye pain	0.9 (0.9–0.9)	0.9 (0.9–0.9)	0.6 (0.3–0.9)
Foreign body in eye	1.8 (0.9–5.3)	1.8 (0.8–4.7)	1.3 (0.9–2.9)
Lacrimation increased	1.3 (0.9–3.6)	0.9 (0.9–0.9)	0.9 (0.9–0.9)
Vitreous floaters	2.1 (0.9–2.8)	2.9 (0.9–4.8)	3.2 (0.9–5.5)

*Included OAEs were observed in ≥50.0% of the entire patient population. †OAEs are classified by MedDRA preferred term. ^Calculated over the total number of resolved events. §Median time to resolution shown only for ocular symptoms with ≥1 occurrence
BCVA, best corrected visual acuity; Gr, grade; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients; OAE, ocular adverse events

Conclusions: No new ocular safety signals were observed with belamaf plus Rd in the upfront treatment of TI pts with NDMM; the observed eye toxicities were within the anticipated range with the use of belamaf. Keratopathy and BCVA change from baseline were resolved by a median of ~2 months; for each of these OAEs, similar times to resolution were recorded, across dose cohorts. Belamaf plus Rd had a minor impact on ADLs, especially in the 1.4 and 1.9 mg/kg doses.

P15 VALIDATION OF THE NOVEL EUROPEAN MYELOMA NETWORK PROGNOSTIC SCORE (R2-ISS) IN AN INDEPENDENT REAL-WORLD SETTING

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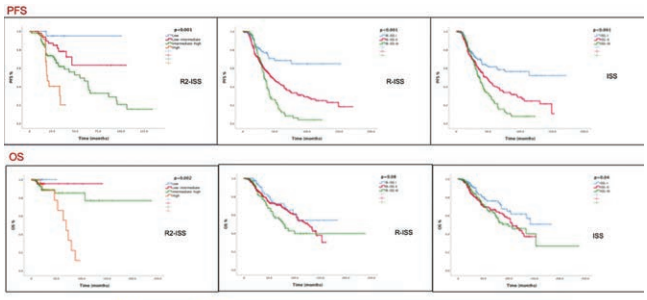
INTRODUCTION: Since the introduction of ISS, there has been a major advance in the field of prognostic biomarkers that led to a revision (R-ISS) which was still beyond expectations. 1q gain (+1q) is a high risk cytogenetic (HCR) feature among newly diagnosed multiple myeloma (NDMM). +1q has recently been integrated into the Second Revision of the ISS (R2-ISS) by the European Myeloma Network (EMN) under the umbrella of the European Union-funded HARMONY project. In this retrospective analysis, we aimed to validate this novel score and evaluate its impact on the outcome of NDMM.
METHODS: This retrospective study is performed on a database of 524 consecutive NDMM patients treated in our center between September 2007- March 2022. As 1q amplification has been added to our FISH panels lately, 208 consecutive patients met the criteria for R2-ISS score parameters. Progression eligible for analysis-free survival (PFS) was defined as the time from the diagnosis until disease progression, relapse, or death due to any cause. Overall survival (OS) was defined as the time from the diagnosis until death due to any cause or last follow-up. Analysis was performed by SPSS software version 26.0 (SPSS, Inc., IBM, Armonk, NY).
RESULTS: Patients (median age 62 years (33-88 years); (44.1% female and 55.9% male)) received either bortezomib-based triplet (90%) without (n: 405) or with an immunomodulatory drug (IMID) (13.2%) as induction therapy. Out of the total, 493 patients underwent autologous hematopoietic stem cell transplantation (AHCT). As a post-ASCT treatment, consolidation (20.2%) and maintenance (46.4%) were given to 243 patients. The median follow-up for all patients is 35.4 months (range: 3-237 mos). HCR was detected in 90 patients (17.8%) among all patients and +1q was identified in 96 cases, accounting for 46.2% of 208 patients. Based on the calculation of risk score in R2-ISS; 21 patients (10.1%) ranked as score 0 (R2-ISS I; low), 50 patients (24%) score 0.5-1 (R2-ISS II; low-intermediate), 111 patients (53.4%) score 1.5-2.5 (R2-ISS III; intermediate-high) and 26 patients (12.5%) score 3-5 (R2-ISS IV; high). The cross-tabulation of R2-ISS with R-ISS is shown in Table 1. With a median follow-up of 33.8 months, patients with +1q had significantly shorter PFS (95% CI: 20.4%-47.1%, p<0.001) than those without +1q. The median PFS was NR vs NR vs 55.3 mos vs 19.7 mos, with 5-year OS of NR vs 95.4% vs 85.3% vs 66.2% in the R2-ISS I, II, III, and IV groups, respectively (p<0.001 and p=0.002). Three-year PFS and OS are statistically significant for ISS, R-ISS, and R2-ISS groups (Figure 1).
CONCLUSION: Our single-center uniform real World data-based study confirms the prognostic role of the new R2-ISS scoring system as a reliable and reproducible method to powerfully predict the prognosis of patients with NDMM. Based on the results of this study, the presence of +1q confers poor outcomes that provide robust proof for the revision of +1q in the R2-ISS. Furthermore, R2-ISS is able to characterize very good prognostic and ultra-high-risk patients not possible in the earlier R-ISS and ISS models.
Acknowledgment: We are indebted to Ankara University School of Medicine Department of Medical Genetics FISH laboratory staff members and especially Asist. Prof. Timur Tuncali performed the FISH analysis of the patients.



R-ISS	R2-ISS			
	Low (n=19)	Low-intermediate (n=47)	Intermediate-high (n=108)	High (n=26)
I (n=37)	17 (8.5%)	17 (8.5%)	2 (1%)	1 (0.5%)
II (n=110)	2 (1%)	30 (15%)	71 (35.5%)	7 (3.5%)
III (n=53)	-	-	35 (17.5%)	18 (9%)

P16 HEALTH-RELATED QUALITY OF LIFE FOR FRAIL TRANSPLANT-INELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA TREATED WITH DARATUMUMAB, LENALIDOMIDE AND DEXAMETHASONE: SUBGROUP ANALYSIS OF MAIA TRIAL

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Introduction: In the primary analysis of the phase 3 MAIA trial (NCT02252172), daratumumab, lenalidomide and dexamethasone (D-Rd) improved progression-free survival (PFS) in transplant-ineligible (TIE) patients with newly diagnosed multiple myeloma (NDMM) vs Rd. With longer follow-up (median: 56.2 months), D-Rd continued to demonstrate PFS benefit, conferred an overall survival benefit, induced deeper responses, and was associated with clinically meaningful improvements in patient-reported outcomes (PROs) vs Rd. The median age of these patients was 73 years with 43.6% of patients aged ≥75 years. Consistent with the overall population, in a frailty subgroup analysis (median age: 77 years), D-Rd also demonstrated deeper responses and PFS benefit vs Rd (not reached vs 30.4 months; HR, 0.62; P = 0.003) in frail patients at a median follow-up of 36.4 months.

Although, D-Rd improved clinical outcomes in these elderly frail patients, little is known about health-related quality of life (HRQoL) outcomes. In frail patients, improving HRQoL and minimizing the risk of toxicity is paramount. Here, we assess PROs in the frail patients in the MAIA trial.
Methods: Patients were randomized 1:1 to D-Rd or Rd until disease progression (PD) or unacceptable toxicity. Frailty was assessed using the simplified frailty score. PROs were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item. Questionnaires were completed at baseline, on day 1 of cycles 3, 6, 9, and 12 for year 1, and every 6 months thereafter until PD. Analyses were conducted on intent-to-treat patients. Treatment effect was assessed for change from baseline by a mixed-effects model for repeated measures. Meaningful thresholds for worsening were defined a priori based on published literature.
Results: Overall, 737 patients were randomized; 341 patients were classified as frail (D-Rd, n=172; Rd, n=169). Over time, frail patients treated with D-Rd showed large reductions in pain from baseline (≥20-point change) and were greater with D-Rd than Rd. Fatigue symptoms were moderately reduced with both treatments. Increases in global health status (GHS) were consistent over time for both treatment groups. Patients treated with D-Rd showed improvements from baseline in physical functioning that were greater than Rd until cycle 42 and increases in emotional and social functioning were seen with both treatments that were numerically greater with D-Rd at several time points. Improvements in role functioning were seen with both treatments with no difference between treatments. No meaningful changes from baseline were observed in nausea and vomiting with either treatment. Median time to first worsening was longer with D-Rd than Rd for GHS. Median time to first worsening for the other functional (emotional, social, role) and symptom (nausea and vomiting) scales numerically favored D-Rd vs Rd, except cognitive functioning and fatigue. Median time to worsening of pain symptoms was not reached for D-Rd.
Conclusions: Frail TIE patients with NDMM treated with D-Rd reported improvements in GHS (an overall HRQoL measure) and physical functioning, with a notable reduction in pain from baseline throughout the duration of therapy. D-Rd is not only clinically effective but also results in a sustained improvement in HRQoL for frail TIE patients with NDMM.

P17 CLONAL PLASMA-CELLS IN STEM CELL APHERESIS AS A PREDICTOR OF PROGRESSION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS ELEGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION

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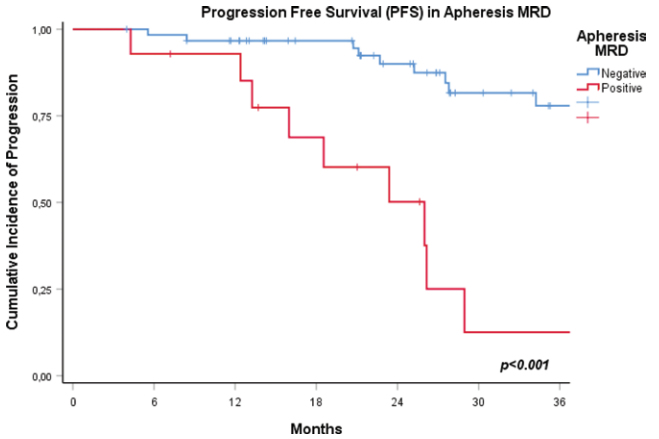
Background: Flow-cytometry is considered crucial for monitoring multiple myeloma (MM) patients, in particularly for evaluation of minimal residual disease (MRD) [1]. Routinely MRD on bone marrow aspirate is the optimal method for assessing depth of response and identifying higher risk of relapse [2]. There are also emerging data about the prognostic role of peripheral plasmacell count on flow-cytometry at diagnosis of MM and after treatment [3]. However, so far limited information is available on the use of flow cytometric MRD for the research of clonal plasma cells on stem cell apheresis as well as its clinical significance.
Aim: Our purpose is to determine whether the contamination of apheresis product with clonal plasma cells predicts the risk of MM disease progression or impacts on patients' overall survival (OS).
Methods: We retrospectively analysed 75 newly MM patients diagnosed at our Center between July 2017 and November 2021. The multiparameter flow cytometry, with a sensitivity of 10(-5), was applied after induction therapy on both bone marrow samples and on apheresis product in order to evaluate the MRD status.
Results: The median age was 60 years and all the patients were treated with triplet induction regimens (89% VTD, 5% VRD, 4% KRD, 2% PAD), followed by autologous stem cell transplantation (ASCT). Stem cell harvest was performed following cyclophosphamide and G-CSF mobilization. Sixty-two patients (91%) received maintenance therapy with lenalidomide and 6 (8%) with daratumumab. Among 75 patients included in the study, 64% and 36% of them achieved MRD positivity and negativity on bone marrow (mMRD), respectively. MRD status on apheresis (aMRD) was negative in 61 patients (81%) and positive in 14 (19%). All patients with positive aMRD had a concomitant mMRD positivity. The median follow-up was 28 months (range, 7 to 58) and progression free survival (PFS) at 24 months was 90% (95% confidence interval [CI], 86 to 94) versus 50% (95% CI, 35 to 65) for the patients aMRD-negative versus those aMRD-positive, respectively ($p < 0.001$). The OS at 24 months was 98% (95% CI, 96 to 100) in the aMRD negative cases and 74% (95% CI, 61 to 87) in the aMRD-positive (p=0.007). According to mMRD status, PFS at 24 months was 94% (95% CI, 88 to 100) and 75% (95% CI, 68 to 82) in the mMRD negative and positive, respectively (p=0.16). There was no statistically significant difference between the two groups according to other prognostic factors (ISS disease stage and cytogenetic profile) and maintenance therapy. Univariate analysis identified only the aMRD positivity as risk factor for reduced PFS.
Conclusion: PFS data showed that the rate of progression was higher in the group of aMRD- positive patients, suggesting a potential deleterious role for graft contamination. Instead, mMRD status had not a significant impact on PFS. These results need to be confirmed in a larger prospective study with quadruplet induction regimen daratumumab-based, in order to provide a larger applicability of aMRD monitoring.



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P18 SKIN EXPRESSION OF P16^{INK4A}, A BIOMARKER FOR CELLULAR SENESCENCE, DOES NOT PREDICT FRAILTY OR TREATMENT OUTCOME IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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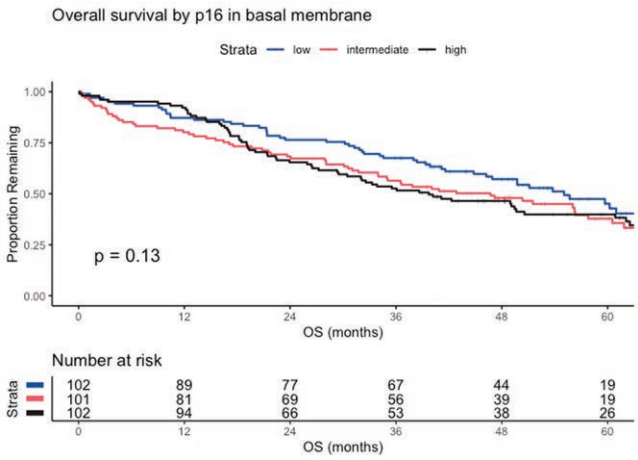
Introduction: The clinical outcome of older patients with multiple myeloma (MM) is heterogeneous, largely depending on frailty level. To assess frailty, clinical scores such as the International Myeloma Working Group frailty index (IMWG-FI) are used to distinguish between 'fit', 'intermediate-fit' and 'frail' patients. However, as the discriminative power of these scores is still insufficient to guide treatment choices, there is an unmet need for novel biomarkers that reflect biological age ('frailty') – rather than chronological age. The cell cycle regulator and tumor suppressor p16^{INK4a} has been found to be a robust biomarker of cellular senescence and aging. Previous studies showed that p16^{INK4a} markedly increases with age and p16^{INK4a} inactivation partially reverses age-related phenotypes. p16^{INK4a} positive cells in skin biopsies have also been found to be reflective of a person's biological age. We therefore investigated whether p16^{INK4a} expression in the skin is associated with

frailty and could predict treatment outcomes in older patients with Newly Diagnosed Multiple Myeloma (NDMM).
Methods: We evaluated $p16^{INK4a}$ expression in skin biopsies taken at baseline from newly diagnosed MM patients who were included in two prospective trials: the HOVON 123 and HOVON 143 study, including intermediate-fit and frail patients based on the IMWG-FI. Before start of treatment, biopsies were obtained from non-sun exposed skin (area above the bone marrow aspirate site at the posterior iliac crest). $p16^{INK4a}$ expression was defined as two variables: the number of $p16^{INK4a}$ positive cells 1) in the basal membrane, normalized to length of the basal membrane (mm) and 2) in the entire epidermis, normalized to the surface of the epidermis (mm^2). Because $p16^{INK4a}$ positivity was not normally distributed, $p16^{INK4a}$ positivity was classified in tertiles (low < 0.93/mm, intermediate 0.93 – 3.03/mm, high > 3.03/mm). Statistical analysis was performed using the Wilcoxon signed-rank test and univariate Cox regression.
Results: Prior to treatment initiation skin biopsies were obtained from 305 NDMM patients with a median age of 78 years (range 65 – 92). Median number of $p16^{INK4a}$ positive cells in the basal membrane was 1.75 per mm (range 0 – 30.8/mm) and 41.5/mm^2 (range 0 – 850.5/mm^2) in the epidermis. We found no significant difference in $p16^{INK4a}$ positivity in the basal membrane (1.55/mm vs 1.96/mm; p=0.26) or in the epidermis (38.0/mm^2 vs 48.5/mm^2; p=0.20) between the intermediate-fit and frail patients. Moreover, $p16^{INK4a}$ expression was not associated with progression free survival or overall survival (Figure 1).
Conclusion: $p16^{INK4a}$ expression in the skin is not associated with frailty level or treatment outcome in intermediate fit and frail NDMM patients. Recent literature suggests that $p16^{INK4a}$ mRNA expression in peripheral T cells could be a more accurate marker for cellular senescence. Based on our results, we discourage the evaluation of $p16^{INK4a}$ protein levels in skin biopsies to improve frailty assessment in older patients with newly diagnosed MM.



P19 EXTERNAL VALIDATION OF THREE EXISTING EARLY MYELOMA RELAPSE SCORES (BY EBMT, CIBMTR, AND GIMEMA) IN A SINGLE CENTER SHOWS MAJOR DIFFERENCES

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Introduction: Despite progress in induction regimens, early relapse of multiple myeloma (MM) following autologous hematopoietic cell transplantation (AHCT) is still a frequent complication that confers poor prognosis. Recently, three groups (CIBMTR, GIMEMA (S-ERMM), and EBMT) have published scoring systems to predict early relapse. In this retrospective analysis, we aimed to validate and compare these novel scores in a homogenous population treated in a single center.
Methods: This retrospective study included 410 consecutive newly diagnosed myeloma patients treated in Ankara University, all of whom received 3-8 cycles (median 4) of mostly (69.5%) bortezomib based doublet or triplet (VCD) regimens prior to AHCT with Mel200 from October 2005 to January 2021, with a minimum follow-up of ≥12 months after ASCT. Consolidation was administered until CR; maintenance was not standard unless high-risk disease was detected at diagnosis. No tandem transplants were included.
Results: The median age of all patients in the analysis was 62 years (36-83 years), and female/male:43.4%/56.6%. In our cohort, 60 (19.5%) patients received consolidation while maintenance treatment was given to 108 (26.3%) patients. The median follow-up after AHCT for all patients is 38.4 m (12-156 m) and 82 patients (20%) have relapsed within 12 months. The characteristics and distribution of the patients within scoring groups are shown in Table. Neither pre- nor post-AHCT response alone or FISH findings were associated with early relapse. With EBMT scoring (which encompasses ISS, response, and performance status at the time of AHCT), early relapse was observed among Score 0 (1.4%) and 1(12.6%), CIBMTR low (13.4%) and S-ERMM low-risk (14.4%) scores showing the EBMT score 0 to recognize very low risk better than CIBMTR and GIMEMA models. Likewise, EBMT score 3(36.3%) and 4(56.3%) compared to CIBMTR high (17.6%), S-ERMM high (43.7%) point to EBMT score 5 to recognize early relapse risk the best. Similarly, "no relapse risk" distribution across risk groups points to EBMT score 0, to recognize very good patients best compared to "low risk" with CIBMTR or S-ERMM scores. The Hazard Risk for early relapse was also the highest and most significant within EBMT scores: 3.4 (95% CI, 1.9-6.6; S-ERMM high vs low; p<0.001), 5.6 (95% CI, 3.1-10.4; EBMT score 3-4 vs. 0-1; p<0.001), and 1.3 (95% CI, 0.4-4.5; CIBMTR high vs low p=NS). The impact of scores on PFS are shown in Figure-1.
Conclusion: Efforts are ongoing on prediction models of early relapse. S-ERMM and CIBMTR scores are either limited to specific populations based on induction/conditioning or parameters not applicable to daily practice worldwide. EBMT score presented at ASH 2021 (Beksac et al.) differs from earlier scores by being based on a large real-world frequently used triplet induction and conditioning regimen dataset. In this analysis, we attempted to validate the EBMT, CIBMTR, and S-ERMM scoring models in an external cohort, demonstrating that the EBMT is a reliable tool that recognizes very low and very high-risk patients at the time of AHCT prior to the onset of clinical relapse. In the future, with the introduction of molecular features, this prototype model may be improved.

P20 LENALIDOMIDE MAINTENANCE AFTER VTD INDUCTION AND AUTOLOGOUS STEM CELL TRANSPLANTATION: PRELIMINARY RESULTS OF A REAL-LIFE STUDY INCLUDING 389 PATIENTS

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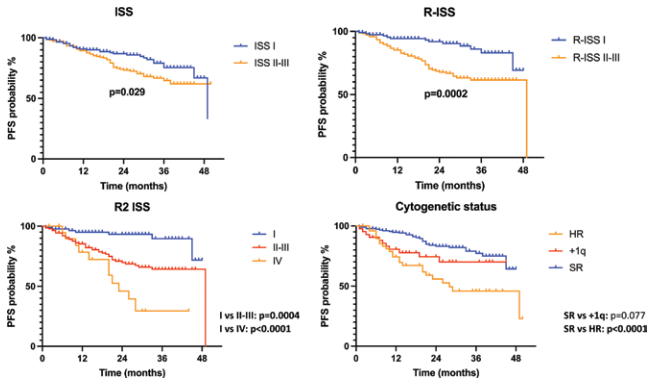
According to 2021 ESMO guidelines, treatment of newly diagnosed (ND) transplant eligible (TE) Multiple Myeloma (MM) patients is settled by an induction phase followed by single or tandem autologous stem cell transplantation (ASCT) and Lenalidomide (Len) maintenance. Before the recent approval of daratumumab-bortezomib-thalidomide-dexamethasone (D-VTD) regimen, VTD induction followed by ASCT and Len maintenance was the standard of care in Italy for ND TE MM patients, however no single perspective trial evaluated this combination overall.

In this context, the aim of this real-life study was to evaluate the efficacy and the safety of Len maintenance after VTD plus ASCT in ND TE MM patients.
The study cohort included 389 patients (median age 60 years) followed in 17 referral centers. Baseline features included ISS III in 67/352 cases (19%), R-ISS III in 28/296 cases (9.5%) and R2-ISS IV in 21/254 cases (8.3%). FISH analysis was available in 306 patients and 50 of them (16.3%) displayed high risk (HR) alterations [including t(4;14), t(14,16) and del17p]. Among the 256 standard risk patients, information about 1q status was available for 230 of them, with 43 patients harboring +1q abnormalities (18.7%). All patients received VTD induction (median number of cycles 4) and single or tandem ASCT was performed in 60.9% and 39.1% of cases, respectively.
A median number of 21 cycles of Len maintenance was administered. Complete response (CR) and stringent CR (sCR) rates before starting Len were 28.3% and 15.9%, respectively (overall 44.2%) and increased with maintenance to 36.2% and 19.8%, respectively (overall 56%). Most importantly 2 years CR and sCR rates in evaluable patients were superimposable (38.6% and 22.3% respectively, 60.9% overall). Ninety-seven patients (24.9%) discontinued treatment, mostly due to progressive disease (83/97, 85.6%).
Toxicities were mostly hematological with neutropenia found in 48.8% of cases (grade 3-4 in 20.3%), followed by thrombocytopenia and anemia in 22.9% and 18%of cases, respectively (grade 3-4 in 2.8% and 1.8% of cases, respectively). Non hematological adverse events were primarily gastrointestinal (26.5%, grade 3-4 in 2.6%) and infections (23.4%, grade 3-4 in 3.6%) while skin related disorders affected 9% of patients.
With a median follow up of 26 months, the 2 years PFS and OS from starting maintenance were 79.5% and 96.5%, respectively. No significant PFS differences were found according to age (>65 years vs < or =65 years, p=0.6581) or ASCT (single vs tandem, p=0.4528). Patients with low-risk disease including ISS I and R-ISS I showed improved PFS as compared to patients with ISS >I and R-ISS >I (2y PFS 86.8% vs 73.3%, p=0.029 and 91.9% vs 67.6%, p=0.0002. respectively). By R2-ISS, low risk disease (R2-ISS I) confirmed a better outcome as compared to R2-ISS II-III (2y PFS 93.3% vs 69.7%, p=0.0004) and to R2-ISS IV (2y PFS 45%, p<0.0001). Finally, considering cytogenetic risk status, standard risk patients displayed a significantly prolonged PFS as compared to high-risk patients (2y PFS 83.1 % vs 52.7%, p<0.0001) and an improved although not significant outcome than patients harboring isolated +1q (2y PFS 74.4%, p=0.077) (Figure 1).
To our knowledge, this is the first study evaluating the safety and efficacy of Len maintenance after VTD plus ASCT. Our results provide evidence that patients with clinical and biological low risk disease benefit the most from Len maintenance with a favorable safety profile.

Figure 1



P21 EFFECTIVENESS AND SAFETY OF DELAYED BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE (VTD) REGIMEN

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Bortezomib, thalidomide, and dexamethasone (VTD) plus autologous stem cell transplantation has been the standard treatment in Europe for transplant-eligible (TE) patients (pt) with newly diagnosed multiple myeloma (NDMM) until monoclonal antibody daratumumab has been added. Approval of the triplet comes from GIMEMA-MMY-3006 clinical trials (four 3-week cycles of bortezomib 1.3 mg/m2 on days 1, 4, 8, and 11; thalidomide 100 mg daily; dexamethasone 40 mg days 1 -4 and 9-12). However, some pt discontinue VTD because of severe adverse events (AE), despite its efficacy. In this real-life survey, we retrospectively evaluated the effectiveness and side effects of a delayed VTD regimen (dVTD) compared to standard VTD (sVTD) in TE NDMM patients. 74 pt were treated between 08/08/2016 and 31/07/2022 with VTD schema. sVTD was administered to 31 pt as in the trial (bortezomib on days 1-4-8-11). dVTD was administered to 43 pt with bortezomib on days 1, 8, 15 and 22 of 28-days cycles. Pt' clinical characteristics are described in Table 1. In the sVTD group, 5 patients (16%) had one or more G3/G4 AE: among them 1 thrombocytopenia, 3 neutropenia and none G3/4 non-hematological AE. Hematological AE occurred in 50% of pt (N=15), and were anemia, thrombocytopenia and neutropenia. Six pt had G2/3 neutropenia (19.5%) resolved with granulocyte growth factors (GCSF). All cases of anemia were G1. One pt with thrombocytopenia needed transfusion. The rate of infections was 10% (N= 3) and included one case of G2 upper respiratory tract infection and two cases of G1 cystitis, resolved with antibiotic therapy. Peripheral neuropathy occurred in 10% of pt (N=3, 2 G1 cases and 1 G2) and skin changes (G1) in one case. In the dVTD group there were no G3/G4 AE. Hematological AE occurred in 9 pt (21%, G1-2). Anemia was found in 4 pt (9%, G2 only in one case, 2 cases treated with erythropoietin). Neutropenia occurred in 4 pt (9%), G2 only in one case treated with GCSF. G1 thrombocytopenia occurred in one pt (2,4%), peripheral neuropathy in 5 pt (12%), cutaneous rush in 4 pt (9%). None of pt belonging to dVTD or sVTD group had to discontinue treatment for toxicities. In sVTD group the responses after induction therapy were CR in 7 pt, VGPR in 16 pt, PR in 5 pt, PD in 3 pt with improvement after transplantation with 13 pt in CR, 10 pt in VGPR (Table 2). During follow up 12 pt progressed and underwent a second line treatment and 3 pt died for PD.
In dVTD group the responses after induction therapy were CR in 6 pt, VGPR in 17 pt, PR in 17 pt, MR in 2 pt.
After transplantation: 16 pt in CR, 18 pt in VGPR, 4 pt in PR, 1 pt in SD and 1 in PD. During follow up 14 pt progressed and underwent a second line treatment and 5 pt died for PD. Median PFS was 81 months in sVTD group ando not reached in dVTD (p=0.496).
Median overall survival was 66 months for dVTD group and not reached for sVTD group (p=0.186). The current standard of care for NDMM pt is the combination of daratumumab with VTD. The schedule includes bortezomib on days 1-4-8-11 However, this schedule represents a discomfort for the patient mostrly for accesses to the hospital twice a week. Our findings suggest that delayed VTD is not inferior in safety and efficacy to standard VTD regimen. Using a delayed schema we achieved better patient compliance with a comparable toxicity profile, without worsening the efficacy and the survival curves. These data may support the use of the same schedule in combination with daratumumab.

TABLE 1

	dVTd (43)	sVTD (31)
Age		
Median range male	41 - 70	43 - 72
Median range female	43-66	43-61
Gender		
Male, N (%)	22 (51%)	19 (61%)
Female, N (%)	21 (49%)	12 (39%)
Paraprotein (isotype)		
IgG-k	20 (46%)	9 (29%)
IgG-L	9 (21%)	5 (16%)
IgA-k	6 (14%)	2 (6.5%)
IgA-L	1 (2%)	2 (6.5%)
Macromolecular k	3 (7%)	7 (22.5%)
Micromolecular lambda	3 (7%)	6 (19.5%)
Others	2 (4%)	0 (0%)
ISS stage at baseline		
I, N (%)	23 (53%)	5 (16%)
II, N (%)	8 (19%)	15 (48.5%)
III, N (%)	13 (30%	11 (35.5%)

(*Continued*)

TABLE 1
(*Continued*)

	dVTd (43)	sVTD (31)
Cytogenetics risk		
High, N (%)	9 (21%)	6 (19.5%)
Standard, N (%)	21 (49%)	20 (64.5%)
Not Evaluable	13 (30%)	5 (16%)
Creatinine clearance		
< 50 ml/min/m2	6 (14%)	9 (29%)
>50 ml/min/m2	39 (86%)	22 (71%)
Bone Lesions		
No one, N (%)	**3 (7%)**	**8 (26%)**
More than 1, N (%)	**40 (93%)**	**23 (74%)**
Extramedullary lesions		
Yes, N (%)	6 (14%)	6 (19.5%)
No, N (%)	37 (86%)	25 (80.5%)
Bone Marrow Involvement		
<60%, N (%)	28 (63%)	18 (58%)
≥60%, N (%)	8 (16%)	13 (42%)
Missed, N (%)	7 (16%)	0 (0%)
LDH		
Normal, N (%)	39 (90%)	27 (87%)
Increased N (%)	4 (10%)	4 (13%)

P22 THE PROGNOSTIC ROLE OF 1Q ABNORMALITIES IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS

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Background: Additional copies of chromosome 1q (+1q) is one of the most common cytogenetic abnormalities in multiple myeloma, with a frequency in newly diagnosed patients (NDMM) around 30-50%. However, its prognostic impact is still debated, since not all studies support an adverse outcome associated with +1q.
Methods: In our observational retrospective study we evaluated 157 consecutive patients with NDMM between September 1, 2017 and December 31, 2020, treated at AOU Careggi Hospital in Florence. All the cytogenetic analysis were performed by fluorescence in situ hybridization (FISH), including probes for 1q abnormalities.
Results: The median age in our cohort was 65, M/F=78/79. Fifty-seven patients (36.3%) had +1q abnormalities: 42 (26.7%) had 3 copies of 1q (gain 1q) and 15 (9.5%) ≥4 copies of 1q (amp1q). Patients with +1q had more frequent a concomitant high risk cytogenetic feature (26% vs 13%, p= 0,03), in particular t(4;14). The presence of additional copies of chr 1q was associated with female sex (33.3% vs 66.7%, p= 0,005), older age (median 64 vs 69), higher tumor burden (≥ 60% of plasma cells in the bone marrow, p< 0,001) and anemia (p= 0,029). There was no statistically significant difference in ISS and R-ISS classification; instead, more patients with +1q had high and intermediate-high risk disease, according to R2-ISS stratification (p< 0,001).
We evaluated PFS and OS of the entire cohort after a median follow-up of 38 months: no statistically significant difference emerged in PFS and OS, between +1q patients and those without +1q. Within the cohort, 84 patients (53.5%) were eligible for autologous stem cell transplant (ASCT) and received induction with proteasome inhibitor-based therapy (i.e., VTD and VCD). Among this group the presence of +1q was, instead, associated to a reduced PFS (median PFS 40 months vs NR; p= 0,05) and OS (median OS 60 months vs NR, p= 0,009); also confirmed in multivariate analysis (p= 0,02). Moreover, 12 patients in this group eventually did not undergo transplant, due to HSC collection failure or onset of acute comorbidities; a subgroup analysis showed a worse outcome of their PFS and OS, compared to the ones who received high dose chemotherapy and HSC rescue (p< 0,001). The other 73 (46.5%) patients were ineligible for high dose chemotherapy and received predominantly bortezomib-based (VMP or VD; 59%) or lenalidomide-based treatment (Rd, 37%). The PFS and OS analysis has not revealed a significant negative impact of +1q in this group. Even if not statistically significant, a sub stratification according to different therapies in this category showed a trend of better PFS outcome for +1q patients treated with lenalidomide.
Conclusions: In our study cohort +1q was associated to unfavorable outcome in patients eligible for ASCT, with only a partial reduction of this negative impact by high-dose chemotherapy. On the contrary, in older patient +1q has not proven to be an independent marker of poor prognosis, possibly due to a less intensive treatment and concomitant comorbidities which contributes to a generally reduced PFS and OS compared to the younger population.

P23 *EM*AGINE/CARTITUDE-6: A RANDOMIZED PHASE 3 STUDY OF DVRD FOLLOWED BY CILTACABTAGENE AUTOLEUCEL VERSUS DVRD FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANT IN TRANSPLANT-ELIGIBLE PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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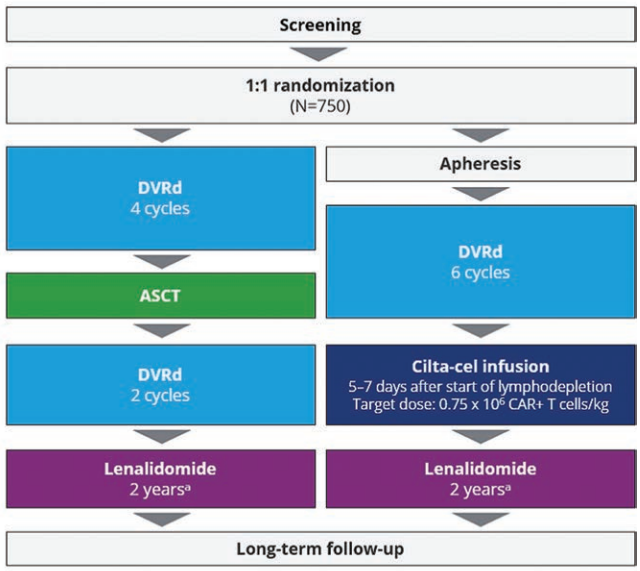
Background: Guidelines from the National Comprehensive Cancer Network recommend daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) as induction therapy followed by autologous stem cell transplant (ASCT), consolidation, and maintenance therapy for transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). In the phase 1b/2 CARTITUDE-1 study, a single infusion of ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor (CAR)-T cell therapy with two B-cell maturation antigen (BCMA)-targeting single-domain antibodies, resulted in deep and durable responses with manageable safety in heavily pretreated patients with relapsed/refractory multiple myeloma. The overall response rate (ORR) was 98% (median follow-up of 27.7 months), with 83% of patients achieving stringent complete response (CR); median duration of response was not reached. The aim of this open-label, multicenter, global, phase 3 *EM*agine/CARTITUDE-6 study (EMN28/68284528MMY3005; NCT05257083) is to evaluate the efficacy of DVRd followed by cilta-cel and lenalidomide versus DVRd followed by ASCT, DVRd, and lenalidomide.
Study design and methods: Patients aged ≥18 years with NDMM (per International Myeloma Working Group criteria), measurable disease at screening, and high-dose therapy and ASCT as part of their intended initial treatment plan are eligible. Patients are excluded if they received any prior therapy for multiple myeloma or smoldering myeloma, except a short course of corticosteroids. After providing informed consent, patients are randomized (1:1) into 2 treatment arms, with target recruitment of N=750. In the cilta-cel arm, patients will undergo apheresis before receiving 6 cycles of DVRd induction treatment. After induction, patients will first receive lymphodepletion (intravenous cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 daily for 3 days), and then a single infusion of cilta-cel (target dose 0.75×10^6 CAR+ viable T cells/kg) 5–7 days later. Following cilta-cel infusion, patients will be given lenalidomide post CAR-T therapy for 2 years (or longer, per investigator discretion). The patients in control arm will receive 4 cycles of DVRd induction, then ASCT and 2 cycles of DVRd consolidation, followed by lenalidomide maintenance therapy for 2 years (or longer, per investigator discretion). Dual primary endpoints are progression-free survival (PFS) and minimal residual disease (MRD)-negative CR sustained for ≥12 months. MRD status is assessed by next-generation sequencing at a sensitivity of at least 10^{-5}. The secondary endpoints include ORR, ≥CR rate, overall MRD-negative CR rate, time to subsequent therapy, PFS on next-line therapy, overall survival, adverse events, pharmacokinetic/pharmacodynamic markers, and health-related quality of life. Exploratory correlative biomarker analyses will also be conducted. Enrollment began in September 2022, with expected primary completion in June 2026. This study will

explore a cellular therapy approach with cilta-cel versus standard of care ASCT in transplant-eligible patients with NDMM.

Figure: *EM*agine/CARTITUDE-6 Study Design



[a]Patients benefiting from therapy have the option to continue lenalidomide therapy until progressive disease per investigator's discretion after benefit-risk assessment and review by the medical monitor.

P24 HIGH-DOSE CYCLOPHOSPHAMIDE 4 GR/M2 AND STEM-CELL COLLECTION AFTER DARATUMUMAB-BASED QUADRUPLET INDUCTION IN NEWLY DIAGNOSED TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA PATIENTS: A SINGLE-CENTER EXPERIENCE

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Background: quadruplet induction with Daratumumab/Bortezomib/Thalidomide/Dexamethasone (Dara-VTd) has become the standard treatment for transplant-eligible newly diagnosed multiple myeloma patients (NDMM). Despite improved response rates, concerns with stem-cell mobilization and collection emerged in CASSIOPEIA trial. Following high-dose cyclophosphamide (HD-CTX) ranging 2 to 3 gr/m2 and granulocyte colony-stimulating factor (G-CSF) 10 µg/kg/day, a greater use of Plerixafor and a lower total number of CD34+cells/Kg collected per patient compared to VTd were reported.

Methods: after Dara-VTd induction, NDMM received inpatient HD-CTX 4 gr/m2 followed by G-CSF 5 µg/kg/day starting on day +2 from HD-CTX until last day of collection, as per institutional practice. Plerixafor was administered on demand in patients with <20 CD34+cells/µl on day of planned leukapheresis or in those predicted as poor mobilizer per institutional practice. Main parameters considered on first day of leukapheresis were: patient body weight (kg)/ CD34+cells/µl ratio and peripheral white blood cells/µl/ CD34+cells/µl ratio. Pre-planned total target dose was $10x10^6$ CD34+cells/Kg for multiple autologous stem-cell transplantation (ASCT).

Results: from 1st December 2021 to 31st December 2022, 45 NDMM received Dara-VTd at our institution. 23 patients completed induction and were included in this analysis (Figure 1). At diagnosis median age was 62 years (range: 39-70), 17% were ISS III, 13% were R-ISS III and 48% were R2-ISS III-IV. 15 patients (65%) had high-risk cytogenetic abnormalities as del17p13, gain1q21, t(4;14), t(14;16) and t(14;20). After a median of 4 Dara-VTd cycle (range: 4-6) overall response rate was 96%, with 43% VGPR and 35% sCR. 1 patient progressed after 4th cycle. Thalidomide and Bortezomib were reduced in 70% and 17% of patients, respectively. After a median of 135 days (range: 113-190) from start of induction, 22 patients received HD-CTX. No relevant grade 3-4 adverse events were reported. After a median of 11 days (range: 9-13) 22/22 patients underwent leukapheresis; 48% received Plerixafor. Twenty-one patients completed stem-cell collection, harvesting a mean total amount of 10,11 x106 CD34+cells/kg (range: 7,6-14,8) (Table 1). One patient discontinued mobilization due to concomitant Sars-Cov2 infection. Unfortunately both subsequent rescue attempts with chemo-free G-CSF 10 µg/kg/day + Plerixafor and then CTX 2 gr/m2 + G-CSF 10 µg/kg/day + Plerixafor failed. One patient progressed soon after leukapheresis. After a median of 201 days from start of induction (range: 168-283), 15/23 (65%) NDMM patients and 15/21 (71%) of those who completed leukapheresis already underwent ASCT. Mean number of infused CD34+cells was 5,16 x106/kg (range: 3,59-9,86). All patient obtained stable neutrophils and platelets engraftments after a median of 12 days (range: 9-14) and 16 days (range: 13-19), respectively. No relevant toxicities were reported. At last follow up, all patients were alive.

Conclusions: after Dara-VTd induction in NDMM, mobilization with HD-CTX 4 gr/m2 and G-CSF 5 µg/kg/day proved feasible and effective in a real-life setting. High incidence of poor mobilizers in Daratumumab-exposed patients was confirmed in our experience. Nonetheless, greater dose of CTX compared to CASSIOPIEA trial together with on-demand and patient-tailored usage of Plerixafor allowed high number of stem-cell collection per patient sufficient for multiple ASCT and favorable transplantation outcomes.

Figure 1. Profile of analyzed population

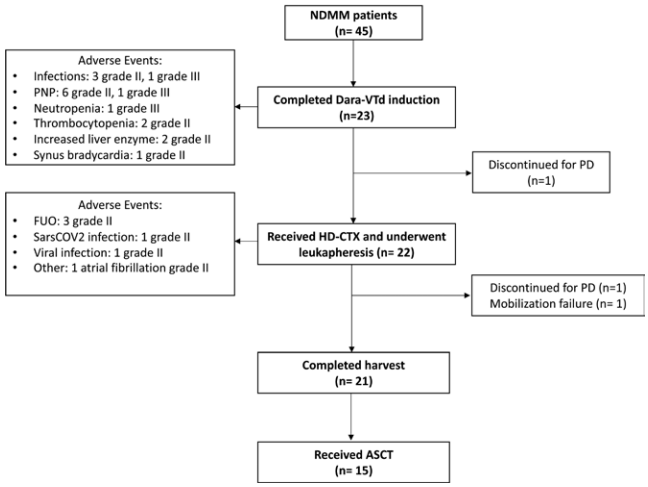

Table 1. Characteristics of stem-cell mobilization and harvesting.	
Days from start of induction to HD-CTX: median (range)	135 (113-190)
Days from last daratumumab to HD-CTX: median (range)	32 (21-53)
Days from HD-CTX to first day of leukapheresis: median (range)	11 (9-13)
Peripheral white blood cells/µl on first day of leukapheresis: median (range)	16.500 (3.600 -67.000)
Peripheral CD34+cells/µl on first day of leukapheresis: median (range)	63.1 (8-153)
Total number of leukapheresis days: median (range)	2 (1-2)
Plerixafor use: number (%)	11 (48%)
Body weight (kg) / CD34+cells/µl ratio in patients who received Plerixafor: median (range)	1.72 (0.6-6.25)
Peripheral white blood cells/µl / CD34+cells/µl ratio in patients who received Plerixafor: median (range)	0.44 (0.21-1)
Amount of CD34+cells $x10^6$/kg collected per patient: mean (range) – Day 1 – Day 2 – Total	 6,51 (1,4-12,9) 5,60 (3,2-10) 10,11 (7,6-14-8)
Collection efficiency: mean (range) – Day 1 – Day 2	 58% (18-83) 71% (43-100)
Total blood volume processed (liter): mean (range)	5,02 (2,5-9,6)

P25 EFFECT OF DARATUMUMAB ON STEM CELL YIELDS IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA: REPORT FROM THE MULTIPLE MYELOMA LAZIO GROUP

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High dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard of care therapy for newly diagnosed multiple myeloma (NDMM) patients (pts).

The anti-CD38 IgG1-k monoclonal antibody daratumumab (dara) demonstrated to improve depth and duration of response in transplant eligible MM pts when added to the standard of care induction regimen. Recent studies have indicated a potential reduction in stem cell yields in MM pts exposed to dara prior to stem cell mobilization.

We retrospectively evaluated 51 pts with NDMM managed at 8 Italian Hematology Centers who underwent induction therapy based on dara-bortezomib, thalidomide and dexamethasone (D-VTD) between November 2021 and July 2022. Following induction, pts underwent mobilization therapy as per institutional guidelines.

The primary endpoint of this study is to investigate the possible impact of dara on stem cell yields with mobilization therapy and to identify possible features that affect stem cell yields.

Fifty-one pts were included in the analysis. The median age was 60 (range: 54-64); 65% were male; 49% of pts were stage I, and 37% were stage II, according to the International Staging System (ISS) and the Revised- ISS, respectively. Forty-eight pts (94%) received 4 cycles of D-VTD as induction therapy after mobilization therapy. The baseline clinical characteristics and the frontline induction therapy were summarized in Table 1. Globally, 48 out of 51 pts (94%) analyzed, met the collection goal after mobilization therapy, however, for 3 pts (6%) a second mobilization attempt was required. In addition, for another 3 pts (6%) a third mobilization attempt was needed. In the majority of pts (92%), a combination of cyclophosphamide with granulocyte colony stimulating factor was used as the first mobilizing regimen attempt. Plerixafor on demand was administered during stem cell mobilization in 15/51 pts (32%) failing to achieve the desired collection goals, confirming that a higher use of plerixafor was necessary in the dara-based induction therapy, as previously reported1. Specifically, 14 out of 15 pts (99%) met the collection goal at the first mobilization therapy attempt receiving plerixafor on demand, and most of these pts (71%) received only one dose of plerixafor. The majority of the pts who did not meet the goal in one apheresis procedure were able to meet the goal with 1 (64%) or 2 (10%) additional procedures. The median number of CD34+ stem cells collection yield was 8 x 106 cells/Kg (range: 1.4-16). The median time between the last day of induction therapy and the first day of mobilization therapy was 31 days (range: 25-45). Univariate analysis showed that a higher level of baseline LDH was associated with a lower rate of collection goal, after the first mobilization attempt (p=0.017). Pts with a median lower pre-mobilization therapy level of neutrophils and platelets showed a significantly lower rate of collection goal after the first mobilization attempt (p=0.013 and p=0.035, respectively), possibly due to prolonged hematological toxicity after induction therapy. On introducing dara to the induction treatment, we observed that a higher use of plerixafor and more days of apheresis procedures are required to meet the collection goal at the first mobilization attempt. A larger cohort of pts are needed to confirm our results and to evaluate a new mobilization therapy schedule to guarantee adequate stem cell yields.

1] Hulin C et al. Haematologica 2021

Table 1

Baseline patient's clinical characteristics and the frontline induction therapy

Characteristics	Patients (N= 51)	%
Gender		
Male	33	65
Female	18	35
Age (years)		
Median (range)	60 (54-64)	
Type of Heavy chain		
G	31	62
A	11	22
Absent	8	16
Type of Light chain		
type	35	71
κ	16	29
λ		
ISS		
I	25	49
II	15	29
III	11	22
Cytogenetic		
abnormalities, n (%)	23	43
High risk	20	39
Standard risk	8	16
Not evaluable/missing		
CRAB		
Hypercalcemia	10	20
Renal insufficiency	5	10
Anemia	19	38
Osteolytic bone lesions	45	88
R-ISS		
I	17	37
II	19	41
III	10	22
NA	5	13
Response after		
induction therapy	7	14
sCR	9	18
CR	28	55
VGPR	7	14
PR		
Cycle of induction		
therapy, n (%)	48	94
4	3	6
2		
Bone marrow plasma		
cell infiltration	60 (38-74)	
Median (range)		
Bone marrow function		
pre-mobilization	13.2 (12.25-13.90)	
therapy, median (range)	222 (170-298)	
Hb, g/dl	2580 (1865-3905)	
Platelets, mm^3		
Neutrophils, mm^3		
Induction therapy		
toxicity	1	2
Haematological	2	4
Anemia	4	8
Thrombocytopenia	14	27
Leucopenia	1	2
Non-Haematological	7	14
Neuropahty	3	6
Infections	2	4
Gastroenteric		
Skin rash		
Cardiac		

P26 LANDSCAPE OF RECURRENT CYTOGENETIC ABNORMALITIES IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA AS DETECTED BY CHROMOSOME MICROARRAY ANALYSIS (CMA)

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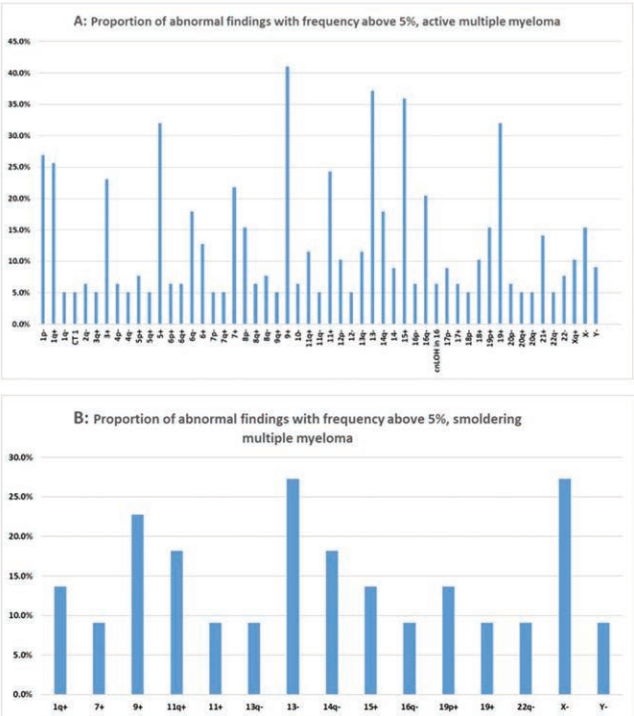
Background: Multiple myeloma (MM) is a plasma cell neoplasm clinically ranging from indolent to aggressive, and characterized by heterogeneous genetic makeup. Cytogenetic abnormalities play important role in myeloma tumorigenicity, and some recurrent abnormalities are known to have prognostic significance. Low proliferative rate of plasma cells limits the yield of conventional cytogenetics. Fluorescent in situ hybridization (FISH) performed on CD138 enriched sample is current standard for detection of clinically significant cytogenetic abnormalities, however it is limited by use of specific set of probes. Chromosome microarray analysis (CMA) allows detection of copy number changes and copy neutral loss of heterozygosity (cnLOH) across the entire genome with high resolution. Importantly, CMA does not detect balanced translocations, and therefore can supplement, but not replace FISH in MM. We previously reported landscape of CMA detected abnormalities and MRD detection by CMA in post-induction/ pre-transplant bone marrow samples. Here, we characterize cytogenetic abnormalities in patients with untreated symptomatic and smoldering MM using CMA.
Methods: We analyzed 78 samples of patients with newly diagnosed, untreated active MM and 22 samples of patients with smoldering MM (sMM), who presented to our program in 2015-2021. CMA was performed on CD138-enriched material using ThermoFisher CytoScan HD microarrays for copy number and heterozygosity alterations.
Results: 70 of 78 (89.7%)patients with active MM and 17 of 22 (77.3%) patients with sMM had CMA detected abnormalities. Abnormal findings detected by CMA included copy number changes (additions/ deletions), cnLOH and chromothripsis (CT). Total of 667 abnormalities were detected in 78 active MM samples (including 33 occurrences of cnLOH and 44 CT) and 72 abnormalities in 22 sMM samples (including 3 cnLOH). 53 types of recurrent abnormalities with frequency above 5% of samples were detected in active MM samples and 15 types in sMM samples (Figure 1, panel A: active MM, panel B: sMM). In the samples with active MM, in addition to the commonly tested MM abnormalities (trisomies of odd chromosomes, 1q+, 1p-, 13q-/13-, 17p-), we identified a number of less known recurrent abnormalities, among which 6q-, 6+, 8p-, 11q+, 12p-, 14q-, 16q-, 19p+, Xq+, X- were observed in above 10% samples.
Conclusions: Our results demonstrate that CMA is a sensitive technique allowing to identify recurrent cytogenetic abnormalities (excluding balanced translocations) in multiple myeloma that cannot be detected by conventional karyotyping or standard FISH panels. In addition to copy number changes, we also detected multiple occurrences of cnLOH, that may promote tumorigenicity by gene inactivation, and chromothripsis, involving complex genomic abnormalities. Further investigation is required to determine clinical correlation and prognostic significance of those abnormalities. Lastly, our results demonstrate increased cytogenetic complexity of active MM compared to smoldering MM.

Figure 1



P27 HIGH DOSE CYCLOPHOSPHAMIDE AS MOBILIZATION REGIMEN IN NEWLY DIAGNOSED MULTIPLE MYELOMA: SAFETY AND EFFICACY IN AN OUTPATIENT SETTING. SINGLE CENTER EXPERIENCE

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Background and aim of the study: High-dose chemotherapy followed by autologous stem-cells transplantation (ASCT) is the standard treatment approach in eligible newly diagnosed multiple myeloma (MM) patients. The use of Daratumumab in frontline therapy seems to affect stem cell mobilization and engraftment with lower number of stem cells collected and delayed neutrophil engraftment respectively. A common standard protocol for hematopoietic stem and progenitor cells (HPSC) mobilization before ASCT in MM is currently not defined but the use of high dose cyclophosphamide (Cy) (3-4 gr/m^2) seems associated with improved stem cell mobilization (SC) and collection with however an increase rates of severe neutropenia, infection and hospitalitazion. Moreover the administration of high dose of Cy, usually requires hospitalization to provide adequate hydration. The primary aim of this study is to assess the safety and efficacy of the mobilization therapy with low and high dose of Cy (2-3-4 g/m^2) plus G-CSF in an outpatient setting.
Materials and methods: From January 2022 to November 2022, 26 newly diagnosed multiple myeloma transplant eligible patients, 81% of them treated with daratumumab combination frontline, underwent mobilization with low (2 gr/m^2; LD) and high dose (3-4 gr/m^2; HD) Cy in outpatient setting. The LD-Cy was administered in one day while HD-Cy was split in two consecutive days (day +1 and +2). G-CSF (5 mcg/kg) was started at day +6. Use of plerixafor was permitted if circulating CD34+ cells were at least 5 uL at day +10. Eighty-five percent of patients received HD-Cy.
Results: Chemotherapy was well tolerated. The most common adverse events (AEs) were hematological: grade 3-4 neutropenia (100%) and grade 3-4 thrombocytopenia (15%). The non hematological AEs of grade 3-4 were limited to one case of febrile neutropenia (G3) which required hospitalization. No treatment-related mortality was observed. 23% of patients reported non hematological mild AEs (G1-G2) including nausea, asthenia and constipation. The rate of AEs is independent of drug dosage. In our cohort no renal impairment neither worsening of renal function were observed. There was no statistically significant difference in median eGFR value before and after chemotherapy (at day +6). The median amount of SCs collected was 9.85×10^6/kg. The rate of mobilization failure (defined as failure to collect ≥2×10^6/kg) was 0%. One patient (3,8%) required use of Plerixafor. In 4 patients two consecutive apheresis sessions were required.
Conclusion: Our results suggest that outpatient mobilization with low and high dose of cyclophosphamide is safe and may be considered for successful stem cell mobilization in MM transplant eligible patients treated with daratumumab frontline.

3. Relapsed/refractory multiple myeloma

P28 EFFICACY AND SAFETY OF CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) IN PATIENTS WITH PROGRESSIVE MULTIPLE MYELOMA (MM) AFTER EXPOSURE TO NON-CELLULAR ANTI-B-CELL MATURATION ANTIGEN (BCMA) IMMUNOTHERAPY

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Introduction: CARTITUDE-2 (NCT04133636) is a phase 2 study evaluating cilta-cel, an anti-BCMA CAR-T therapy, in several MM patient populations. We present updated data with longer follow-up on cohort C patients with previous exposure to a non-cellular anti-BCMA immunotherapy.
Methods: Cohort C patients with progressive MM after treatment with a proteasome inhibitor, immunomodulatory drug, anti-CD38 antibody, and non-cellular BCMA-targeting agent received a single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg) 5–7 days post lymphodepletion. Primary endpoint: minimal residual disease (MRD) negativity at 10^{-5}. Secondary endpoints: overall response rate (ORR), duration of response (DOR), and adverse events (AEs).
Results: As of June 1, 2022, 20 patients received cilta-cel (13 ADC exposed; 7 BsAb exposed). 6 patients (30%) received anti-BCMA treatment as last line of therapy (LOT; n=4 ADC, n=2 BsAb). During prior anti-BCMA treatment, best responses included very good partial response (ADC group: 2 patients, BsAb group: 1 patient), stringent complete response (ADC group: 1 patient), and complete response (BsAb group: 1 patient); the rest had best response of stable disease or PD (1 patient was not evaluable). At baseline (median age: 62.5 years, male: 60%), 3 (15%) patients had high-risk cytogenetics (all del17p), and 5 (25%) had baseline extramedullary disease. Patients had a median of 8 prior LOT; triple-class refractory (n=18 [90%]), penta-drug refractory (n=11 [55%]), refractory to non-cellular anti-BCMA treatment (n=16 [80%]) (Fig 1A). Median time from last anti-BCMA agent to cilta-cel infusion was 195 days. At a median follow-up of 18.0 months, 7/10 evaluable patients (70%) were MRD-negative at 10^{-5} (ADC group [n=5/7 evaluable, 71.4%]; BsAb group [n=2/3 evaluable, 66.7%]). ORR was 60% for the full cohort, 61.5% in the ADC group, and 57.1% in the BsAb group (Fig 1B). Median DOR was 12.8 months in the full cohort, 12.8 months in the ADC group, and 8.2 months in the BsAb group. Median PFS was 9.1 months in the full cohort, 9.5 months in the ADC group, and 5.3 months in the BsAb group. Cilta-cel responders had a shorter median duration of last anti-BCMA agent exposure (29.5 days) compared with non-responders (63.5 days). Responders also had a longer median time from last anti-BCMA treatment exposure to apheresis (161.0 days) than non-responders (56.5 days). Most common AEs were hematologic. CRS occurred in 12 (60%) patients (all grade 1/2); median time to onset was 7.5 days and median duration was 6.0 days. ICANS occurred in 4 (20%) patients (2 grade 3/4); median time to onset was 9.0 days and median duration was 7.0 days. ICANS was recovered or resolved in 3 patients. No patient had movement or neurocognitive treatment emergent AEs/parkinsonism. 12 deaths occurred: 8 due to PD, 2 due to COVID-19 pneumonia (not treatment related), 1 due to subarachnoid hemorrhage (not treatment related), and 1 due to *C. difficile* colitis (treatment related).
Conclusions: Heavily pretreated patients with MM and previous exposure to a non-cellular anti-BCMA therapy showed favorable responses following cilta-cel treatment. However, depth and DOR appear lower than that seen in anti-BCMA-naive patients treated with cilta-cel (median DOR was not reached in heavily pretreated but anti-BCMA naive CARTITUDE-1 patients at 27.7 months). These data may help inform treatment plans, including sequencing and washout period between BCMA-targeting agents.

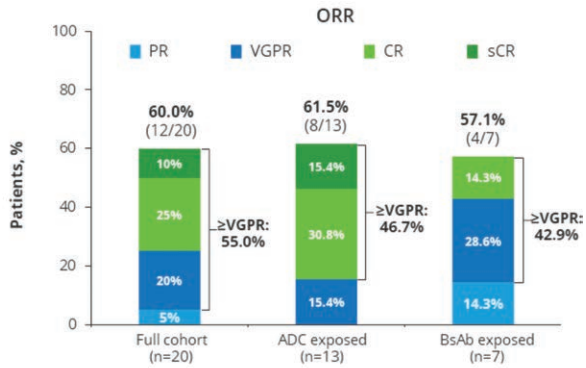
Figure 1: (A) Patient Demographics and Disease Characteristics, (B) ORR

A)

Characteristic	Full Cohort N=20	ADC exposed N=13	BsAb exposed N=7
Age, years, median (range)	62.5 (44–81)	66.0 (44–81)	60.0 (49–71)
Male, n (%)	12 (60.0)	8 (61.5)	4 (57.1)
Race, n (%)			
White	19 (95.0)	13 (100)	6 (85.7)
Black	1 (5.0)	0	1 (14.3)
Bone marrow plasma cells[a] ≥60%, n (%)	6 (31.6)	4 (33.3)	2 (28.6)
Extramedullary plasmacytomas, n (%)	5 (25.0)	5 (38.5)	0
High-risk cytogenetic profile[b], n (%)	3 (15.0)	2 (15.4)	1 (14.3)
Time from initial MM diagnosis, median (range) years	6.3 (2.5–16.3)	6.4 (3.6–16.3)	5.0 (2.5–14.5)
ISS stage (at study entry), n (%)			
I	8 (40.0)	6 (46.2)	2 (28.6)
II	4 (20.0)	3 (23.1)	1 (14.3)
III	8 (40.0)	4 (30.8)	4 (57.1)
Number of prior LOT, median (range)	8 (4–13)	8 (4–13)	8 (6–12)
Therapy in last line, n (%)			
Anti-BCMA	6 (30.0)	4 (30.8)	2 (28.6)
Other treatments	14 (70.0)	9 (69.2)	5 (71.4)
Refractory status, n (%)			
Triple-class[c]	18 (90.0)	11 (84.6)	7 (100)
Penta-drug[d]	11 (55.0)	7 (53.8)	4 (57.1)
Anti-BCMA treatment refractory	16 (80.0)	11 (84.6)	5 (71.4)
To last LOT	19 (95.0)	13 (100)	6 (85.7)

[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available; n=19 in the full cohort and n=12 in ADC exposed. [b]All del17p; missing data in 8 (40%) patients in full cohort. [c]At least 1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, ≥2 IMiDs, and 1 anti-CD38 Ab.

B)



ADC, antibody-drug conjugate; BsAb, bispecific antibody; CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

P29 PHASE 1/2 RESULTS OF TALQUETAMAB, A G PROTEIN-COUPLED RECEPTOR FAMILY C GROUP 5 MEMBER D X CD3 BISPECIFIC ANTIBODY, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) (MONUMENTAL-1)

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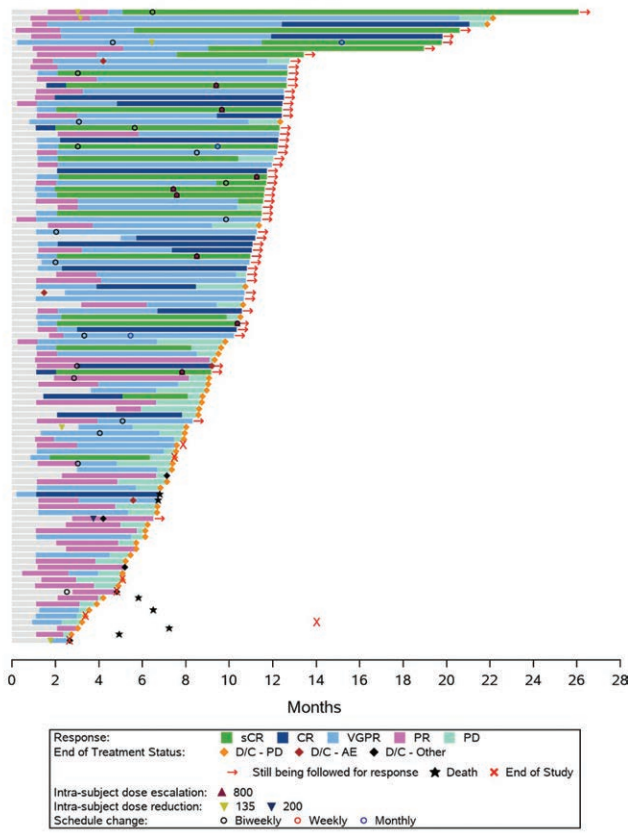
Introduction: G protein-coupled receptor family C group 5 member D (GPRC5D) is a promising immunotherapy target for patients (pts) with multiple myeloma (MM). Talquetamab (Tal), a first-in-class, off-the-shelf, T-cell redirecting bispecific antibody, targets both GPRC5D and CD3. In phase (ph) 1 of MonumenTAL-1, two recommended ph 2 doses (RP2Ds) for Tal were identified. We report ph 1/2 results pts with RRMM treated at the RP2Ds.
Methods: Ph 1 enrolled pts with measurable MM that progressed or were intolerant to standard therapies. Pts enrolled in ph 2 received ≥3 prior lines of therapy (LOT, including ≥1 proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody [triple-class exposed]). Ph 1 putative RP2D 0.405mg/kg SC once weekly (QW) was modified to 0.4mg/kg SC QW in ph 2, with step-up dosing used to mitigate risk of severe cytokine release syndrome (CRS). Ph 1/2 data were combined for analysis. Ph2 primary endpoint was overall response rate (ORR). Secondary endpoints were duration of response (DOR), rate of very good partial response or better (≥VGPR), rate of complete response or better (≥CR), time to response (TOR), progression-free survival (PFS), and adverse events (AEs). Pharmacodynamics (PD) parameters were measured at baseline (BL) and through Cycle 2 Day 1.
Results: As of May 16, 2022, 288 pts with no prior exposure to T-cell redirecting therapies received Tal RP2Ds in ph 1 or 2. In 143 pts (median age, 67 years [y]) treated at 0.4mg/kg QW (median time since diagnosis: 6.7 y), pts received a median of 5 prior LOT, 100%/74% were triple-class exposed/refractory, and 73%/29% were penta-drug exposed/refractory. Median follow-up was 11.0 months (mo) (range 0.5±26.1). BL characteristics were similar in 145 pts treated at 0.8 mg/kg every two weeks (Q2W) (median follow-up 5.1 mo). In 143 pts treated at 0.4 mg/kg QW, ORR was 73% (≥VGPR: 58%; ≥CR: 29%), and responses were durable and deepened over time (Figure). Median TOR was 1.2 mo (range 0.2–5.0), median time to CR was 2.1 mo (range 1.1–12.4), median DOR was 9.3 mo (95% CI, 6.6–20.2; range 1–23+), and median PFS was 7.5 mo (95% CI, 5.7–9.2 [38% censored]). ORRs in triple-class refractory (72%

[76/106]) and penta-drug refractory (71% [30/42]) pts were comparable to overall population. Efficacy at 0.8 mg/kg Q2W will be presented at meeting. Most common AEs (0.4 mg/kg QW/0.8 mg/kg Q2W) were CRS (79%/72%; grade 3 [gr]: 2%/1%; gr 4: 0%/0%), dysgeusia (48%/46%; gr 3/4: not applicable [NA]), anemia (45%/39%; gr 3: 31%/25%; gr 4: 0%/0%]), skin-related AEs (56%/68%; gr 3: 0%/1%; gr 4: NA), and nail disorders (52%/43%; gr 3: 0%/0%; gr 4: NA). Neutropenia 34%/28% (gr 3: 20%/17%; gr 4: 10%/6%) and thrombocytopenia 27%/27% (gr 3: 10%/8%; gr 4: 10%/8%) were limited to few cycles. Infections occurred in 57%/50% pts (gr ≥3: 19%/13%), 4.9%/6.2% discontinued, 8.4%/13.8% had dose delays, and 14.7%/6.2% had dose reductions due to AEs. Two deaths reported due to COVID-19 (1 pt at each RP2D). Tal exposure was comparable at the 2 RP2Ds. No clinically significant effect of anti-Tal antibodies on pharmacokinetics, efficacy, or AEs were observed. PD changes were comparable at both RP2Ds and consistent with Tal activity, including T-cell activation, redistribution, and induction of cytokines.

Conclusion: Tal demonstrated robust efficacy and manageable safety in heavily pretreated pts with RRMM. Tal in combination with other agents is being evaluated in additional ph 1 studies (NCT04586426; NCT04108195; NCT05050097) in pts with RRMM.

Figure: Response to talquetamab 400 µg/kg QW



AE, adverse event; CR, complete response; D/C, discontinued; PD, progressive disease; PR, partial response; QW, weekly; sCR, stringent complete response; VGPR, very good partial response.

P30 SINGLE COHORT RESULTS FROM MAJESTEC-2: TECLISTAMAB (TEC) IN COMBINATION WITH SUBCUTANEOUS DARATUMUMAB (DARA) AND LENALIDOMIDE (LEN) IN PATIENTS WITH MULTIPLE MYELOMA (MM)

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Introduction: DARA and LEN plus dexamethasone is approved for treating MM. Both DARA and LEN have immunomodulatory effects that may enhance the function of TEC, potentially resulting in improved antimyeloma activity in a broader population of patients (pts). Here we report preliminary safety and efficacy results from MajesTEC-2 (NCT04722146) of TEC combined with DARA and LEN (TEC-DARA-LEN) in pts with MM).

Methods: Pts who received 1–3 prior lines of therapy (LOT), including a proteasome inhibitor and immunomodulatory drug, were eligible for TEC-DARA-LEN. In this cohort, pts were given weekly doses of TEC (0.72 or 1.5 mg/kg with step-up dosing) combined with an approved regimen of DARA 1800 mg+LEN 25 mg. Investigator responses were assessed by International Myeloma Working Group criteria, and adverse events (AEs) by CTCAE v5.0, except for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) which were graded per ASTCT guidelines.

Results: 32 pts (87.5% male; median age, 62 years) received TEC-DARA-LEN (0.72 mg/kg, n=13; 1.5 mg/kg, n=19). At data cutoff (July 11, 2022), median follow-up was 5.78 months (mo; range, 1.0–10.4) and median treatment duration was 4.98 mo (range, 0.10–10.35). 18.8% were refractory to DARA and 28.1% refractory to LEN and median prior LOT was 2 (range, 1–3). Most frequent AE was CRS (81.3% [n=26]; grade [gr] 1/2) and 95% of the events occurred during cycle 1 treatment doses. Median time to onset was 2 days and median duration was 2 days. No ICANS events were reported. Other frequent AEs (≥25.0% across both dose levels) were neutropenia (75.0% [n=24]; gr 3/4: 68.8% [n=22]), fatigue (43.8% [n=14]; gr 3/4: 6.3% [n=2]), diarrhea (37.5% [n=12]; all gr 1/2), insomnia (31.3% [n=10]; gr 3/4: 3.1% [n=1]), cough (28.1% [n=9]; all gr 1/2), hypophosphatemia (25.0% [n=8]; all gr 1/2), pyrexia (25% [n=8]; gr 3/4: 6.3% [n=2], and febrile neutropenia (12.5% [n=4]). Infections occurred in 24 pts (75.0%; gr 3/4: 28.1% [n=9]) and most common were upper respiratory infection (21.9% [n=7]), COVID-19 (21.9% [n=7]), and pneumonia (21.9% [n=7]). 3 pts (9.4%) had COVID-19 pneumonia. 1 pt (3.1%) discontinued due to an AE (COVID-19) and died due to COVID-19. Overall response rate (ORR) was 13/13 evaluable pts (median follow-up: 8.61 mo) at 0.72 mg/kg and 13/16 evaluable pts (median follow-up was less mature at 4.17 mo) at 1.5 mg/kg. Very good partial response or better was achieved in 12 pts at the 0.72 mg/kg dose and was not mature for the 1.5 mg/kg group. Median time to first response was 1.0 mo (range, 0.7–2.0). Preliminary pharmacokinetic concentrations of TEC in combination with DARA-LEN were comparable with those seen with TEC monotherapy. TEC-DARA-LEN treatment led to proinflammatory cytokine production (induction of interleukin-6, soluble interleukin-2Rα, interferon-γ, and tumor necrosis factor-α) and T-cell activation (upregulation of programmed cell death protein-1 and CD38 on peripheral T cells).

Conclusions: TEC-DARA-LEN has a safety profile consistent with TEC or DARA-LEN individually. Promising ORR findings support the potential of combined treatment on enhanced early disease control through the addition of tec. The phase 3 MajesTEC-7 study will compare TEC-DARA-LEN vs the combination of DARA, LEN, and dexamethasone in pts with NDMM ineligible or not intended for autologous stem cell transplant as initial treatment.

P31 SINGLE-AGENT BELANTAMAB MAFODOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA: FINAL ANALYSIS OF THE DREAMM-2 TRIAL

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Objectives: Belantamab mafodotin (belamaf)—a first-in-class, antibody-drug conjugate targeting B-cell maturation antigen—demonstrated deep and durable responses with a manageable safety profile in previous analyses of the pivotal DREAMM-2 study in patients with relapsed/refractory myeloma (RRMM). Here, we present final efficacy and safety data from DREAMM-2.
Methods: DREAMM-2 (NCT03525678) is a Phase 2, open-label study of single-agent belamaf (2.5 or 3.4 mg/kg every 3 weeks) in patients with triple-refractory RRMM who had ≥3 prior therapies and were refractory to an immunomodulatory agent and a proteasome inhibitor, and refractory or intolerant to an anti-CD38 monoclonal antibody. The primary endpoint was overall response rate (ORR); secondary endpoints included progression-free survival (PFS), overall survival (OS), safety, ocular symptoms, and health-related quality of life (HRQoL).
Results: As of 31 March 2022, median follow-up was 12.48 and 13.77 months for patients randomised to belamaf 2.5 mg/kg (N=97) and 3.4 mg/kg (N=99), respectively (Table). ORR in the 2.5 and 3.4 mg/kg cohorts was 32% and 35%, respectively; 19% and 24% of patients (58% and 69% of responders, respectively) achieved very good partial response (VGPR) or better. Median time to response was 1.5 and 1.4 months in the 2.5 and 3.4 mg/kg cohorts, respectively. The minimal residual disease negativity rate of patients with ≥VGPR was 36% and 23%, and median duration of response was 12.5 and 6.2 months in the 2.5 and 3.4 mg/kg cohorts, respectively. Median PFS was 2.8 and 3.9 months, and median OS was 15.3 and 14.0 months in the 2.5 and 3.4 mg/kg cohorts, respectively. In patients who achieved ≥VGPR, median PFS was 14.0 and 16.8 months, and OS was 30.7 and 35.5 months in the 2.5 and 3.4 mg/kg cohorts, respectively. The three most common Grade ≥3 adverse events (AEs) were keratopathy, anemia, and thrombocytopenia (Table). Incidences of AE-related dose reductions, delays and permanent discontinuations were 36% and 44%, 54% and 62%, and 9% and 5% in the 2.5 and 3.4 mg/kg cohorts, respectively. Discontinuation due to ocular events was rare (3% in both cohorts). The most commonly reported ocular events in the 2.5 mg/kg cohort included keratopathy (71%), blurred vision (23%), BCVA reduced to 20/50 (21%) and dry eye (15%). BCVA reductions and blurred vision were transient; ≤86% of patients experiencing these events had resolution by completion of follow-up. No permanent complete vision loss occurred. Despite changes in BCVA and blurred vision, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire data suggest that overall global health status/HRQoL, physical and role functioning, and overall disease symptoms were maintained or improved during treatment.
Conclusions: This final analysis of DREAMM-2 confirms earlier reports that single-agent belamaf (2.5 and 3.4 mg/kg) results in rapid, deep, durable and clinically meaningful responses, with a manageable safety profile in patients with RRMM. No new safety signals were observed. Dose modification remained effective in resolving ocular events, and HRQoL was maintained or improved.

Table.

Key efficacy and safety outcomes of the DREAMM-2 final analysis

Outcome	Belamaf 2.5 mg/kg Q3W (N=97; N=95 for safety analyses)	Belamaf 3.4 mg/kg Q3W (N=99)
Median time on therapy, months (range)	2.1 (0.5–41.0)	2.8 (0.5–42.8)
Median follow-up, months (range)	12.48 (0.1–40.4)	13.77 (0.1–42.8)
ORR, % (97.5% CI)	32 (21.7–43.6)	35 (24.8–47.0)
≥VGPR, %	19	24
MRD-negativity rate in ≥VGPR, % (95% CI)*	36 (12.8–64.9)	23 (5.0–53.8)
Duration of response, months (95% CI)	12.5 (4.2–19.3)	6.2 (4.8–18.7)
Median PFS, months (95% CI)	2.8 (1.6–3.6)	3.9 (2.0–5.8)
Median PFS in ≥VGPR, months (95% CI)	14.0 (9.7–NR)	16.8 (7.7–NR)
Median OS, months (95% CI)	15.3 (9.9–18.9)	14.0 (10.0–18.1)
Median OS in ≥VGPR, months (95% CI)†	30.7 (19.7–37.9)	35.5 (14.1–NR)
AE-related dose reductions, %	36	44
AE-related dose delays, %	54	62
AE-related permanent discontinuations, %	9	5
Permanent discontinuation due to ocular events, %	3	3
Grade ≥3 AEs, %	84	83
Keratopathy, %	29	25
Anemia, %	21	28
Thrombocytopenia, %	19	29

*MRD was measured by next generation sequencing with a threshold of 10^{-5}.
†Median OS in ≥VGPR patients was a post-hoc analysis.
AE, adverse event; CI, confidence interval; DREAMM, DRiving Excellence in Approaches to Multiple Myeloma; MRD, minimal residual disease; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; VGPR, very good partial response.

P32 MAJESTEC-1: CORRELATIVE ANALYSES OF TECLISTAMAB, A B-CELL MATURATION ANTIGEN (BCMA) X CD3 BISPECIFIC ANTIBODY, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

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Introduction: Teclistamab, a BCMA bispecific IgG4 antibody, redirects CD3+ T cells to mediate T cell activation and subsequent BCMA-expressing myeloma cell lysis. MajesTEC-1, a multicohort, open-label, phase 1/2 study, investigated teclistamab safety/efficacy in patients (pts) with RRMM previously receiving ≥3 lines of therapy. In phase 1, recommended phase 2 dose (RP2D) of teclistamab was 1.5mg/kg subcutaneous (SC) once weekly, preceded by 0.06 and 0.3mg/kg step-up doses. Initial results of RP2D-treated pts in phase 1/2 (no prior BCMA-targeted treatment exposure) demonstrated teclistamab was well tolerated with encouraging efficacy. Here, we report translational research data from MajesTEC-1 of the pivotal RP2D and active dose pt cohorts.
Methods: Baseline/on-treatment whole blood and bone marrow aspirate samples from pivotal RP2D pts (SC) were analyzed by flow cytometry for BCMA expression/immune populations; serum samples were analyzed for soluble BCMA (sBCMA) by electrochemiluminescence ligand binding, and cytokines by MSD/Luminex assays; whole blood from active dose cohorts (intravenous/SC) was analyzed by cytometry by time of flight (CyTOF).
Results: Baseline BCMA expression on bone marrow plasma cells was prevalent and highly variable among pts with RRMM but not associated with clinical responses to teclistamab; higher baseline sBCMA levels associated with lower response rates and high-risk disease characteristics (higher revised International Staging System stage, high bone marrow plasma cells [>60%], extramedullary plasmacytoma presence). Nonresponders had lower peripheral CD8 T cell counts, higher regulatory T cells (Tregs) and CD38+ Tregs, higher overall T cells expressing PD-1, TIM-3, CD38 in peripheral blood and bone marrow at baseline. Baseline analysis also showed enhancement of a naïve phenotype in T cells in responders. Higher baseline T cells expressing PD-1, TIM-3, CD38, CD25, PD-1/TIM-3, PD-1/CD38 observed in blood and bone marrow of pts with high bone marrow plasma cells (>60%), high composite tumor score (plasmacytosis ≥80%, serum M-spike ≥5g/dL, serum free light chain ≥5000 mg/L). Shorter progression-free survival (PFS) was associated with higher peripheral PD-1+ CD8 and baseline Tregs. Higher baseline CD25+ CD4, CD38+ CD4 bone marrow T cells correlated with lower PFS after tumor burden adjusting. Baseline T cell profile associated with worse clinical outcome likely reflects dysfunctional and exhausted T cell phenotype. Accordingly, lower interferon-g and PD-1+ CD8, CD25+ CD4, CD38+ CD4 T cell induction was observed with teclistamab treatment (nonresponders); teclistamab-mediated induction of peripheral PD-1+ CD38+ CD8 T cells lower in pts with high tumor burden. Cytokine release syndrome was associated with higher CD3 T cells and lower baseline sBCMA, TIM-3, PD-1/TIM-3 expressing CD4 T cells in the periphery.

Conclusions: Baseline correlative analysis for pivotal RP2D pts suggests emerging profile for nonresponders of unfavorable baseline immune characteristics, including lower T cell numbers, higher baseline T cells expressing PD-1, TIM-3, CD38, increased Tregs and CD38+ Tregs, and lower proportion of naïve T cells. These data support clinical combinations of teclistamab with agents like daratumumab or checkpoint inhibitors.

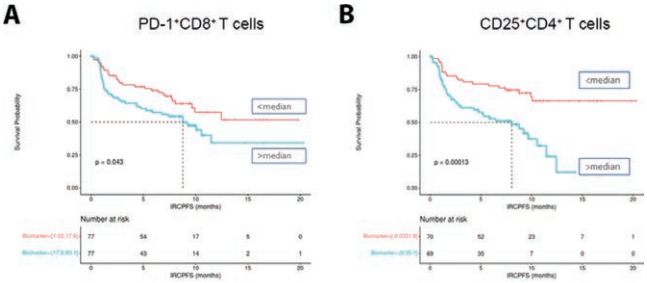

Figure 1. Kaplan-Meier curves of progression-free survival (PFS) at baseline in patients from the recommended phase 2 dose (RP2D) cohort of teclistamab associated to peripheral PD-1+ CD8+ T cells (A) and bone marrow CD25+CD4+ T cells (B). Statistical significance was calculated using Cox proportional hazards model

P33 EFFECTIVENESS AND SAFETY OF BELANTAMAB MAFODOTIN IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA IN REAL-LIFE SETTING: THE ALFA STUDY

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Objectives: Patients with relapsed/refractory multiple myeloma (RRMM) refractory to immunomodulators, proteasome inhibitors and anti-CD38 antibodies have few therapeutic alternatives. Belantamab mafodotin (belamaf)—an antibody-drug conjugate targeting B-cell maturation antigen—showed promising results in the DREAMM-2 trial. The ALFA study aims to describe real-world belamaf effectiveness and safety in patients with RRMM.
Methods: ALFA is a non-interventional, retrospective study of patients with RRMM initiating belamaf in 45 centres in France during early access programmes from 27 April 2020 to 30 June 2021. Patient characteristics, overall response rate (ORR) (≥partial response [PR]), clinical benefit rate (CBR) (≥minimal response [MR]), ≥very good PR (VGPR) rate, progression-free survival (PFS), overall survival (OS) and safety were assessed. Subgroup analyses for PFS and OS were performed.
Results: In total, 184 patients initiated belamaf (median follow-up, 7.8 months). Median time from diagnosis to belamaf initiation was 6 years; 107 patients (58.2%) had ≥5 prior therapy lines. At initiation, 53.3% were male; median age was 70 years (29.9% aged ≥75 years); 47.7% had renal failure; 78.8% were penta-exposed; and 8.3% had extramedullary disease. Among patients with available data (n=156), 36.5% had an Eastern Cooperative Oncology Group Performance Status ≥2. Cytogenetic profiles at diagnosis were available for 83 patients (45.1%), 27 (32.5%) of whom had high cytogenetic risk defined as either t(4;14) or del(17p) or t(14;16); 47.7% had ophthalmological history (cataract, 52.7%). Belamaf was delivered by intravenous infusion in 21-day cycles. Median dose at initiation was 2.5 mg/kg (range, 1.6–3.0). Median number of belamaf cycles was 3 (Q1–Q3, 2–7). The ORR was 32.7% (≥VGPR, 20.4%; PR, 12.3%) and 59 patients (36.4%) achieved clinical benefit; 26.5% had stable disease (SD) and 37.0% had progressive disease (PD). Overall, median PFS (mPFS) was 2.4 months (95 CI%, 1.9–3.2) and median OS (mOS) was 8.8 months (95 CI%, 6.3–11.6). No differences were found in subgroups according to cytogenetic risk, renal failure, age at belamaf initiation, penta-exposure and number of prior therapy lines. According to best response, mPFS was 20.6 months (95 CI%, 12.1 to not reached [NR]) in patients with ≥VGPR, 7.1 months (95 CI%, 4.6–9.4) in patients with PR and 1.6 months (95 CI%, 1.4–2.0) in the other patients (P<0.01). mOS was not reached in patients with ≥VGPR (1-year survival rate, 96.8% [95 CI%, 79.2–99.5]), 17.5 months (95 CI%, 7.7 to NR) in patients with PR and 5.6 months (95 CI%, 3.9–7.7) in the other patients (including MR, SD and PD) (P<0.01). In patients with a clinical benefit, mPFS was 9.7 months (95 CI%, 7.5–14.9) and mOS was not reached. Adverse events (AEs) were reported in 159 patients (86.4%); the most frequent were ocular AEs (n=103 [56.0%]). Keratitis/keratopathy and thrombocytopenia occurred in 41.8% and 13.6% of patients, respectively. Incidence of infusion reaction was 3.3%. Ocular AEs led to dose modification, temporary interruption and permanent discontinuation in 19.6%, 11.4% and 12.5% of patients, respectively.
Conclusions: These data, presented from the largest real-life study conducted to our knowledge, confirm previous results from DREAMM-2.

P34 LIGHTHOUSE (OP-108): MELFLUFEN PLUS DARATUMUMAB (DARA) AND DEXAMETHASONE (DEX) VERSUS DARA IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) REFRACTORY TO AN IMMUNOMODULATORY DRUG (IMID) AND A PROTEASOME INHIBITOR (PI) OR HAD RECEIVED ≥3 PRIOR LINES OF THERAPY INCLUDING AN IMID AND A PI

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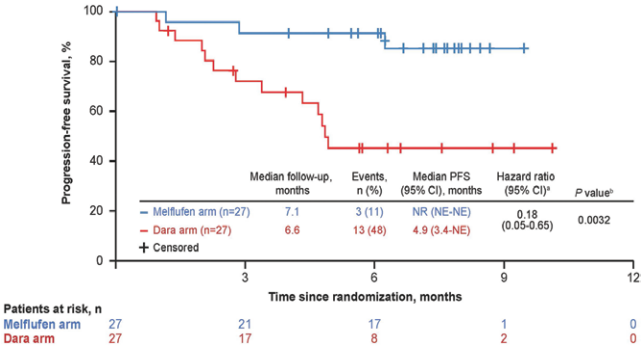
Background: Patients (pts) with RRMM often develop resistance to standard therapies. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages peptidases and esterases to rapidly release alkylating agents into tumor cells. Melflufen+dex was approved in Europe for the treatment of pts with ≥3 prior lines of therapy (LoTs) and triple-class refractory RRMM (time to progression [TTP] >36 mo if pt had a prior autologous stem cell transplant [ASCT]). Approval was based on results from the phase 2 HORIZON study supported by the phase 3 OCEAN study (Richardson PG, et al. *J Clin Oncol*. 2021;39(7):757-767; Schjesvold FH, et al. *Lancet Haematol*. 2022;9(2):e98-e110). Melflufen+dex+dara showed clinical activity and manageable safety in the phase 1/2 ANCHOR study (Ocio EM, et al. ASH 2020, abstract 417), and was further assessed in the phase 3 LIGHTHOUSE study (NCT04649060).
Methods: Pts had RRMM and were refractory to an IMiD and a PI or had received ≥3 prior LoTs including an IMiD and a PI. Prior anti-CD38 monoclonal antibody therapy was allowed, but no pts had received it. Pts were randomized (1:1) to 28-day (D) cycles (C) of intravenous melflufen (30 mg on D1 of each C) + oral dex (40 mg weekly; 20 mg if aged ≥75 y) + subcutaneous dara (1800 mg on D1, 8, 15, and 22 in C1-2, D1 and 15 in C3-6, and D1 in C7+) or dara monotherapy (regimen as in the melflufen arm) until disease progression or unacceptable toxicity. Pts with confirmed disease progression in the dara arm could cross over to the melflufen arm. Primary endpoint was progression-free survival (PFS); key secondary endpoints were overall response rate (ORR) and safety. A partial clinical hold issued by the FDA for all melflufen studies led to premature study closure on 23 Feb 2022 (data cutoff date).
Results: From 21 Dec 2020 to 7 Jul 2021, 54 of 240 planned pts were randomized (melflufen arm, n=27; dara arm, n=27); 2 pts crossed over to the melflufen arm. In the melflufen vs dara arm, median (range) age was 65 y (43-80) vs 68 y (50-83), 11 (41%) vs 13 (48%) had no prior ASCT, and 3 (11%) vs 2 (7%) had a TTP >36 mo after a prior ASCT, respectively. Median PFS was not reached (NR) in the melflufen arm vs 4.9 mo in the dara arm (hazard ratio [HR], 0.18 [95% CI, 0.05-0.65]; *P*=0.0032; Figure). ORR (95% CI) was 59.3% (38.8-77.6) in the melflufen arm vs 29.6% (13.8-50.2) in the dara arm (*P*=0.0300). OS was immature, with 2 events in the melflufen arm vs 4 events in the dara arm (HR, 0.47 [95% CI, 0.09-2.57]; *P*=0.3721). Among pts with no prior ASCT or with a TTP >36 mo after a prior ASCT (melflufen arm, n=14; dara arm, n=15), median PFS was NR in the melflufen arm (1 event) vs 3.9 mo in the dara arm (11

events; HR, 0.06 [95% CI, 0.01-0.49]; *P*=0.0005), ORR was 64.3% vs 13.3% (*P*=0.0055), and 1 vs 4 OS events occurred (*P*=0.0369), respectively. In the melflufen vs dara arm, the most common grade ≥3 treatment-emergent adverse events were neutropenia (50% vs 12%), thrombocytopenia (50% vs 8%), and anemia (32% vs 19%); those leading to discontinuation occurred in 2 pts (9%) and 4 pts (15%), respectively.

Conclusion: Melflufen+dex+dara demonstrated superior PFS and ORR vs dara in the overall population and in pts with no prior ASCT or with a TTP >36 mo after a prior ASCT, which resembles the population with confirmed benefit from OCEAN. The safety profile of melflufen as a triplet regimen was consistent with that reported in ANCHOR and previous reports of melflufen+dex.



P35 ANALYSIS OF DARATUMUMAB CLINICAL TRIALS: CHARACTERISTICS AND OUTCOMES IN PATIENTS WITH LENALIDOMIDE-REFRACTORY RELAPSED/REFRACTORY MULTIPLE MYELOMA TREATED WITH 1-3 PRIOR LINES OF THERAPY

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Introduction: Survival outcomes in patients with multiple myeloma (MM) have improved with new treatment combinations using proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and anti-CD38 monoclonal antibodies. However, for patients with multiple lines of therapy (LOT), especially those who are PI exposed and refractory to lenalidomide (len), selecting the next regimen can be challenging. Data that characterize treatments and outcomes in this difficult-to-treat population are limited.

Methods: Individual patient-level data were derived from a pooled analysis of daratumumab clinical trials, which included the initial study, long-term follow-up, and all treatment arms and regimens with or without daratumumab (ALCYONE, APOLLO, CANDOR, CASSIOPEIA, CASTOR, EQUULEUS, GRIFFIN, MAIA and POLLUX). MM patients with 1-3 prior LOT (including a PI and IMiD) who were len-refractory and had an ECOG <2 were identified. Time zero (T0) was defined as the time when the subsequent LOT started after patient met inclusion criteria for each eligible index line. Patients with multiple therapies subsequent to meeting eligibility criteria contributed multiple observations. Treatment outcomes and patterns were analyzed by number of prior LOT. For all index lines, descriptive statistics for patient characteristics were assessed at T0. The Kaplan-Meier method was used to estimate time-to-event analyses starting at T0 for progression-free survival (PFS), time to next treatment (TTNT) and overall survival (OS).

Results: Of 4764 patients, 915 with 1230 index lines (prior LOT, 1 [n=114]; 2 [n=516]; 3 [n=600]) met inclusion criteria. For all indexed lines, median age was 65.5 years (range 30-90), 57.5% were male, 76.4% were White, and 3.2% were Black. Median time from diagnosis was 3.6 years (range 0-23). At T0, 5.4% had baseline plasmacytoma, 16.1% had ISS stage III disease, and 14.3% had high-risk cytogenetics. 13.8% of all eligible index lines were triple-class refractory. 58.9% had stem cell transplant prior to T0. Most common treatment regimens subsequent to meeting eligibility criteria were DPd (13.3%), DKd (13.2%), Pd (11.4%), and Kd (8.9%). For all patient indices, the overall response rate was 50.1% (29.0% with very good partial response or better; 12.0% with complete response or better) (Figure 1A). Estimated median OS for all patient indices was 23.9 months (95% CI 21.8, 25.8), PFS was 12.2 months (95% CI 10.9, 13.5), and TTNT was 8.34 months (95% CI 7.7, 9.3). Estimated median OS, PFS, and TTNT by number of prior LOT are shown in Figure 1A. Response rates and PFS decreased as the number of prior LOT increased (Figure 1B).

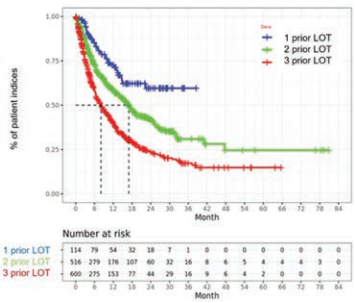
Conclusions: This analysis of patients from daratumumab randomized clinical trials demonstrates that response rates decrease with each additional prior LOT for PI-exposed, len-refractory patients with 1-3 prior LOTs. PFS is also poor in these patients, and they move quickly through available treatments, highlighting the need for a new effective and safe regimen for this patient population.

Figure 1: (A) Response rates and time-to-event analyses by number of prior LOT; (B) PFS by number of prior LOT

A

	1 prior LOT n=114	2 prior LOT n=516	3 prior LOT n=600	Total n=1230
ORR, n (%)	84 (73.7)	266 (51.6)	266 (44.3)	616 (50.1)
≥VGPR, n (%)	57 (50.0)	161 (31.2)	139 (23.2)	357 (29.0)
≥CR, n (%)	22 (19.3)	75 (14.5)	50 (8.3)	147 (12.0)
Median OS, months (95% CI)	28.9 (23.9, 59.7)	29.2 (24.4, 33.8)	18.8 (16.8, 21.3)	23.9 (21.8, 25.8)
Median PFS, months (95% CI)	NR (22.3, NE)	17.0 (14.1, 19.4)	8.1 (6.5, 9.8)	12.2 (10.9, 13.5)
Median TTNT, months (95% CI)	13.6 (10.8, 16.4)	9.0 (7.9, 10.4)	6.7 (6, 7.7)	8.34 (7.69, 9.3)

B



P36 BELANTAMAB MAFODOTIN IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST ONE PROTEASOME INHIBITOR, ONE IMMUNOMODULATORY AGENT AND ONE ANTI-CD38 MONOCLONAL ANTIBODY: A RETRO-PROSPECTIVE ITALIAN OBSERVATIONAL STUDY

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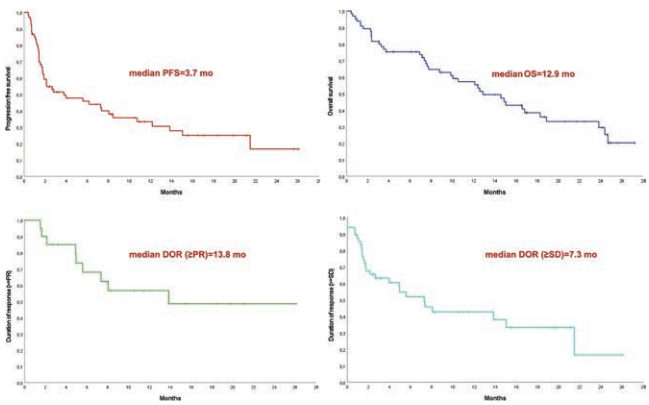
Recent therapeutic advances in multiple myeloma (MM) patients, like the introduction of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs), have dramatically improved patients' outcomes. But the occurrence of resistance is an emerging challenge resulting in a poor survival with the urgent need for effective therapies, mostly in the setting of triple-refractory MM. Belantamab mafodotin (belamaf) is the first-in-class antibody-drug conjugate (ADC) targeting B-cell maturation antigen (BCMA) to have demonstrated efficacy in monotherapy in DREAMM-2 trial and to be approved for treatment of relapsed/refractory MM (rrMM) patients with at least four previous lines of therapy (LOT).

Being real-world data of belamaf use scarce, we designed a retroprospective study aiming to evaluate its efficacy and safety in RRMM patients treated in compassionate use programmes as Named Patient Program (NPP) and Expanded Access Program (EAP) in Italy, under the aegis of European Myeloma Network (EMN). The primary endpoint was the rate of patients achieving a clinical benefit (at least minimal response according to IMWG criteria). Secondary endpoints were safety, ORR (at least PR), duration of response (DoR), progression-free survival (PFS) and overall survival (OS). Eligible patients must be ≥18 years of age with a MM diagnosis according to IMWG criteria. They must have received at least 4 LOTs and be triple-refractory (at least one PI, one IMID and one anti-CD38 mAb).

Overall, 67 patients have been enrolled by 18 Italian centers. Their median age was 66 years (range 42-82) and they received from 4 to 10 previous lines of therapy (median 6). ECOG was <2 in 65% of patients, MM was IgG, IgA and light chain in 60%, 19% and 21% of patients, respectively. High risk cytogenetic was observed in 22.4% and ISS3 stage in 37% of cases. CBR was 37%, ORR was 31% and at least SD was achieved in 71% of patients. After a median follow up of 12 months, median PFS was 3.7 months, median OS 12.8 months with a median DoR of 13.8 months. As for safety, the most frequent adverse events were ocular: corneal toxicity and ocular symptoms were reported in 74% and 16% of patients, respectively, but only 10% had changes in BCVA. Ocular adverse events recovered in 46% of cases so far, they requested drug discontinuation in 45% and only dose reduction in 13% of cases. Thrombocytopenia was described in 87.5% of patients, 50% of them grade 3, but reversible. Then, 8 infections, 4 infusion reactions (clinically showing as fever), one pulmonary embolism and one grade 5 secondary neoplasia were reported. Belamaf was globally discontinued in 37 patients (55%), due to disease progression in 28, death in 3, toxicity in 5, other in 1 patient. Twenty-seven patients (40%) are still alive andforty (60%) patients died (82.5% for disease progression,10% for adverse events and 7.5% others). Explorative univariate Cox regression analysis suggests that PFS was negatively affected by age>65, p=0.094 and ECOG≥2, p=0.012

In conclusion, our cohort had fewer previous LOTs but similar median age than DREAMM-2 population. We found similar outcomes in terms of ORR and OS but median PFS and DOR seems to be longer. PFS seems to be not affected by disease prognostic factors,. We observed a similar safety profile, being the ocular adverse events the most frequent ones and thrombocytopenia the second one. The most important cause of discontinuation was disease progression.



P37 MULTIPLE MYELOMA MONITORING FROM ARCHIVED SERUM PROTEIN ELECTROPHORESIS GELS BY MASS SPECTROMETRY AND DE NOVO SEQUENCING

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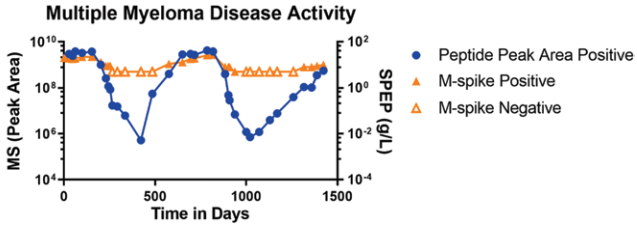
In multiple myeloma (MM), the plasma cells overproduce monoclonal immunoglobulins, called M-proteins. Serum protein electrophoresis (SPEP) is a blood-based analysis commonly used to detect and measure the M-protein, but it has a relative limited sensitivity of 0.5 g/L. More sensitive techniques exist to monitor minimal residual disease (MRD) in MM, such as flow cytometry or next-generation sequencing, but they require samples from invasive bone marrow procedures. Mass spectrometry (MS) is arising as a sensitive approach for longitudinal M-protein monitoring that relies on blood samples rather than bone marrow procedures. By using RNA data obtained from the initial bone marrow sample, clonotypic peptides of the M-protein can be used as a surrogate to monitor MM. In this study, de novo sequencing of the M-protein was performed using routine SPEP gels as starting material for MS analysis. With this approach an SPEP band is sufficient to detect M-protein without use of bone marrow. Sensitivity of MS to longitudinally monitor M-proteins was compared with routine diagnostics.

Nine MM patients were retrospectively selected based on the data in the Erasmus MC hospital information system, without available RNA data. Each patient had SPEP detectable M-protein at diagnosis (>1 g/L) and at the end of the disease course, with at least one period in between when the M-protein was absent by routine diagnostics. To validate the de novo sequencing approach and quantitative performance of our method, one sample of a MM patient with available RNA data was used as a reference to prepare a dilution series. The M-protein bands were digested with trypsin, extracted from gel, and measured with MS. Patient-specific M-protein peptides were selected based on unique presence in the patient and homology of the de novo sequence to the immunoglobulin germline sequences. The selected peptides were used as surrogates to monitor the M-protein in all patient's samples with MS.

With de novo sequencing, at least one patient-specific peptide of the M-protein was identified for all of the MM patients, showing 100% feasibility. For the reference patient, 2 patient-specific M-protein peptides from the heavy chain were identified. When compared to the translated DNA sequence, one patient-specific peptide differed in only one amino acid while the other had all the correct amino acids but some were misplaced in the sequence. Nevertheless, neither of the inaccuracies interfere with monitoring the associated signals in the MS. The dilution series of the reference patient showed that MS can detect M-protein concentrations as low as 5 mg/L, while with SPEP no visible M-protein band was detected when the M-protein concentration was less than 664 mg/L. One patient is displayed in the Figure as an example where the M-protein was detected in all time points (blue), compared to routine diagnostics (orange) that did not detect the M-protein between 265-485 days and 938-1259 days. Additionally, relapse was detected sooner by MS than by SPEP.

MS-analysis on M-protein from archived SPEP gels is feasible by using de novo sequencing. This approach enables retrospective analysis of patients in the clinic or from completed clinical trials. Additionally, MS-analysis on patient blood can be used to measure MRD instead of or complimentary to bone marrow MRD detection, lowering the burden of sequential MRD measurements using invasive bone marrow-based techniques.

Figure 1.



P38 PATIENT-REPORTED OUTCOMES (PRO) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM) TREATED WITH MELFLUFEN AND DEXAMETHASONE (DEX) OR POMALIDOMIDE (POM) AND DEX: ANALYSES FROM THE PHASE 3 OCEAN STUDY

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Background: The phase 3 OCEAN study (OP-103; NCT03151811) met its primary endpoint; melphalan flufenamide (melflufen) + dex showed superior progression-free survival vs pom+dex in patients with RRMM refractory to lenalidomide, but overall survival (secondary endpoint) numerically favored pom+dex (Schjesvold FH, et al. *Lancet Haematol*. 2022;9[2]:e98-e110). Hematologic adverse events (AEs) were more frequent with melflufen+dex, but grade 3/4 infections were more common with pom+dex. Melflufen+dex was approved in Europe for the treatment of patients with ≥3 prior lines of therapy and triple—class refractory RRMM; if patients had prior autologous stem cell transplant (ASCT), time to progression (TTP) must have been >36 months.

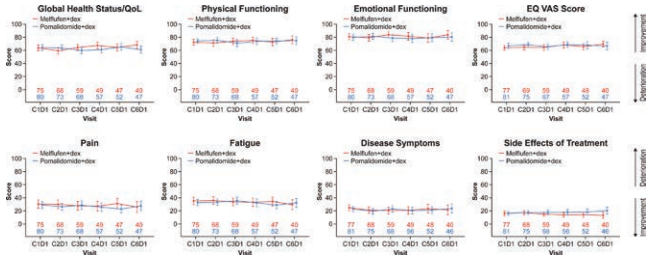
RRMM is associated with severe symptoms, of which pain, fatigue, physical functioning, and emotional functioning have been strongly linked to impairments in health-related quality of life (HRQoL) for patients. Because HRQoL is known to deteriorate with each subsequent line of therapy, treatment goals should include preserving or even improving HRQoL (Engelhardt M, et al. *Clin Lymphoma Myeloma Leuk*. 2020;21[2]:e160-e175).

Objective: To evaluate functional status and well-being based on PRO assessments in patients receiving treatment with either melflufen+dex or pom+dex in the OCEAN study. Secondly, to assess PROs in the subgroup of patients with TTP >36 months after an ASCT or had no prior ASCT to understand whether results are generalizable to patients in the global target population.

Methods: EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D-3L were included in the OCEAN trial beginning with protocol version 4.1 and assessed before treatment in each cycle. Mean scores per cycle and change from baseline to cycle 6 were analyzed for Global Health Status/QoL, Physical Functioning, Emotional Functioning, Pain, Fatigue, Disease Symptoms, and Side Effects of Treatment. Within the melflufen+dex arm, the target population was compared vs the non–target population (ie, patients with TTP <36 months after an ASCT).

Results: Baseline characteristics were generally well matched between patients reporting PROs (n=158) and the overall study population (N=495). Overall, mean baseline scores before treatment were similar between melflufen+dex and pom+dex treatment groups: 63.8 vs 64.3 in Global Health Status/QoL, 72.4 vs 74.2 in Physical Functioning, 81.0 vs 79.8 in Emotional Functioning, 35.1 vs 32.6 in Fatigue, 30.2 vs 28.7 in Pain, 24.7 vs 22.6 in Disease Symptoms, 16.1 vs 16.1 in Side Effects of Treatment, and 64.0 vs 66.9 for the EQ-5D-3L VAS, respectively. Mean scores remained generally constant between baseline and follow-up timepoints (Figure). Mean baseline scores before treatment with melflufen+dex were similar between the target population and the non–target population groups: 65.3 vs 61.9 in Global Health Status/QoL, 73.2 vs 71.5 in Physical Functioning, 83.3 vs 78.0 in Emotional Functioning, 30.7 vs 40.7 in Fatigue, 26.2 vs 35.4 in Pain, 23.0 vs 27.1 in Disease Symptoms, 15.9 vs 16.3 in Side Effects of Treatment, and 64.8 vs 62.8 for the EQ-5D-3L VAS, respectively. Despite small patient numbers (n=44), the target population group showed a similar trend to that of the overall population.

Conclusion: Given the negative impact of treatment-related AEs on HRQoL in RRMM, results from OCEAN are encouraging. HRQoL was maintained throughout treatment with melflufen+dex, including in the target population, and was similar to that with pom+dex.



P39 DEDALO: PHASE II STUDY OF DARATUMUMAB PLUS POMALIDOMIDE AND DEXAMETHASONE (DPD) IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA AND 17P DELETION

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Introduction: Deletion of the short arm of chromosome 17 (del(17p)) is a well-established high-risk feature in multiple myeloma (MM) and is included in current disease staging criteria. Treatment of del(17p) MM is a major challenge due to rapid development of chemoresistance and short survival. The size of del(17p) clone correlates with prognosis, and the 55-60% threshold has the worst prognosis. Approximately 1/3 of pts have a concomitant TP53 mutation, with a complete abolition of the protein function. TP53 biallelic inactivation is defined as double-hit myeloma.

Pomalidomide-dexamethasone showed promising results in this setting (Leleu et al, Blood 2014). Daratumumab is an attractive strategy for treatment of MM pts with del(17p).

In the phase II DEDALO trial (NCT04124497), we assessed daratumumab-pomalidomide-dexamethasone (DPd) in RRMM pts with del(17p).

Methods: Key eligibility criteria included: RRMM; up to 3 prior lines of therapy, del(17p) observed by FISH in at least 10% of plasma cells at any time of MM history, previous exposure to lenalidomide, no refractoriness or intolerance to pomalidomide, nor previous exposure to an anti-CD38 monoclonal antibody.

Continuous DPd treatment consisted of daratumumab (1800 mg subcutaneously or 16 mg/kg intravenously) weekly during cycles 1 and 2, every 2 weeks during cycles 3–6, and every 4 weeks thereafter; oral pomalidomide (4 mg, once daily on days 1–21); and oral or intravenous dexamethasone (40 mg once daily on days 1, 8, 15, and 22; 20 mg for pts ≥75 years) at each 28-day cycle. The primary endpoint was MRD 10-5 negativity within the first 12 months of treatment. NGF and NGS MRD analyses were performed. The key secondary endpoints were PFS, ORR and OS.

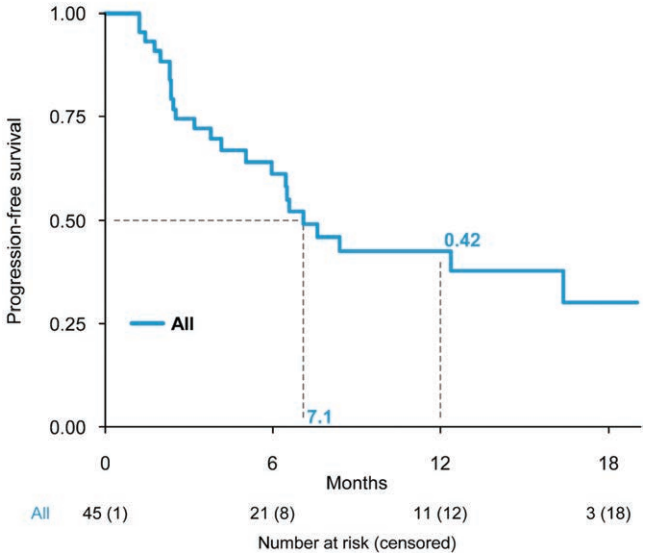
Results: Forty-five pts were enrolled. The median age was 63 (range 43-83) years (yrs), and 60%/29%/11% of pts had ISS stage I/II/III. All pts had >10% del(17p) and 14 pts had ≥55% del(17p); t(4;14) was observed in 6, t(14;16) in 6, del(1p) in 10, and 1q+ in 16 pts. Median number of prior lines of therapy was 1 (range 1-3); 100% had been previously exposed to lenalidomide and 86% to a proteasome inhibitor.

Three pts achieved MRD negativity by NGF, while NGS analysis is ongoing. ORR was 60%, including 13 pts with PR, 12 with VGPR, and 2 with ≥CR. Median time-to-response was 2.5 months. With a median follow-up of 8.5 months (range 6.3-13.9), median PFS was 7.1 months (range 5.9 – not reached [NR]; Figure).

By subgroup analysis, PFS was: 8.4 months in pts with del(17p) clone size <60% and 6.5 months in pts with del(17p) clone size ≥60% (HR, 0.75; 95% CI 0.33-1.7; P=0.48); 12.4 months in pts with ISS I vs 4.2 months in pts with ISS II-III (HR, 2.48; 95% CI 1.12-5.51; P=0.02); 6.6 months in pts at first relapse vs 7.1 months beyond first relapse (HR 0.95; 95% CI 0.42-2.12; P=0.89); 7.1 months in pts <65 yrs and 7.6 months in those ≥65 yrs of age (HR 0.84; 95% CI 0.37-1.92; P=0.68). Median OS was NR. No new safety concerns were observed. TP53 mutational analysis is underway.

Conclusion: In this difficult-to-treat population, DPd is a therapeutic option for pts of all ages and can be considered as a bridge to other immunotherapies, such as T-cell engagers and CAR-T cells.

Figure. Progression-free survival



P40 REAL-WORLD TREATMENT PATTERNS OF PATIENTS INITIATING THIRD-LINE THERAPY IN RELAPSED/REFRACTORY MULTIPLE MYELOMA IN EUROPE

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Objectives: Real-world (RW) evidence can provide valuable insights into clinical practice and help identify and address unmet medical needs. We report RW treatment utilisation in patients from European data sets who initiated third-line (3L) treatment for relapsed/refractory multiple myeloma (RRMM).

Methods: This retrospective, noninterventional analysis used claims data from the German AOK PLUS health insurance fund and Italian Local Health Units (2012–2020). Patients initiating 3L treatment from 2016–2020 (index) were identified using an algorithm based on prescription and procedure codes. New lines of treatment were defined as introduction of a new agent not part of the prior line. Agents given ≤30 days of start of the line defined the regimen. Retreatments after >6 months of discontinuation were considered a new line. Baseline characteristics and treatment patterns were reported.

Results: Patients were identified from Germany (N=276) and Italy (N=289) (Table). Baseline characteristics were similar between countries. Prior to 3L treatment, immunomodulatory imide drug (IMiD) use was higher (74% vs 56%) and proteasome inhibitor (PI) use was lower (52% vs 96%) among patients in Italy versus Germany. At 3L, the proportion of double-class exposed patients in Italy was lower versus Germany (33% vs 52%).

In Germany, common first-line (1L) regimens were bortezomib (BORT) + dexamethasone (DEX; Vd, 46%), BORT + melphalan (MEL) + prednisone (PRED; VMP, 14%), and Vd + cyclophosphamide (CyBORD, 8%). The most common second-line (2L) treatment regimens were lenalidomide (LEN) + DEX (Rd, 30%), Vd (11%), and carfilzomib (CFZ) + Rd (KRd, 8%). By 3L, 95% and 54% of patients had received prior BORT- and LEN-based regimens, respectively. In 3L, combinations were often LEN- and/or CFZ-based with daratumumab (DARA) monotherapy and pomalidomide + DEX (Pd) also contributing ~4% each (Table).

Table

Baseline (12 months) and treatment characteristics in patients with relapsed/refractory multiple myeloma who initiated 3L treatment

Characteristic	Germany (N=276)	Italy (N=289)
Male, n (%)	139 (50)	141 (49)
Median age at index (interquartile range), years	75 (65–80)	73 (66–79)
Median time since diagnosis (range), years	2.7 (0.4–7.4)	2.1 (0.3–6.7)
Year of 3L treatment initiation, n (%)		
2016	58 (21)	35 (12)
2017	57 (21)	48 (17)
2018	57 (21)	52 (18)
2019	54 (20)	80 (28)
2020	50 (18)	74 (26)
Prior treatment (excluding maintenance), n (%)		
PI	264 (96)	151 (52)
Immunomodulatory drug	154 (56)	213 (74)
anti-CD38	30 (11)	13 (4.5)
LEN + PI-exposed and POM-naive	135 (49)	61 (21)
Double-class exposed	144 (52)	96 (33)
Triple-class exposed	15 (5)	8 (3)
Stem cell transplant	75 (27)	43 (15)
3L treatment regimens ≥4% in either country, n (%)		
Rd	53 (19)	79 (27)
KRd	27 (10)	11 (4)
Kd	22 (8)	9 (3)
DRd	22(8)	15 (5)
DVd	18 (7)	≤3[a]
Pd	11 (4)	35 (12)
DARA	11 (4)	0 (0)
Melphalan + prednisone	0 (0)	21 (7)

a
Not issuable due to anonymisation regulations.
Rd, LEN + DEX; KRd, CFZ + LEN + DEX; Kd, CFZ + DEX; DRd, DARA + LEN + DEX; DVd, DARA + BORT + DEX; Pd, POM + DEX.
3L, third-line; BORT, bortezomib; CFZ, carfilzomib; DARA, daratumumab; DEX, dexamethasone; LEN, lenalidomide; PI, proteasome inhibitor; POM, pomalidomide.

In Italy, common 1L regimens included MEL ± DEX ± PRED (22%), Vd (6%), and thalidomide (THAL) + DEX (5%). Rd (40%) and Vd (8%) were the most common 2L regimens; by 3L, 56% and 49% of patients had received prior LEN- and BORT-containing regimens, respectively. Overall, use of Pd in 3L in Italy was higher than in Germany (12% vs 4%), whereas use of CFZ- (10% vs 21%) and DARA-based (9% vs 29%) regimens was lower. In 3L, use of conventional therapies, such as MEL (15% vs 3%), was higher in Italy versus Germany.

Retreatment patterns in Germany and Italy showed that 60% and 82% of patients initiating 3L treatment, respectively, had prior exposure to the same agent class (IMiD, PI, monoclonal antibodies). Of 50 patients in Germany receiving BORT in 3L, 47 (94%) had prior BORT; of 135 patients receiving LEN in 3L, 47 (35%) had prior LEN. Of 40 patients in Italy receiving BORT in 3L, 31 (78%) had prior BORT; of 131 patients receiving LEN in 3L, 82 (63%) had prior LEN. Additionally, of 13 patients in Italy who received prior THAL, all were retreated with THAL in 3L.

Conclusions: This study provides a perspective of RW clinical practice from 2012-2020 for comparison with the evolving treatment landscape for RRMM.

P41 NO EVIDENCE OF B-CELL MATURATION ANTIGEN (BCMA) EXPRESSION LOSS OR SYSTEMIC IMMUNE IMPAIRMENT AFTER TREATMENT WITH THE BCMA-TARGETED ANTIBODY-DRUG CONJUGATE BELANTAMAB MAFODOTIN IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

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Objectives: Belantamab mafodotin (belamaf)—an antibody-drug conjugate targeting B-cell maturation antigen (BCMA)—demonstrated deep and durable responses in the DREAMM-2 trial of patients with relapsed/refractory

multiple myeloma (RRMM). Belamaf eliminates multiple myeloma (MM) cells by both direct cell killing and anti-MM immune response. We explored whether complete target loss and/or immune impairment were observed in belamaf-treated patients in the DREAMM-1 and -2 trials.
Methods: DREAMM-1 was a Phase 1 dose-escalation study to investigate the safety, pharmacokinetics/pharmacodynamics, immunogenicity and clinical activity of belamaf. DREAMM-2 was an open-label, two-arm, Phase 2 study of belamaf (2.5 or 3.4 mg/kg, once every three weeks). Both trials enrolled adults with RRMM with ≥3 prior lines of therapy including an immunomodulatory drug, proteasome inhibitor and an anti-CD38 monoclonal antibody (DREAMM-2 only). Free serum (s)BCMA—a shed form of BCMA that circulates in the blood after membrane cleavage—was measured using an electrochemiluminescence assay. Absolute sBCMA concentrations were examined at baseline, with absolute concentration and fold-change from baseline assessed at best achieved response and latest progression. After the first post-infusion timepoint, samples were taken >4 days post infusion. In this post hoc analysis, association of sBCMA with time-on-study was modelled using a linear mixed model. Immune cell populations in peripheral blood were analysed using flow cytometry and clinical hematology tests. Neutrophil-to-lymphocyte ratio and total lymphocyte counts were modelled by categorical patient visit adjusted for continuous or count-based biomarkers; T-cell subpopulation counts were modelled using negative binomial mixed effects models.
Results: At progression, sBCMA levels were detectable in 98% (50/51) of eligible patients in DREAMM-1 and in 98.9% (181/183) of eligible patients in DREAMM-2, regardless of response status. Decreased sBCMA versus predose levels was observed immediately post infusion in all response groups. In non-responders, sBCMA returned to predose levels within one cycle. Responders (≥partial response) had a quantitatively lower but measurable sBCMA level. In 97% (64/66) of patients who responded but later progressed in DREAMM-2, sBCMA levels dropped markedly during response but returned to near baseline upon progression. Previously, sBCMA levels have been shown to correlate with disease burden markers (e.g., M-protein) and International Staging System stage; we modelled sBCMA correcting for these associations to evaluate on-treatment dynamics, predicting a decrease in sBCMA with increasing time-on-treatment. After correcting for lower average baseline and on-treatment sBCMA levels in responders, sBCMA levels tended to decrease over time. There were no changes in immune cell ratios or major cell populations, regardless of response status. Immune cell profiles of responders and non-responders were similar and consistent over time.
Conclusions: We found no evidence that BCMA expression is completely lost after belamaf treatment, suggesting that complete target loss is not the primary mechanism driving tumour escape in these patients. Regardless of response status, belamaf does not appear to negatively impact total lymphocyte numbers while mediating anti-MM activity. These data may help inform sequencing of belamaf with other BCMA-targeted therapies.

P42 HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA TREATED WITH TALQUETAMAB, A G PROTEIN-COUPLED RECEPTOR FAMILY C GROUP 5 MEMBER D X CD3 BISPECIFIC ANTIBODY, FROM MONUMENTAL-1

van de Donk N.[1]; Rasche L.[2]; Touzeau C.[3]; Chari A.[4]; Schinke C.[5]; Minnema M.[6]; Berdeja J.[7]; Oriol A.[8]; Rodriguez-Otero P.[9]; Askari E.[10]; Mateos M.[11]; Costa L.[12]; Caers J.[13]; Krishnan A.[14]; Vishwamitra D.[15]; Ma J. [15]; Qin X.[15]; Gries K.S.[16]; Kato K.[16]; Campagna M.[17]; Masterson T.[15]; Hilder B.[15]; Tolbert J.[15]; Renaud T.[18]; Goldberg J.[18]; Heuck C.[15]; Moreau P.[19]; San-Miguel J.[1]

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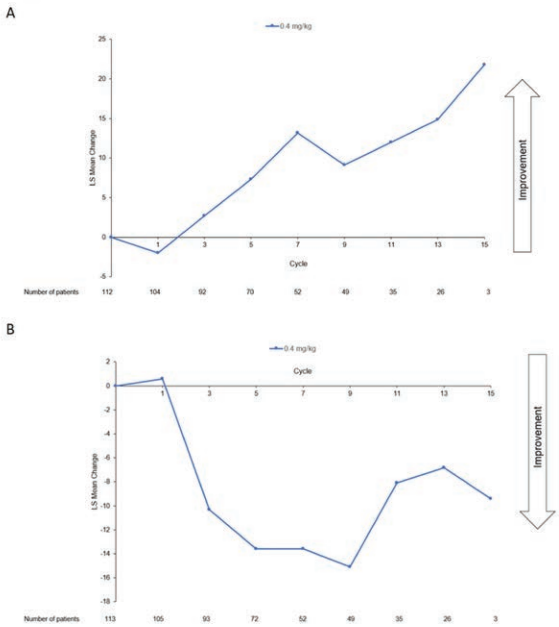
Introduction: Studies of patients (pts) with multiple myeloma (MM) indicate that those with more advanced and heavily pretreated disease have worse health-related quality of life (HRQoL) than those with early stage disease. In addition, treatment options are limited for triple-class exposed relapsed/refractory MM (RRMM), with less hope of improving HRQoL. Talquetamab (TAL), a first-in-class, off-the-shelf, T-cell redirecting bispecific antibody targeting both GPRC5D and CD3 receptors. Patient reported outcomes (PROs) data on HRQoL, symptoms, and functioning were collected in phase (ph) 2 cohorts of MonumenTAL-1, a ph 1/2 trial (NCT03399799/NCT04634552) of TAL in RRMM pts. Here we report PROs, focusing on global health status (GHS), physical functioning, pain, and fatigue, for 0.4 mg/kg subcutaneous (SC) weekly (QW) cohort. Data for 0.8 mg/kg SC every other week (Q2W) cohort are immature.
Methods: Enrolled pts in ph 2 had received ≥3 prior lines of therapy, including ≥1 proteosome inhibitor/≥1 immunomodulatory drug, and ≥1 anti-CD38 monoclonal antibody (triple-class exposed). Post screening, pts received TAL priming doses, requiring hospitalization, before Cycle (Cy)1. European Organization for Research and Treatment of Cancer Quality of Life Core 30 item (EORTC QLQ-C30) questionnaires was administered at screening, Cy1, and then every other cycle. It included a subscale to measure HRQoL, 5 functional scales, 3 symptom subscales, and 6 additional single items. Score range from 0-100; higher scores indicate better GHS and functioning, with higher scores indicating more symptom severity. PRO compliance was calculated as number of completed assessments divided by number of pts on study treatment at each assessment time point. Treatment effect was assessed with a mixed-effects model with repeated measures. For analysis of proportion of pts with meaningful improvement, threshold for meaningful improvement from baseline was change ≥10 points. Kaplan-Meier estimate was used to determine time to worsening.
Results: For pts treated with 0.4 mg/kg SC QW (n=122) compliance for EORTC QLQ-C30 was 96% at screening and >80% at most post-treatment visits. After an immediate decline in overall HRQoL between screening and Cy1, pts had meaningful improvements in EORTC QLQ-C30 GHS and a meaningful reduction in pain symptoms (**Figure**). For fatigue symptoms, mean change for the 0.4 mg/kg cohort was -8 (95% CI -13.83, -2.26) at Cy9 and reached a mean decrease (ie improvement) of 10 points (95% CI -19.31, -0.93) at Cy13. Similar results were noted in physical (LS mean [LSM] change for 0.4 mg/kg at Cy9: 6.5 (95% CI 2.05, 10.93) and role (LSM change at Cy9: 11.4 (95% CI 4.55, 18.25) functioning subscales. With treatment, proportion of pts with meaningful improvement was high; for example, at Cy9 for the 0.4 mg/kg cohort, 42% improved in GHS, 34% physical functioning, 40% role functioning, 86% pain symptoms, and 78% in fatigue symptoms. Median time to worsening for the 0.4 mg/kg SC QW cohort ranged from 2 months (role and social functioning) to 9 months (nausea/vomiting). Overall, changes in PROs were similar in 0.8 mg/kg SC Q2W cohort; however, conclusions are limited due to short follow-up and small sample size.
Conclusions: With TAL, pts reported improvement in overall HRQoL and physical and role functioning, and a decrease in pain and fatigue. These results are consistent with clinical benefits of TAL as observed for the efficacy results of MonumenTAL-1 study.

Figure. Least squares mean change from screening in (A) global health status and (B) pain symptoms



P43 CIRCULATING CLONAL PLASMA CELLS AT START OF SALVAGE REGIMEN PROVIDE POWERFUL PROGNOSTICATION BIOMARKER IN MULTIPLE MYELOMA PATIENTS AT FIRST RELAPSE

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Introduction: There is a growing interest in investigating the clinical impact of circulating clonal plasma cells (CCPC) quantitation reflecting the tumor burden in multiple myeloma (MM), due to its easy access and non-invasive nature. Recent studies have highlighted the value of quantification of CCPC at diagnosis for risk stratification of transplant eligible and not MM. However, prospective data on the real-world utility of CCPC quantitation in relapsed-refractory patients (RRMM) treated with novel immunotherapies is extremely scarce.

Aims: To investigate the prognostic value of CCPC quantitation in treated with novel immunotherapies using high-sensitivity multicolor-flowcytometry (HS-MFC) and the relevance of their assessment in predicting overall survival (OS).

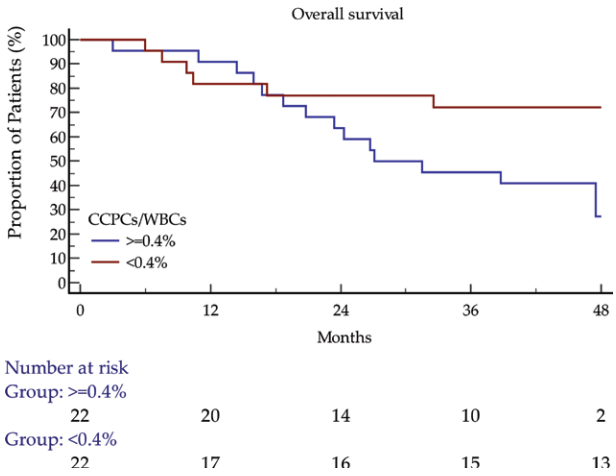
Methods: We prospectively evaluated 44 consecutive MM patients requiring first salvage regimen containing daratumumab from July 2018 through July 2021 (age: median-65 years; range-44-81 years; M/F-30/14). CCPC levels were studied using 10-13 color HS-MFC (sensitivity- 0.0001% or 1x10e- 6) at the start of the salvage regimen. CCPC levels were calculated as CCPC percentages in total WBCs (%CCPC/WBC). The cut-off value was identified using ROC analysis against OS. Initial therapeutic response (ITR) was monitored at the end of the second cycle of treatment.

Results: The median follow-up was 46 months (range 1-51 months). ITR included CR-VGPR 6.5%, VGPR/PR-63.0%, SD-21.7%, and 4 (8.7%) patients died during initial therapy.

CCPCs were detected in all patients. Median %CCPC/WBC was 0.41% (range, 0.004-6%). CCPCs from patients with higher LDH and extra-medullary disease carried significant lower amount of CD27 and CD81 and higher amount of CD200 although no difference in the percentage of CCPCs was recorded.

%CCPC/WBC ≥0.4% was strongly associated with OS (27.1 months vs 48.5; HR-2.5; p=0.04).

Conclusion: This prospective study showed that CCPC quantification (≥0.4% of WBC) at start of daratumumab-based salvage regimen in RRMM patients treated at the first relapse provides a powerful independent biomarker for the prediction of OS. Such assessment is more convenient for routine clinical practice and should be confirmed in larger studies.



P44 DETECTION OF SOLUBLE BCMA IN TEARS OF MM PATIENTS TREATED WITH BELANTAMAB MAFODOTIN

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Belantamab mafodotin (Belamaf) is the first BCMA targeted therapy approved for the treatment of Multiple Myeloma patients with relapsed or refractory disease who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. This antibody-drug conjugate containing monomethyl auristatin F (MMAF) provides deep and durable remissions in this hard-to-treat MM population, but also induces significant ocular toxicity. This includes microcytic-like epithelial changes leading to transient blurred vision, dry eyes symptoms and loss of visual acuity. The underlying mechanisms are not yet fully understood, but clinical evidence from other ADC studies suggests that the cytotoxic payload MMAF is associated with the ocular toxicity observed. Of note, the cornea itself is not vascularized and does not express BCMA, thus, it remains an open question how toxic effects are transmitted to the cornea. It has been hypothesized that ADC may be transported via the vessels of the corneal limbus, but also transportation via the tear fluid is possible. To date, dose reduction of Belantamab Mafodotin is the only way to efficiently reduce ocular side effects of the treatment and no other mitigation strategies have been successfully established.

We screened for soluble BCMA (sBCMA) in peripheral blood and tear fluid in seven healthy young volunteers and in 10 randomly selected MM patients from our institution. Tear fluid was collected using polyvinyl sponges and later eluted via high speed centrifugation. A commercially available human BCMA ELISA kit was used for BCMA quantification. Plasma samples were diluted within range of 1:40 to 1:500 and tear fluid was diluted 1:50 using dilution buffers provided according to manufacturer's instruction.

In our healthy cohort, peripheral blood sBCMA (PBsBCMA) levels ranged from 10-20ng/ml with no difference between plasma and serum. Strikingly, we detected sBCMA in the tear fluid, but quantities were 10-fold reduced (0,5 to 3ng/ml). This, to the best of our knowledge, is the first report of sBCMA in human tear fluids (TFsBCMA), providing a novel potential transport mechanism of MMAF or of the ADC to the cornea epithelium.

We next measured PBsBCMA and TFsBCMA levels in 10 MM patients from our institution and, likely reflecting their active and variable tumor burden, we found an increase not only in PBsBCMA (50-3500ng/ml) but also TFsBCMA load (3ng to 772ng/ml) compared to our healthy individuals. Interestingly, three patients with the highest TFsBCMA levels were treated with Belantamab Mafodotin at the timepoint of sampling, with a 50- to 100-fold increase compared to MM patients not treated with anti-BCMA therapy. The ongoing DREAMM-5 trial interrogates the addition of the gamma-secretase inhibitor Nirogacestat to minimize sBCMA levels in patients treated with Belantamab Mafodotin. Our novel finding of TFsBCMA suggests that it may be of additional value to also track TFsBCMA levels in these patients, and that such a strategy, lowering sBCMA levels, may not only increase treatment efficiency but may also hold potential to reduce ocular side effects under Belantamab Mafodotin therapy.

P45 HIGH-DOSE CARFILZOMIB ACHIEVES SUPERIOR ANTI-TUMOR ACTIVITY OVER LOW-DOSE AND RECAPTURES RESPONSE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA RESISTANT TO LOW-DOSE CARFILZOMIB BY CO-INHIBITING THE B2 AND B1 PROTEASOME SUBUNITS

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The proteasome is a multi-subunit complex responsible for intracellular protein degradation, while only 3 subunits harbor proteolytic activity, the. β1, β2, and β5 subunits. Carfilzomib (CFZ), a second-generation proteasome inhibitor (PI), induces cell death in multiple myeloma (MM) by selective and irreversible β5 inhibition. Currently, the optimal CFZ dosing is still controversial, with the approved dosage ranging from 20 to 70mg/m2 in different regimens. Moreover, it remains to be explored whether high-dose CFZ can achieve superior anti-MM efficacy over low-dose and recapture response in relapsed/refractory (RR) MM patients progressing under low-dose CFZ. To address these issues, we analyzed

the clinical data and the inhibition profiles of proteolytic proteasome subunits β1, β2, and β5 of RRMM patients treated with different CFZ doses. We prospectively collected clinical data and peripheral blood mononuclear cells (PBMC) of 103 patients with RRMM before and 3 hours after CFZ. PBMC were lysed and labelled for the activity of individual proteasome subunits using activity based proteasome probes and the proteasome subunits were separated using SDS-PAGE. The activity of constitutive and immunoproteasome β1, β2 and β5 subunits was evaluated by densitometry analysis. We then investigated the clinical data of 114 patients treated with CFZ combinations.
Overall, 23, 27, 38, and 15 patients received 20, 27, 36, and 56 mg/m2 of CFZ, respectively. β5 activity was inhibited (median inhibition >50%) in vivo by 20 mg/m2, whereas β2 and β1 were co-inhibited only by 36 and 56 mg/m2, respectively. Co-inhibition of β2 (P=0.0001) and β1 activity (P=0.0005) differed significantly between high-dose (36 or 56 mg/m2) and low-dose (20 or 27 mg/m2) CFZ. Subsequently, high-dose CFZ showed significantly more effective proteasome inhibition than low-dose drug in vivo (P=0.0003). We then investigated the clinical data of 114 MM patients treated with CFZ combinations Kd, KRD, and D-Kd. In the entire group, high-dose CFZ demonstrated a higher overall response rate (P=0.03) and longer progression-free survival (PFS) (P=0.007) than low-dose. In the subgroup analysis of Kd, high-dose CFZ likewise showed improved PFS over low-dose (P=0.0006). In patients treated with KRD, PFS was significantly longer in patients who had received high-dose CFZ than low-dose (P=0.02), while lenalidomide dose did not affect PFS in our cohort. In light of this finding, we escalated the dose of CFZ to ≥ 36 mg/m2 in 16 patients who progressed during low-dose CFZ-containing therapies, and the doses of agents other than CFZ in the combination regimens remained the same. High-dose CFZ recaptured response (≥ partial remission) in 9 (56%) patients with a median PFS of 4.4 months.
Here, we provide the first in vivo evidence in RRMM patients that the molecular activity of high-dose CFZ (≥ 36 mg/m2) differs from that of low-dose CFZ by co-inhibition of β2 and β1 proteasome subunits and, consequently, high-dose CFZ achieves a superior anti-MM effect than low-dose and recaptures response in RRMM being resistant to low-dose CFZ.

P46 SEER-MEDICARE DATABASE: REAL-WORLD TREATMENTS AND OUTCOMES IN PATIENTS WITH LENALIDOMIDE-REFRACTORY RELAPSED MULTIPLE MYELOMA TREATED WITH 1–3 PRIOR LINES OF THERAPY, INCLUDING A PI AND IMID

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Background: Significant advances in multiple myeloma treatments have been made in recent years, but real-world data on outcomes with these newer agents in patients with relapsed/refractory disease are limited. We report treatment patterns and survival outcomes from the Surveillance, Epidemiology, and End Results (SEER)-Medicare database for patients with multiple myeloma who have received 1–3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and are lenalidomide-refractory.
Methods: Data collected from January 2016 to December 2019 (last available data) were assessed. Adult multiple myeloma patients were included if they had received 1–3 prior LOT, were exposed to a PI and IMiD, and were lenalidomide-refractory. Time zero (T0) was defined as the start date of the first treatment post eligibility. Descriptive statistics were used to evaluate patient characteristics at baseline and treatment patterns, stratified by prior LOT. The Kaplan-Meier method was used to analyze survival outcomes, including overall survival and time to next treatment. Overall survival was defined as the time interval between T0 and all-cause mortality. Time to next treatment was defined as the time interval between T0 and start of subsequent treatment or death, whichever occurred first.
Results: From 70,262 multiple myeloma patients, 1,319 were identified (1 prior LOT: n=466; 2 prior LOT: n=641; 3 prior LOT: n=212), with a median time from multiple myeloma diagnosis to T0 of 25.1 months. The median age of patients was 75 years, 52.5% were male, 82.6% were White, and 10.9% were Black. The mean Charlson comorbidity index was 3. Overall, approximately 85 unique subsequent treatment regimens were identified. The most common regimens based on hierarchy were daratumumab- (24.2%), pomalidomide- (16.5%), and carfilzomib-based (13.0%). Doublet therapies were the most common regimen for patients with 1 prior LOT (36.7%) and 2 prior LOT (38.2%), whereas triplet therapies were the most common for those with 3 prior LOT (35.4%). Overall, the most common regimens were pomalidomide/dexamethasone (7.6%), daratumumab/pomalidomide/dexamethasone (6.5%), daratumumab/bortezomib/dexamethasone (6.4%), and bortezomib/pomalidomide/dexamethasone (5.6%). Median overall survival was 32.1 months for patients with 1 prior LOT, 17.7 months for patients with 2 prior LOT, and 10.8 months for patients with 3 prior LOT; median time to next treatment (serving as a proxy for progression-free survival) was 5.5, 5.7, and 4.5 months, respectively.
Conclusion: Patients with 1–3 prior LOT who are PI- and IMiD-exposed, and lenalidomide-refractory progress quickly through currently available treatments, and survival outcomes remain poor. This population-based analysis shows the absence of a clear standard of care for this difficult-to-treat, older, comorbid patient population, and highlights the need for new and effective treatment regimens, as well as multidisciplinary supportive care.

P47 REAL-WORLD DATA OF ATTRITION RATES BY SUBSEQUENT LINES OF THERAPY IN MULTIPLE MYELOMA PATIENTS TREATED IN A TERTIARY CARE ITALIAN CENTRE

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Despite therapeutic progress leading to a significant improvement of outcomes, most Multiple Myeloma (MM) patients relapse and require subsequent lines of therapy (LOTs). Nevertheless, several cross-sectional real-life studies demonstrated that many patients were not able to receive subsequent LOTs [Raab MS et al, Br J Haematol 2014; Raab MS et al, Br J Haematol 2019; Coriu D et al, Pol Arch Int Med 2018]. Retrospective longitudinal studies reported that Attrition Rates (ARs), defined as the rate of patients who fail to receive a subsequent LOT for any reasons, like death or lack of fitness, was high and increasingly across all LOTs [Fonseca R et al, BMC Cancer 2020; Steinmetz T et al, Oncol Res Treat 2021].
In order to verify these data in an Italian real life setting, we conducted a retrospective observational monocentric study on treatment patterns and ARs across all LOTs in newly diagnosed MM patients recorded in our database from 2011 to 2021, evaluating treatment patterns of each LOT; AR across LOTs; ORR, CR and survival rates of each LOT and potential factors affecting AR by logistic regression analysis.
We analyzed 413 patients with a median age of 69 years (range 30-93), 61.5% older than 65 years, with ECOG PS ≥ 2 in 22% and 118 (30%) who had more than 2 comorbidities. R-ISS stage 2-3 and renal failure were detected in 74% and 18% of patients respectively. Median follow-up was 48.7 months (range 6-140). In LOT-2 the most frequently used regimens were lenalidomide (L)-based (35%) and bortezomib (B)-based (33%). In LOT-3 patients received mainly L- (21.5%), pomalidomide (P)- (20.5%) and B-based (18%) regimens whereas both carfilzomib (K)- and antiCD38 MoAbs-based regimens were given to 14% of patients. In LOT-4 and LOT-5 P-based regimens were the most used (26.5% and 32%, respectively). Rate of patients receiving therapy from LOT1 to LOT-5 are summarized in the Table. AR was found to be 25% in LOT-1, 39%, 37% and 39% across LOT-2, LOT-3 and LOT-4, respectively, and 50% in subsequent LOTs. Moreover, we examined differences in AR by time, finding that patients who did not receive a LOT-2 were 43/71 (≤2018) and 28/71 (>2018). So, AR was 60.5% in the cohort before 2018 vs. 39.5% after 2018. In univariate analysis age >65 years, ISS 2-3, > 2 comorbidities, no transplant, response < VGPR and no maintenance were significantly associated with higher AR but regression analysis selected only age > 65 years [OR 7.4 (3.3-16.5)] and > 2 comorbidities [OR 2.5 (1.5-5.6)] as factors affecting AR. Of note, comparing transplant eligible with not transplant eligible patients, AR was 8% vs 42% (p<0.0001) in LOT-2, 16% vs 60% (p<0.0001) in LOT-3 and 29% vs 50% (p=0.053) in LOT-4, respectively. ORR and CR rates, TTNT and OS throughout the lines of therapy are reported in the Table.

In our real-life experience a quarter of patients was not able to receive a LOT-2 and a LOT-3 after a first and a second relapse, respectively. In the subsequent relapses ARs were higher sinceabout a third of patients did not receive a LOT-4 and a LOT-5 and half of patients did not receive further lines. However, AR seems to be globally lower than that described by cross-sectional studies. We found fit and young patients are able to receive many LOTs, whereas older patients and/or patients with comorbidities are not. But in recent years this scenario is also improving for older patients, reinforcing the idea to continue new drugs experimentation also in the later LOTs.

	LOT-1	LOT-2	LOT-3	LOT-4	LOT-5
Patients, n (%)	413	200 (48)	92 (22.5)	45 (11)	25 (6)
Relapsed, n	270	145	68	40	24
Ongoing or in response, n (%)	140 (34)	50 (25)	21 (23)	4 (9)	1 (4)
Death without relapse (%)	3 (1)	5 (2.5)	3 (3)	1 (2)	-
Next LOT, n (%)	200 (73)	92 (61)	45 (63)	25 (61)	12 (50)
Attrition rate (%)	27	39	37	39	50
ORR (%)	85	70	52	31.5	9.5
CR (%)	37	25	16.5	8	0
TTNT, median, months	40.5	19.5	10.3	6	4.7
OS, median, months	83	38.3	24	12.2	10.5

P48 CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE IN RELAPSED REFRACTORY MULTIPLE MYELOMA: A PROSPECTIVE REAL-LIFE EXPERIENCE OF THE REGIONAL TUSCAN MYELOMA NETWORK (RTM)

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Background: In recent years, the clinical outcome of multiple myeloma (MM) patients has improved due to the introduction of several new agents, such as the third-generation immunomodulator, the next-generation proteasome inhibitors (PIs) and the introduction of immunotherapy. Carfilzomib, a potent, irreversible, selective proteasome inhibitor, has demonstrated consistent results in relapsed/refractory myeloma (RRMM) combined with lenalidomide and dexamethasone (KRd) [1]. However, no prospective studies are yet available that analysed the efficacy of KRD combination.
Aim: We evaluated the response and safety data in patients prospectively treated with the KRd regimen outside of clinical trials.
Methods: We reported a multicentre prospective observational study on 85 patients, treated with KRd combination as second or third line of therapy between December 2016 and December 2019. The patients were then followed for the next two years (data cut-off December 2021).
Results: Median age was 61 years old; high-risk cytogenetic and renal impairment (eGFR < 60 ml/min) were referred in 26% and 17% of the patients, respectively. Nearly all patients (98%) had received prior bortezomib-based treatment, among them 43% were refractory. Instead, nine patients (10.5%) were exposed to lenalidomide, with a refractory rate of 60%. After a median follow up of 40 months, patients received a median number of 16 cycles of KRd and the median duration of treatment was 18 months (range: 16.1–19.2 months). The overall response rate was 95%, with high-quality response (≥ very good partial remission [VGPR]) in 57% of the patients: stringent complete remission and complete remission were achieved in 10% and 28%, respectively, VGPR in 19%. The median progression free survival (PFS) was 36 months (range: 29.1–43.2 months). PFS was improved by the achievement of at least VGPR (median 38 vs 17 months; HR=1.73, 95% confidence interval [CI]: 0.98-3.13, p=0.002) and by previous ASCT (median 38 vs 28 months, HR=0.59, 95% CI: 0.32-0.83, p=0.02). The median OS was NR (5-year OS rate 73%). Patients with high-risk cytogenetic abnormalities showed a significantly lower OS than those with standard risk (median NR vs 47 months, HR=3.3, 95% CI: 1.06-10.39, p=0.028). Nineteen patients performed KRd treatment as a bridge to autologous transplantation, obtaining a post-transplant MRD negativity in 65% of cases. The most common adverse events were haematological, followed by infection and cardiovascular events. Grade 3 or higher anaemia, thrombocytopenia and neutropenia occurred in 11%, 21% and 28%, respectively. Among the cardiovascular events, the most frequent was arterial hypertension, which occurred in 12%, while congestive heart failure, arrhythmia and ischemic heart disease were less frequent and rarely grade 3-4.
Conclusion: Our data confirm that KRd regimen is effective and relatively safe in the early stages of the disease and can be used as a re-induction for a salvage autologous transplant. The prior use of bortezomib did not influence the efficacy of KRd treatment in terms of outcome, unlike high-risk cytogenetic abnormalities. A longer follow-up is needed to also confirm the benefit of the KRd combination after 18 cycles.
[1] Stewart AK. et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. N. Engl. J. Med.372, 142–152 (2015)

P49 A REAL-WORLD RETROSPECTIVE-PROSPECTIVE ANALYSIS OF EFFICACY AND SAFETY OF COMBINED IXAZOMIB, LENALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: THE NORTHERN ITALY EXPERIENCE

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Ixazomib-lenalidomide and dexamethasone (IRd) has been approved for the treatment of relapsed/refractory multiple myeloma (RRMM) based on the results of the pivotal Tourmaline MM-1 trial. We conducted an observational analysis of 81 RRMM patients (pts) treated with IRd between January 2017 and May 2021 in 18 Northern Italy centers, with the aim to evaluate efficacy and safety of IRd in real-life. The study comprises a retrospective phase (chart review of the period from ixazomib initiation to enrolment) followed by a 18-month prospective follow-up period.
At IRd initiation, 32% of pts were aged ≥75 (median age 72), 30% had an ECOG performance status ≥2, 54% of evaluable (64/81) pts carried high risk cytogenetic abnormalities (HRCA) [del17p and/or t(4;14) and/or t(14;16)] and/or 1q gain/amp], median number of prior lines of therapy was 2 (1-6) with 57% receiving ≥2 prior lines, 71% were exposed to lenalidomide, 24% were lenalidomide-refractory. Median time from diagnosis was 60 months. At the median of 31 months, 81% of the pts had discontinued treatment, mainly (62%) for progression. Main grade 3-4 adverse events (AEs) were neutropenia (11%) and thrombocytopenia (11%). Non-hematological grade 3-4 AEs were infections, venous thromboembolism, gastrointestinal toxicity, reported in 2 (2.5%), 3 (3.7%) and 4 (5%) pts respectively.
Overall, the response rate was 53% (≥VGPR 32%). With a median follow up of 31 months, median PFS (mPFS) was 12 months, ranging from

21 months in pts receiving 1 prior line and 7.4 months in pts receiving >3 prior lines respectively. 1-year OS rate was 53%.
By subgroup analysis, extended PFS was observed for pts aged ≥75 (mPFS 26.2 months), with 1 prior line of therapy (21 months), achieving at least a VGPR (21 months), prolonged time (>5 years) from diagnosis to IRd (20 months), without HRCA (18.6 months). An inferior PFS was seen in lenalidomide-refractory pts (4.8 months).
At multivariate analysis using Cox's regression, the only independent prognostic factors for PFS were age ≥75 (HR 0.35, 95% CI: 0.15-0.82, p=0.016), prolonged time (>5 years) from diagnosis (HR 0.29, 95% CI: 0.13-0.65, p=0.03) and refractoriness to a previous lenalidomide-based treatment (HR 2.23, 95% CI: 1.06-4.70, p=0.035). With regards to survival, lenalidomide-refractory pts had a 2-fold increase in the risk of death (HR 2.1, 95% CI: 0.91-4.8, p=0.08).
PFS appears to be superior in the older population possibly related to IRd treatment in earlier lines of therapy (52% of pts aged ≥75 had received IRd after 1 prior line and only 24% after >3 lines); notably, 70% of pts aged ≥75 had HRCA.
In conclusion, in a real-life population with adverse prognostic characteristics in terms of older age, performance status, cytogenetic risk, exposure and refractoriness to lenalidomide, IRd demonstrated inferior OR rates, rates of ≥VGPR and PFS as compared to the pivotal trial, with a good tolerability profile and no new safety concerns. Favorable PFS outcomes, however, emerged for pts achieving at least a VGPR, with 1 prior line of therapy, prolonged time from diagnosis to IRd, and aged ≥75. Moreover, as emerged from the analysis of the elderly population, treatment with IRd in earlier lines of therapy might overcome the adverse impact of high risk cytogenetics. IRd might, therefore, represent an effective and safe combination in selected RRMM pts with an indolent disease course in early lines of treatment, independent of age.

P50 OVERALL SURVIVAL ADVANTAGE OF MONOCLONAL ANTIBODIES BASED-TREATMENTS IN MULTIPLE MYELOMA PATIENTS RELAPSED AFTER ALLOGENEIC STEM CELL TRANSPLANTATION

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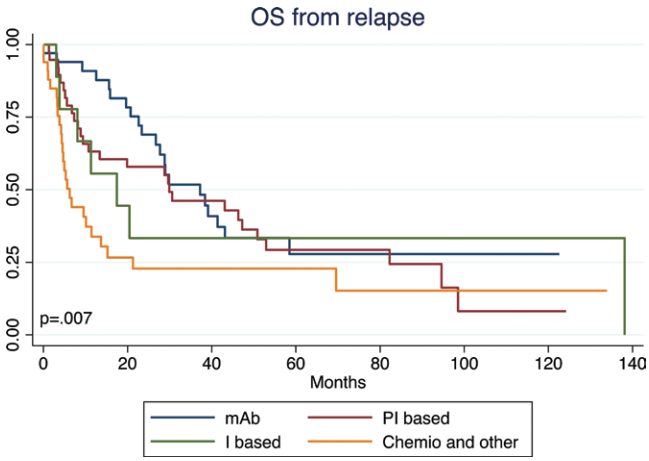
Even if allogeneic stem cell transplantation (allo-SCT) is curative for a minority of patients with multiple myeloma (MM), the patients who have relapsed after allo-SCT can experience long term survival, suggesting a synergy between anti-myeloma drugs administered after allo-SCT and donor T cells.
We evaluated 202 allo-SCTs for MM reported to the Gruppo Italiano Trapianto Midollo Osseo (GITMO) registry between 2009 and 2018: at a median follow-up of 40.9 months after allo-SCT 46 out of 202 patients (23%) died because of non mortality (NRM) causes, 37 patients (18%) were alive without disease progression and 119 (59%) had relapsed. We retrospectively evaluated the outcome of those patients who had relapsed and had received one or more lines of salvage treatment with the aim of collecting data about efficacy of novel drugs after allo-SCT.
Median age at transplant was 53 years (range 29-77). Staging according ISS was evaluable for 78 patients and was 1, 2 or 3 in 20 (25%), 24 (31%) and 34 patients (44%) respectively. High risk FISH cytogenetic was present in 35 out of 77 evaluable patients (45%). Allo-SCT was performed after more than 2 lines of treatments in 59 patients (49%). Myeloablative conditioning was administered prior to 72 allo-SCTs (60%). Stem cell source was peripheral blood for 105 allo-SCTs (88%). Cells came from 48 HLA-identical sibling donors (40%), 66 unrelated donors (56%) and 5 haploidentical donors (4%). Relapse occurred at a median of 14.3 months (IQR 7.2-26.9) after allo-SCT, it involved extramedullary sites in 42 patients (35%) and was associated with CRAB symptoms or signs in 59 patients (49%). Thirty-seven patients (31%) were observed without treatment or received chemotherapy or radiotherapy, 9 patients (7%) received at least one salvage treatment including immunomodulating agents, 39 patients (33%) were treated with at least one salvage therapy including proteasome inhibitors, 34 patients (29%) received at least one salvage treatment including monoclonal antibodies (33 daratumumab, 1 elotuzumab). Lines of therapy were ☐ 1 for 68 patients (57%), 2 for 23 patients (19%), 3 or more for 28 patients (24%). Seventeen patients (14%) died because of NRM causes (2 GVHD, 9 infections, 6 other causes) and 67 patients (56%) died due to MM progression. Two-year and 5-year OS of the whole population were 67.6% (95% IC 58.4-75.3) and 40.8% (95% IC 31.7-49.7) after allo-SCT and 49.3% (95% IC 39.7-58.2) and 26.4% (95% IC 17.9-35.7) after relapse, respectively. OS after relapse was significantly longer after monoclonal antibodies or proteasome inhibitors in comparison with regimens including only immunomodulating agents or chemo-radiotherapy (2-year OS 69.0% vs 57.9% vs 33.3 vs 22.8%, p=0.007)(Fig 1). OS after relapse was longer in patients who had received 3-4 salvage treatment lines in comparison with patients who were treated with ☐ 2 lines (p=0.064). Donor lymphocyte infusions (DLI) were administered to 27 patients and significantly prolonged OS after relapse (p=0.009). Our study suggested that the administration of monoclonal antibodies-based salvage treatments can enhance the graft-versus-myeloma in patients who experienced relapse after allo-SCT. Moreover, it confirmed that DLI have a significant antimyeloma activity with acceptable severe toxicity.



P51 EFFICACY AND SAFETY OF THIRD-LINE OR LATER TREATMENTS, INCLUDING THE CD38 MONOCLONAL ANTIBODY CLASS, IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: A SYSTEMATIC LITERATURE REVIEW

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Objectives: There is a need to contextualize treatment outcomes in relapsed/refractory multiple myeloma (RRMM) in light of prior therapies and disease/treatment characteristics. Comparisons across studies are challenging, especially in later lines of RRMM where treatment is highly heterogenous. We conducted a systematic literature review exploring efficacy and safety outcomes across approved and investigational agents in third-line/later (3L+) RRMM treatment and in patients refractory to anti-CD38 antibody therapy.

Methods: Searches were conducted on 28 Mar 22 for publications (2008–2022) and grey literature (2018–2020) reporting interventional studies in patients receiving RRMM treatment after ≥2 prior lines of therapy (LOTs). 2 reviewers screened the studies without geographical/language restrictions. Results were synthesised descriptively.
Results: 147 unique studies met eligibility criteria including 1 randomised controlled trial (RCT)/single-arm trial, 41 RCTs, 87 single-arm trials, 12 non-RCTs and 6 pooled analyses. Median progression-free survival (PFS) and overall survival (OS) varied widely across studies; trial populations also differed substantially regarding potential key treatment outcome modifiers. The shortest median PFS (0.9 months; median follow-up, 23 months) was seen in heavily pretreated patients mostly refractory to lenalidomide (LEN). PFS was longest (≤38.8 months; median follow-up, 44.3 months) in patients who had received as few as 2 prior LOTs and were not LEN-refractory. Median OS ranged from 6.4 months (follow-up not reported) in patients exposed to ≥3 prior LOTs to 54.3 months (median follow-up, 85 months) in patients who had received as few as 2 prior LOTs and were not LEN-refractory. Similarly, overall response rates (ORRs) varied widely from 0% for LEN-refractory patients to 100% for anti-CD38 refractory patients.
Among 19 studies reporting data for anti-CD38 refractory patients, most enrolled <50 patients per trial and were Phase I or I/II trials; only 2 were RCTs. 2 trials exclusively included triple-class refractory populations (refractory to ≥1 proteasome inhibitor, an immunomodulatory drug and an anti-CD38 monoclonal antibody). 10 trials included a subset of triple-class refractory patients (65–97% of total populations) and 5 studies enrolled broader populations but provided data for subgroups of triple-class refractory patients. Many studies provided safety/ORR data only; few reported median PFS and/or OS.
Where reported, adverse event rates were high (94–100%). Anaemia, thrombocytopaenia and neutropaenia were most frequently reported considering all 3L+ treatments.
Conclusions: We identified a large body of data related to 3L+ treatments in RRMM. Considerable heterogeneity in previous treatment exposures, and disease and patient characteristics were observed, along with substantial diversity in outcomes and endpoints reported. Careful consideration of these factors is relevant as the standard of care (SOC) in early LOTs could change, which could impact treatment options for later LOTs. It is challenging to identify a SOC for the 3L+ setting given the evidence observed, particularly due to heterogeneity in populations, subgroups and outcomes. Treatment choice could therefore be dictated by multiple prognostic and patient characteristics. A network meta-analysis that considers these differences could facilitate robust quantitative comparative efficacy and safety evaluations for RRMM treatment options.

4. Special conditions

P52 RISK STRATIFICATION COMBINING SKY92 GENE EXPRESSION PROFILING AND TRADITIONAL FISH IN MULTIPLE MYELOMA: THE FIRST PROSPECTIVE EVIDENCE IN THE R2-ISS ERA

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High-risk (HR) multiple myeloma (MM) patients still have a very poor prognosis. However, the definition of HR MM remains controversial. Currently, FISH is the most commonly used method for risk stratification in MM. According to the Second Revised International Staging System (R2-ISS), HR cytogenetics is defined as presence of at least one of the following: del(17p), t(4;14), and 1q CNA. In recent years, gene expression profiling (GEP) approaches, e.g. SKY92, have been developed for detection of HR patients. In the R2-ISS era, however, data on MM risk stratification applying SKY92 in combination with traditional FISH is still lacking. Therefore, we performed the first prospective study evaluating the prognostic value of the combined SKY92 and FISH HR detection in newly diagnosed (ND) and relapsed/refractory (RR) MM.
We prospectively collected bone marrow (BM) samples and clinical data of 147 MM patients. Cytogenetics were analyzed on purified CD138 positive MM cells by FISH, and HR cytogenetics was defined according to the R2-ISS classification. SKY92 risk status was determined with MMprofiler gene expression assay. Whole genome sequencing (WGS) was performed to compare the both risk stratification systems SKY92 and FISH.
We included 147 patients in our study (NDMM: n=51, RRMM: n=96). SKY92 classification was available for 121 (82.3%) patients. HR SKY92 was significantly enriched in RRMM (40/76) compared with NDMM (6/45) (P<0.0001). RRMM patients with HR SKY92 showed significantly shorter progression free survival (PFS) (P<0.0001) and overall survival (OS) (P=0.0004) than standard-risk (SR). In NDMM, HR SKY92 also indicated a significantly inferior PFS (P=0.001) in comparison with SR. Of note, samples of 26 (17.7%) patients, who showed significantly lower bone marrow infiltration than the remaining patients (median: 25% vs 55%, P=0.038), did not meet the SKY92 quality control criteria.
We then combined the SKY92 classification with cytogenetic analyses by FISH, which were available in 99 patients (NDMM: n=33; RRMM: n=66). We noticed a discrepancy between both risk stratification systems, with 44 (44.4%) and 58 (58.6%) patients being classified as HR by SKY92 and FISH, respectively. In total, 28 (42.4%) RRMM patients and 6 (18.2%) NDMM patients displayed HR in both SKY92 and FISH (double-HR). Regarding survival outcome in RRMM, double-HR patients showed the worst PFS (P<0.0001) and OS (P=0.0007). In NDMM, double-HR presented a negative prognostic factor for PFS (P=0.01).
To compare the FISH and SKY92 classifications, we performed WGS in 16 patients who exhibited either only HR SKY92 (n=7) or only HR FISH (n=9). Interestingly, 1 patient with bi-allelic TP53 inactivation (deletion + mutation) and 6 patients harbouring 1q CNA were determined as SR by SKY92 but as HR by FISH. The median PFS was not reached after a median follow up of 371 days in these 9 patients. Moreover, 4 out of 7 patients with only HR SKY92 but SR FISH displayed 1q CNA, which was detected only by WGS, and del1p32 was found in 1 patients. Interestingly, we found CRBN mutation in 3 out of 7 patients with only HR SKY92 but SR FISH. The remaining 2 patients did not show any known HR genomic alterations, suggesting that HR MM may be associated with other factors, e.g. epigenetic modifications.
Here, we provide the first prospective evidence in the R2-ISS era that advanced risk stratification combining SKY92 and FISH may help to identify the highest-risk MM.

P53 REAL-WORLD TREATMENT SEQUENCES AND COSTS OF 96 PATIENTS WITH MULTIPLE MYELOMA FROM DIAGNOSIS TO DEATH

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Introduction: The development of treatment options for multiple myeloma (MM) has improved survival, but also come with increased treatment costs, which can pose a burden on health care funding and limit access to drugs. Therefore, costs and cost-effectiveness analyses are increasingly important in medical decision making. Such analyses are often based on average health outcomes and costs over a lifetime perspective. However, specifically the end of life (EOL) phase is accompanied by high health care costs, while the contribution of active drug treatment to survival time and quality of life might be minimal. Therefore, we investigated the drug costs from diagnosis to death in detail, in a real-world cohort of MM patients.
Methods: We analysed health care records from all MM patients who received (a part of) their treatment in Amsterdam University Medical Centre, and who died between January 1st 2017 and July 1st 2019. We extracted all anti-MM treatments from diagnosis to death, including dose adjustments and start- and stop dates. We calculated drug costs using the Dutch Z-index (indicating drug costs), of August 2020.
Results: 96 patients were eligible for analysis and received a median of 5 (range: 1-16) lines of therapy; 61 (63.5%) received a stem cell transplantation (SCT). Time to next treatment or death from 1st to 2nd line

of therapy was longer in patients who received an SCT (median 23.9 vs 13.0 months, p=0.002) and was progressively shorter at later lines of therapy, without significant differences between patients who did or did not receive an SCT. Mean total drug costs of MM treatments (from diagnosis to death) were €211,563 (range: €3,942 - €776,185; €3,139 per month [range: €54 – €8,309]). Eighty-two patients (85.4%) received anti-MM treatment in the last 3 months before death and the mean drug costs in this period were €20,361 (range: €70 - €50,466; 9.6% of total). Forty-nine (51.0%) patients received anti-MM treatment in the last 14 days before death and 33 (34.4%) in the last seven days. Mean drug costs per month were approximately twice as high as compared to costs per month over the myeloma life time. (approximately €6,700 versus €3,139 per month), **Table 1**.

Conclusion: The majority of patients received anti-MM therapy during the 14 days preceding death. Associated drug costs were considerable, especially in light of limited survival benefit. Moreover, this is expected to increase as the novel drugs that are currently available also been given at later lines are more expensive. In view of the increasing budget impact of anti-myeloma treatment, hampering access to novel drugs, and the possible negative impact of EOL treatment on QoL, the identification of factors predicting efficacy and clinical benefit of continuing EOL therapy, warrant further investigation.

Table 1

Numbers of patients and (relative) costs of treatment per period.

Period	Patients receiving treatment (% of total)	Mean costs of treatment (range; % of total costs)	Mean relative costs per month (range)*
Diagnosis to death	96 (100)	€211,563 (€3,942 - €776,185; 100)	€3,139** (€54 – €8,309)
- With SCT	*- 61 (63.5)*	*- €210,863 (€17,317 - €621,756)*	*- €2,921** (€87 - €8,309)*
- Without SCT	*- 35 (36.5)*	*- €212,784 (€3,942 - €776,185)*	*- €3,607** (€54 - €8,072)*
Last 3 months	82 (85.4)	€20,361 (€70 - €50,466; 9.6)	€6,787 (€23 - €16,822)
Last 30 days	66 (68.8)	€6,188 (€10 - €17,444; 2.9)	€6,271 (€10 - €17,677)
Last 14 days	49 (51.0)	€3,001 (€9 - €9,512; 1.4)	€6,516 (€20 - €20,655)
Last 7 days	33 (34.4)	€1,662 (€3 - €4,757; 0.8)	€7,218 (€13 - €20,659)

(*) 30.4 days

(**) mean total costs divided by mean OS per group

Abbreviation: SCT = Stem cell transplantation

P54 ORAL ANTIVIRALS RITONAVIR-NIRMATRELVIR AND MOLNUPIRAVIR ARE HIGHLY EFFECTIVE IN PATIENTS WITH MULTIPLE MYELOMA AND COVID-19; A SINGLE-CENTER, PROSPECTIVE STUDY

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Severe SARS-CoV-2 infection is characterized by an initial viral phase, often followed by a severe inflammatory phase. In patients with multiple myeloma (MM), SARS-CoV-2 infection has been associated with severe clinical course and high mortality rates, due to the concomitant disease and treatment-related immunosuppression. Moreover, MM patients do not seem to respond well to vaccination despite adequate immunization, especially those who are on treatment with anti-CD38 or anti-BCMA therapies. Thus, MM patients are at a higher risk for breakthrough infection compared with noncancer patients or patients with solid tumor and supportive treatment with prophylactic use of monoclonal antibodies against SARS-CoV-2 is needed. At the time of COVID-19 infection, the use of antiviral therapy is necessary. Specific antiviral treatment involves viral replication control with monoclonal antibodies and antivirals, including molnupiravir and the ritonavir-boosted nirmatrelvir. Molnupiravir is the prodrug of the ribonucleoside analogue β-D-N4-hydroxycytidine, which inhibits the SARS-CoV-2 replication and reduces viral load. In phase I/II/III studies, it has shown both safety and efficacy, reducing the risk of hospitalization and mortality by approximately 50% in non-hospitalized adults with mild-to-moderate COVID-19 disease who are at risk for poor prognosis. Ritonavir-nirmatrelvir is an oral protease inhibitor that has also reduced the hospitalization and death in clinical trials by approximately 90%. Although available evidence supports the use of antivirals in patients with SARS-CoV-2 infection to prevent severe disease, relevant data on MM patients is scarce. The use of specific antiviral treatment with molnupiravir and ritonavir-boosted nirmatrelvir aims to reduce severe infection and hospitalization in patients with MM, who undergo mild SARS-CoV-2 infection and do not require supplemental oxygen.

This prospective study investigates the effect of these two agents on SARS-CoV-2 infection severity and mortality in patients with MM. Patients received either ritonavir-nirmatrelvir or molnupiravir.

Consecutive patients with MM and SARS-CoV-2 infection were prospectively enrolled in the study. All patients had microbiologically confirmed SARS-CoV-2 with polymerase chain reaction (PCR). The patients received either ritonavir-nirmatrelvir or molnupiravir according to the national guidelines for five days. Treatment with antivirals was initiated within the first five days from SARS-CoV-2 infection symptoms onset in patients with no need of supplemental oxygen. All patients were at high risk for severe SARS-CoV-2 infection due to the underlying MM. Baseline demographic and clinical characteristics, as well as levels of neutralizing antibodies (NAbs) were collected and compared. The effect of different treatments on SARS-CoV-2 infection severity and mortality was examined.

A total of 169 patients infected with SARS-CoV-2 were included. 74 of them were females with an average age of 64.4 years and a mean Body Mass Index (BMI) of 26.91 kg/m2. Regarding their medical history, 14 patients (8.3%) were diagnosed with diabetes mellitus (DM), 71 (42%) had hypertension, six (3.6%) had coronary artery disease (CAD) and 16 (9.5%) had chronic obstructive pulmonary disease (COPD).

All patients except for one, were vaccinated, mostly with BioNTech Pfizer vaccine (96.4%). 153 patients had already received 3 doses, seven (7) had received four (4) doses and eight (8) had received two (2) before COVID-19 diagnosis.

Regarding treatment, several drug combinations were administered to patients depending on their medical condition and history of MM. These included proteasome inhibitors based regimen, immunomodulatory drugs based regimen, anti-CD38 monoclonal antibody based regimen, anti-BCMA based regimen, and other treatments, such as selinexor and cyclophosphamide. For most of the patients, specifically for 100 of them, this was the 1st line of treatment, for 36 the 2nd, for 16 the 3rd, for 7 the 4th and for 3 patients the 5th line of treatment.

As far as the SARS-CoV-2 infection is concerned, 139 patients (82.2%) were treated with ritonavir-nirmatrelvir while the remaining 30 patients (17.8%) with molnupiravir. The duration of antiviral treatment was equal to five (5) days in all but three (3) cases. In total, 149 (88.2%) patients had mild infection, 15 (8.9%) had moderate infection, and five (5) (3%) had a severe one.

Severe cases were treated differently, as expected, compared to mild or moderate cases. The special treatment included hospitalization in 6.7% of patients with moderate infection (1 patient) and 100% of patients with severe infection (5 patients), tocilizumab in 5 patients with severe infection, intubation in 2 patients severely infected (40% of patients with severe infection) and corticosteroids in 13 patients with moderate infection (86.7% of these patients) and 5 with a severe one (100% of these patients). An exception was observed regarding use of corticosteroids since it appears that they were given almost equally in patients with moderate and severe outcomes.

As far as the antiviral drug type is concerned, no difference in mild, moderate or severe infection was observed (p=0.236). Regarding BMI, age or medical history defined as the presence of DM, COPD, CAD or hypertension no statistically significant difference was observed in the outcome of the infection. Regarding PS, a statistically significant difference of mild versus severe cases was observed (p=0.041), while the difference between mild and moderate cases was borderline non-significant (p=0.052).

A difference between severe and mild cases was observed concerning neutralizing antibody response levels before SARS-CoV-2 infection. Patients with severe disease appeared to have lower neutralizing antibody levels before SARS-CoV-2 infection compared to patients with mild disease (p=0.04). The mean and standard deviations for NAbs levels were 67.49%±28.85%, 59%±24.69% and 35.4%±37.57% for the groups of mild, moderate, and severe outcomes respectively.

Regarding treatment, despite the various drug types included in the study and their combinations, it was observed that treatment with belantamab

mafodotin was significantly related to the outcome. There was a statistically significant higher risk for severe SARS-CoV-2 infection (p<0.001) according to the Fisher's exact test.
In conclusion, the Covid-19 pandemic is a major cause of mortality worldwide and patients with MM are at high risk for severe infection. Unfortunately, the infection cannot be completely controlled, although many antiviral drugs have shown promising therapeutic results. The majority of immunocompromised patients may not be fully protected after vaccination and the use of oral antiviral drugs in case of infection seems to be effective.
Ritonavir-nirmatrelvir and molnupiravir seem to be highly effective in preventing severe disease and mortality from SARS-CoV-2 infection in MM patients who are under treatment for the underlying disease. This prospective study indicates the comparable effects of the two treatment options providing an important background for further research.

P55 MULTIPLE MYELOMA AND SARS-COV-2 INFECTION: AN EUROPEAN HEMATOLOGY ASSOCIATION SURVEY (EPICOVIDEHA) OF 1,221 PATIENTS THROUGH THE DIFFERENT PHASES OF COVID-19 PANDEMIC

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Patients with multiple myeloma (MM) appear particularly vulnerable to SARS-CoV-2 infection due to compromised humoral and cellular immunity and to anti-tumor treatments. The aim of this multicenter, observational study was to describe and analyze the outcome of a large number of MM patients with COVID-19 during the different phases of the pandemic. We enrolled 1,221 MM patients with confirmed SARS-CoV-2 infection between February, 2020 and August,2022, reported in the EPICOVIDEHA registry, an international, web-based, open platform for patients with hematological malignancies infected with SARS-CoV-2. The median age was 68 years (range: 30-95), with a male predominance (57.5%). Eight-hundred-eleven patients (66.4%) had at least one underlying comorbidity, mostly a cardiovascular disease. At the time of analysis, only 414 patients (34%) resulted vaccinated with 1 or more doses (mainly 3). Concerning MM status, 793 patients (64.9%) had controlled/stable disease while in 390 cases (31.9%) MM was active, including 56 newly diagnosed subjects. Regarding last MM treatment before SARS-CoV-2 infection, most patients had received chemotherapy (57.2%) or immunochemotherapy (20.2%) while, about transplant setting, 61 patients had received autologous-HSCT, 2 patients allogenic-HSCT, 4 patients CAR-T cell therapy. At COVID-19 onset, 728 patients (59.7%) had respiratory/pulmonary symptoms, 224 (18.4%) exhibited only extra-pulmonary symptoms and 269 (22%) were asymptomatic. COVID-19 was critical in 169 patients (13.8%), severe in 471 (38.6%), mild in 350 (28.7%), and asymptomatic in the remaining cases (18.9%). Four-hundred-forty-six patients (36.5%) were confined at home and managed as outpatients during SARS-CoV-2 infection, while 775 patients (63.5%) were hospitalized. One-hundred-sixty-nine patients (13.8%) were admitted to an intensive care unit (ICU) and 63.3% of them required invasive mechanical ventilation. No specific pharmacologic treatment for COVID-19 was reported in 270 patients (22.1%), while in 346 (28.3%) it included various combinations of antivirals, monoclonal antibodies, corticosteroids and convalescent plasma. With a median follow-up of 52 days (range: 0-763) for the entire cohort and 83.5 days for survivors, 303 patients died (total mortality rate: 24.8%). The reported primary reason for death was COVID-19 in 196 (64.7%) patients, a combination of MM and COVID-19 in 72 (23.8%) and a combination of MM and other reasons in 35 (11.5%). Overall survival (OS) was significantly higher in vaccinated patients with both stable and active MM versus not vaccinated ones (p=0.002 and p=0.003, respectively). At multivariate Cox regression analysis, age (p=0.001), renal failure (p=0.001), active disease (p=0.001), hospital admission (p=0.001), and ICU admission (p: 0.001) were also independently associated with poor survival. A time-dependent analysis revealed that mortality rates progressively reduced throughout the different pandemic waves, from 34% (first wave) to 10.2% (last wave) (Figure 1). The overall improvement realistically reflects a combination of factors, including novel targeted treatments for symptomatic patients, improved healthcare experience dealing with this type of patients, different severity of the dominant COVID-19 variants of concern, detection of a larger number of asymptomatic/mild cases by screening programs and, above all, extensive vaccine policies.

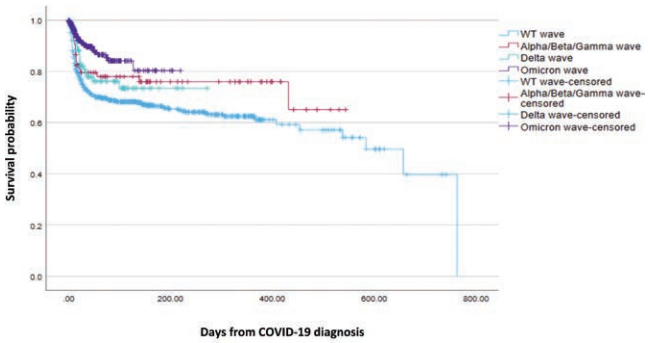

Figure 1. Survival probability by COVID-19 waves (variants of concern)

P56 SURVIVAL BENEFIT OF BIRTAMIMAB IN MAYO STAGE IV AL AMYLOIDOSIS IN THE PHASE 3 VITAL STUDY WAS CONSISTENT ACROSS ALL KEY BASELINE VARIABLES

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Introduction: Amyloid light chain (AL) amyloidosis – a progressive disorder caused by misfolded light chains (LCs) that aggregate and deposit in vital organs – is associated with high mortality, poor quality of life, and increased healthcare costs, particularly in newly diagnosed patients (pts) with advanced disease (Mayo 2012 Stage IV, median overall survival [OS] <6 months [mos]).
Birtamimab is an investigational humanized monoclonal antibody that directly binds a conserved epitope on κ and λ LCs and is designed to

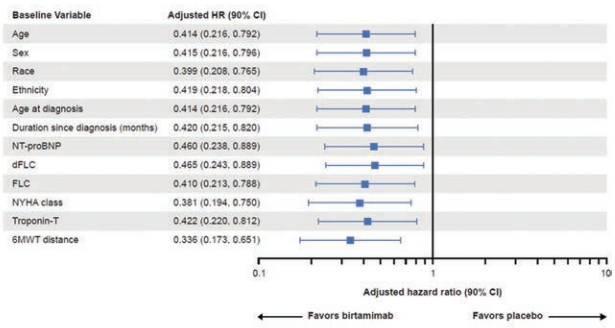
neutralize circulating soluble and deplete deposited insoluble amyloid by promoting phagocytic clearance. In 2018, the Phase 3 VITAL study – a multicenter, global, randomized, double-blind, placebo (PBO)-controlled study (NCT02312206) conducted in newly diagnosed, treatment-naïve pts with AL amyloidosis and cardiac involvement – was terminated per a futility analysis of the primary endpoint (time to all-cause mortality [ACM] or time to cardiac hospitalization ≥91 days after first study drug infusion); the final hazard ratio (HR) numerically favored birtamimab + standard of care (SOC) over PBO + SOC (0.826 [95% confidence interval (CI): 0.574,1.189]). Post hoc analysis of ACM over 9 mos revealed a significant survival benefit (HR=0.413 [95% CI: 0.191,0.895]) in pts at high risk for early death (ie Mayo 2012 Stage IV). Here we report the results of ACM sensitivity analyses in the subgroup of pts with Mayo 2012 Stage IV AL amyloidosis, adjusting for key baseline variables.

Methods: For ACM, the HR and 90% two-sided CIs were estimated from the semi-parametric Cox Regression model stratified by randomization strata (ie Mayo Stage I/II vs III/IV, renal stage I vs II/III, and 6-minute walk test [6MWT] distance). Separately, key baseline variables were added to the Cox Regression model to evaluate the impact on OS benefit. All adjudicated deaths before 9 mos were included in the analysis. Pts who had no events were censored at 9 mos.

Results: Of the 260 pts enrolled in the VITAL study, 77 (29.6%) were characterized as Mayo 2012 Stage IV at baseline, 38 randomized to birtamimab + SOC, and 39 to PBO + SOC. Pts had a median age of 64 years and were primarily white (93.5%) and male (68.8%). Baseline demographic and clinical characteristics were generally balanced between Mayo Stage IV pt treatment groups. After adjusting for key baseline demographic, clinical, and laboratory variables, the HRs with each of the baseline variables added separately to the Cox Regression model ranged from 0.336 to 0.465, with all the upper bounds of the 90% CIs <1 (**Figure**). Consistent with previous studies, birtamimab was generally well tolerated in Mayo Stage IV pts.

Conclusions: Birtamimab is the only investigational therapeutic that has shown a significant survival benefit in Mayo Stage IV AL amyloidosis pts. The survival benefit of birtamimab was consistent across all key baseline variables, including demographic factors (age, sex, race, ethnicity), clinical characteristics (age at diagnosis, duration since diagnosis, NYHA class, 6MWT distance), and laboratory parameters (NT-proBNP, dFLC, FLC, troponin-T), reinforcing the strength of the survival data in Mayo Stage IV pts. The AFFIRM-AL study (NCT04973137), designed to confirm the VITAL study results in Mayo Stage IV AL amyloidosis pts, is currently being conducted under a Special Protocol Assessment agreement with the US FDA with α=0.10 for the primary endpoint of ACM. This study is active and enrolling.

Figure. Forest plot of birtamimab survival benefit adjusted for key baseline variables for Mayo Stage IV patients – intent-to-treat population [9 months]



6MWT, 6-minute walk test; CI, confidence interval; dFLC, difference between involved minus uninvolved serum free light chains; FLC, free light chain; HR, hazard ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

P57 PRE-EXPOSURE PROPHYLAXIS FOR COVID-19 WITH TIXAGEVIMAB/CILGAVIMAB (EVUSHELD) IN PATIENTS WITH MULTIPLE MYELOMA

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Introduction: In patients with multiple myeloma (MM), SARS-CoV-2 infection has been associated with severe clinical course and high mortality rates, due to the concomitant disease- and treatment-related immunosuppression. Furthermore, immune response to COVID-19 vaccination is attenuated. Therefore, patients with MM are eligible to receive pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld).

Methods: Consecutive patients with MM were prospectively enrolled in the study. All patients were at high risk for severe COVID-19 due to the underlying MM. All patients had negative polymerase chain reaction (PCR) test for SARS-CoV-2 before the administration of monoclonal antibodies for COVID-19 prophylaxis. All patients had measurement of neutralizing antibodies (NAbs) against SARS-CoV-2 using an FDA approved methodology (enzyme-linked immunosorbent assay, cPass SARS-CoV-2 NAbs Detection Kit; GenScript, Piscataway, NJ, USA) before the administration of tixagevimab/cilgavimab and at one month thereafter. Baseline demographic and clinical characteristics, NAbs levels and patient outcomes were collected and analyzed. Evusheld was administered at 150mg as two intramuscular injections.

Results: Fifty-five patients with MM were included in this analysis and were followed for a median of 5 months (range 3-6 months) after receiving tixagevimab/cilgavimab. The median age was 63 years (range 36-84), whereas 27 (49%) were females. The majority of the patients had performance status (PS) 0 (n=27, 49%), 22 patients (40%) has PS 1 and 6 patients (11%) had PS 2. Thirty patients (55%) were ISS 1, 17 (30%) were ISS 2 and 8 (15%) were ISS 3. Most patients (n=37, 67%) were at their first line of treatment, 16 (19%) were receiving their second line of treatment, one patient was at the third and one at the fifth line of treatment. Thirty-one patients (56%) had previously received autologous stem cell transplant. At the time of tixagevimab/cilgavimab administration, 19 patients (34%) were receiving combinations including anti-BCMA agents, 24 patients (44%) were receiving combination including anti-CD38 drugs and 12 (22%) were on other treatments. Four patients had a prior history of COVID-19. Regarding vaccination status for COVID-19, 42 patients (76%) had received 4 vaccine doses and 13 patients (24%) had received 3 vaccine shots. All patients were vaccinated with mRNA-based vaccines. The median NAb level before the administration of tixagevimab/cilgavimab was 87% (range 0-98%), whereas it increased to 97% (range 0-98%) at one month thereafter. Overall, 5 patients (9%) were diagnosed with COVID-19 at a median of 1 month (range 1-2) after receiving tixagevimab/cilgavimab. All of these patients received nirmatrelvir/ritonavir (Paxlovid) for 5 days as outpatients along with supportive care as per standard clinical practice and recovered completely. There were no COVID-19-related hospitalization or deaths. Tixagevimab/cilgavimab was well tolerated; no infusion-related reactions or major adverse events were reported. Fifteen patients (27%) experienced pain at the injection site that resolved after a few days.

Conclusions: Tixagevimab/cilgavimab (Evusheld) seems beneficial in patients with MM who had a low incidence of COVID-19 infections during the Omicron wave. No new safety concerns emerged. An anamnestic dose is scheduled at 6 months after the prime dose.

P58 LOW CD38 EXPRESSION BY PLASMA CELLS IN EXTRAMEDULLARY DISEASE IN MULTIPLE MYELOMA PATIENTS

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Extramedullary disease (EMD) is a possible rare manifestation in multiple myeloma (MM) and it represents an unmet medical need in the treatment of MM patients (pts). Thus a better characterization of plasma cells (PCs) of the EMD is critical to improve the treatments. Pervious works have suggested that the expression modulation of adhesion molecules, including CD44 and CD56, supports clonal PCs migration through the bloodstream.

CD38 is a multifunctional transmembrane glycoprotein, expressed by PCs, which also plays a role as adhesion molecule. CD38 is considered a hallmark of MM cells and a therapeutic target for anti-CD38 antibody-based approach. Interestingly recent clinical reports suggest that the response to the anti-CD38 monoclonal daratumumab is unsatisfactory in MM patients with EMD. Overall the CD38 expression profile by extramedullary PCs is still unknown and has been investigated in this study.

We enrolled 22 MM pts with a biopsy-proven EMD. The expression of CD38 and CD56 and CD44 was evaluated either by flow cytometry at BM level or by immunohistochemistry from both BM and EMD biopsies. Immunohistochemical data were scored using a semiquantitative evaluation of the percentage of CD56, CD44 and CD38, on MM cells on a 5-tiered scale.
3 pts presented EMD at diagnosis while 19 pts presented EMD at relapse. Overall, 55% of pts developed multiple plasmacytomas. The most common site was soft tissue and liver/spleen which represents 42% of the total EMD followed by lymph nodes (15%). In 41% the EMD relapse was dissociated from BM relapse. CD56 showed a high score (3-4) in 5 of 22 (23%) EMD samples and was absent in 14 of 22 (64%) pts. Discordant CD56 expression was observed in 18% of samples with a strong down-regulation of CD56 in the EMD samples compared to BM. CD44 showed a high score in 16 of 20 (80%) EMD samples and was absent in 2 of 20 (10%). 4 pts with discordant CD44 expression (27%) showed an up-regulation of CD44 in the EMD samples compared to BM. CD38 had a high score in 16 of 22 BM samples (73%) and was absent in 3 of 22 (14%) EMD samples. Discordant CD38 expression was observed in 26% of samples with a down-regulation of CD38 in the EMD samples compared to BM.
In conclusion, our data indicate that a discordant expression profile of the CD56, CD44 and CD38 may occur in EMD sites as compared to BM. The possible lack of CD38 expression in EMD was highlighted for the first time and it could have a critical therapeutic impact in MM patients with EMD.

P59 ACTIVE TREATMENT AND LOW IGM ARE ASSOCIATED WITH INFERIOR SARS-COV-2 SPIKE ANTIBODY RESPONSE TO THREE DOSES OF COVID-19 RNA VACCINATION IN PATIENTS WITH MULTIPLE MYELOMA

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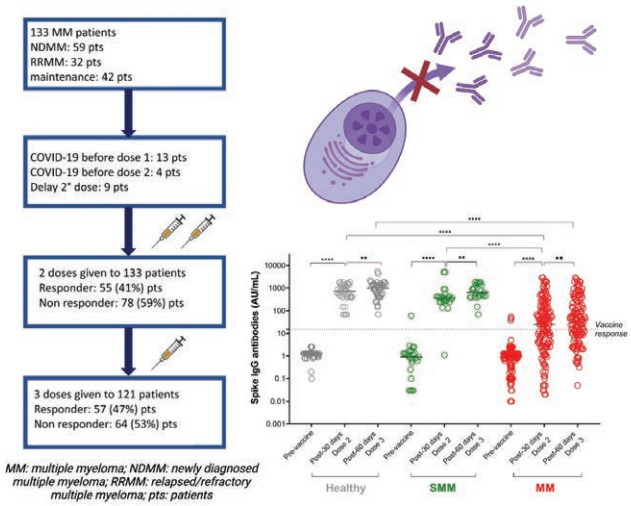
Introduction: Patients with multiple myeloma (MM) frequently present with substantial immune impairment and an increased risk for infection-related mortality. From the end of January 2020, infection by SARS-CoV-2 has radically changed our lives. Since the COVID-19 (COronaVIrus Disease-2019) pandemic is still ongoing, counting more than 514 million confirmed cases and 6.24 millions deaths, it is still to clarify why the response to infection differs from person to person and which immunopathological mechanisms lead to severe disease. Concerning this, it is well documented that patients with impairment of the immune system are more at risk of developing severe COVID-19 with reduced survival. In this setting, the development of vaccines against SARS-CoV-2 represented a central point in the fight against the pandemic. Regarding this, we aimed to evaluate the immune response in MM patients vaccinated for SARS-CoV-2 during their active anti-MM treatment.
Methods: This study included 158 patients affected by active MM or smoldering MM (SMM) and 40 healthy subjects. All subjects received 2 or 3 doses of the BNT162b2 (Pfizer/BioNTech) vaccine. A serology sample was collected before the first vaccination, 30 days after the second, and 60 days after the third dose.
Results: At 30 days from the double dose, the median anti-spike IgG levels in MM was 25.2 (IQR, 3-135 AU/mL), significantly lower than those in SMM (360.2 IQR, 245-424 AU/mL, p<0.0001), and in the control group (704 IQR, 390-1340 AU/mL, p<0.0001). At 60 days from the third dose, the median anti-spike IgG levels in MM was 38 IQR (8-248 AU/mL), significantly lower than those in SMM (650 IQR, 419-1370 AU/mL, p<0.0001) and in the control group (995 IQR, 455-1502 AU/mL, p<0.0001). Our results indicate that continuous treatment (p=0.0003), therapy with monoclonal antibodies alone (p=0.006) or associated to immunomodulatory agents (p=0.02), high-dose of dexamethasone (p=0.002), and IgM <50 mg/dL (p=0.003), are associated with an inadequate response to COVID-19 vaccination and a not stable anti-SARS-CoV-2 titer. Moreover, in our series of 40 patients undergoing prophylaxis with tixagevimab/cilgavimab, 9 (22.5%) experienced COVID-19, with a practically asymptomatic course, underlining the effectiveness of this therapy in preventing serious infection and ensuring the best clinical management (Figure 1).
Conclusions: A third mRNA vaccine failed to warrant long-term humoral immune responses against SARS-CoV-2, in the setting of patients undergoing continuous MM treatment and reporting a low value of IgM. After two months from the third dose, most non-responder patients at two doses did not show a stable anti-SARS-CoV-2 titer. These patients should be addressed to receive passive immunization with tixagevimab/cilgavimab instead of a further dose of vaccine to warrant long-term protection.



MM: multiple myeloma; NDMM: newly diagnosed multiple myeloma; RRMM: relapsed/refractory multiple myeloma; pts: patients

P60 EVOLVING OUTCOMES OF EXTRAMEDULLARY DISEASE IN MULTIPLE MYELOMA: 20-YEARS SINGLE CENTER EXPERIENCE

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Extramedullary disease (EMD) represents an aggressive form of multiple myeloma (MM) characterized by hematogenous spread of a clone or a subclone of disease able to thrive and grow independently form bone marrow microenvironment. This form of disease has poorer outcome and dismal prognosis. In the last two decades therapeutic armamentarium for treatment of MM is increased and there is a trend toward more prolonged therapy, leading to a better outcome of MM patients. However, the efficacy of the new treatments on patients with EMD is not clear.
We retrospectively evaluated patient characteristics and treatment durations in terms of time to next treatment and outcomes in our center from January 1994 until December 2022. A total of 52 patients were evaluable and were investigated.
All the patients were diagnosed with multiple myeloma and EMD and received at least one line of therapy during their life. EMD was present at diagnosis or at relapse in 27 (52%) and 25 (48%) patients respectively. Pure extramedullary plasmocytomas were present in 23 (44%), among them seven patients had bone-related plasmocytomas too. Sites involved were: central nervous system (CNS, 7 cases), lung (4 cases), skin (4), lymph nodes (1),pleura (1), eye (1 case), mediastinum (1), liver (1), gallbladder(1), abdomen (1), stomach (1), uterus (1). Bone-related plasmocytomas were present in 29 patients (55%). FISH analysis was evaluable in 33 patients: 16 standard risk, 17 high risk (51,5%). The majority of patients were treated outside controlled clinical trials (39, 75%); 25% of patients (13) have been enrolled in a clinical trial during their life (10, in trials on upfront therapy, 2, in trials on therapy at relapse, one patient in both).
On the basis of the year when a patient was exposed to first line therapy, patients were divided in two groups: patients diagnosed and treated

from 1994 to 2012 (group A, 11 patients, 21%), and patients diagnosed and treated from 2013 (group B, 41 patients, 79%).
Less than a half of patients (24, 46%) are still alive; among them more than 95% were diagnosed and treated after 2012 (group B).
100% (52) of patients were exposed to first line therapy, 81% (42) to second, 73% (38) to third, 46% (24) to fourth, 33% (17) to more than fifth, 9% (3) to more than eight, 3 were allotransplanted (6%) (Table 1).
For group A mean and median of lines of therapies were 4.7 and 4 months (range 1-9), for group B were 3.7 and 3 months (range 1-9). Time to next treatment was unfortunately lower from one line of therapy to the next one, particularly in patients belonging to group A where relapses and need of a new treatment occurred more frequently than for patients belonging to group B (introduction of novel agents, maintenance/continuous therapy.
Observed cumulative median overall survival (m OS) is 65 months, range 1-202 months.
These real-world data show an evolution of EMD patient outcomes in the last two decades. Data are encouraging to design prospective studies including EMD patients for optimal treatment decisions to translate in clinical practice.

Table 1

Patients characteristics	52
EMD	
At diagnosis	27 (52%)
At relapse	25 (48%)
Pure EMD	23 (44%)
Bone-related plasmacytomas	29 (55%)
FISH	
Standard risk	16
High risk	17 (51.5%)
Not evaluable	19
Clinical trials	
Not included	39 (75%)
First line	11(21%)
At relapse	2 (4%)
First exposition to therapy	
1994-2012	11 (21%)
>2013	41 (79%)
Lines of therapy	Median 3 (1-9)
First	52 (100%)
Second	42 (81%)
Third	38 (73%)
Fourth	24 (46%)
>fifth<eighth	17 (33%)
>eighth	3 (9%)
Median OS	65 (range 1-202 months)

P61

Not publishable.

P62 USE OF ANTIVIRAL FOR PAUCISINTOMATIC COVID-19 INFECTION IN MULTIPLE MYELOMA PATIENTS UNDERGOING TREATMENT

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Patients with multiple myeloma are at increased risk of mortality from COVID-19 infection and show a lower rate of sieroconversion after vaccination and usually late negativization. In this regard, some studies have shown slight changes in mortality during the post-vaccine era. COVID-19 infection, during treatment creates several issues such as discontinuation of active treatment for the disease and a rapid negativization is useful to allow early resumption of therapy.
From February 2022, it is possible to set up antiviral treatment with Nirmatrelvir or Molnupiravir in paucisymptomatic patients by reducing hospitalization and evolution in more severe infection.
In this study, we collect data on 75 patients with active Multiple Myeloma and COVID-19 infection from Center District (Lazio, Umbria, Marche, Abruzzo) to evaluate the efficacy of this treatment.
Of 75 pts, 57 (76%) were in first line of treatment and 18 (24%) in different lines; 62 (82.6%) were treated with antivirals, specifically 49 (65%) with oral antivirals (Nirmartelvir or molnupinavir) and 14 (18.6%) with intravenous antivirals (remdesivir); the remaining 13 (17.4%) patients had no treatment.
Of the 62 patients treated with antivirals, 14 (22.6%) were hospitalized for worsening general condition, and 5 (8%) died. This group of patients resolved the infection with swab negativization with a median of 10 days (range 4-72) while the 13 patients who did not undergo any antiviral treatment presented a median of negativization of 15 days. (range 5-20).
The majority of patients (67/75 subjects; 89%) had been vaccinated with at least two doses of mRNA vaccine; of these, 54 patients were treated with antivirals presenting a median time to negativization of 9 days compared with 16 days for the unvaccinated and antiviral-treated (P=NS). No difference in hospitalization and mortality.
Mortality from COVID-19 infection in the sample was 8% (6/75).
In conclusion despite the limitations of the sample size, the use of antivirals in patients with multiple myeloma under active treatment seems to offer a more rapid negativization of the infection promoting a rapid resumption of chemotherapy treatment despite an important effect on mortality and hospitalization.
A larger sample will be useful in providing further information on mortality and hospitalization in this patient setting

P63 BREAKTHROUGH COVID-19 IN FULL VACCINATED PATIENTS WITH MULTIPLE MYELOMA: A SINGLE CENTER EXPERIENCE OF 54 PATIENTS

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COVID-19-related mortality in the onco-hematological setting is higher than in general population and patients with multiple myeloma (MM) are reported to be particularly vulnerable to SARS-CoV-2 infection, due to compromised humoral and cellular immunity (related to disease itself) and to anti-tumor treatments. Thus, along with general measures, vaccines against SARS-CoV-2 have become, from their approval, the most important strategy to prevent poor outcome from COVID-19 in MM patients. However, limited data have been so far published about epidemiology and outcome of breakthrough COVID-19 in MM patients after three anti-SARS-CoV-2 vaccine doses. We performed a retrospective analysis of 54 consecutive patients with active MM who experienced SARS-CoV-2 infection between December, 2021, and December, 2022 at our Institution (Table 1). Among them, four cases of "reinfection" were documented. All patients had received three doses of anti-SARS-CoV2 vaccines (mostly mRNA) and 6 of them had also received a fourth, "second booster" dose. SARS-CoV-2 infections were diagnosed by RT-PCR or by antigen rapid test on nasopharyngeal swabs. Data about sex, age, ongoing treatment, symptoms, hospitalization, mortality, and additional use of antiviral drugs or monoclonal antibodies for the treatment of COVID-19 were collected. The median age of the whole group was 65 years (IQR: 60-76; range: 39-84), with male preponderance (59.3%). Half of the patients (27) had at least one underlying comorbidity, with chronic cardiopathy (i.e., hypertension, atrial fibrillation) being the most reported. The most frequent isotype was IgG, followed by IgA, light chain and non-secreting subtype. Median number of days between the last dose of vaccine and infection was 136.5 (IQR: 89-199.2; range: 11-381). About disease status at SARS-CoV-2 breakthrough infection, 27 cases (50%) were newly diagnosed/first line MM, 20 (37%) were first relapses, 7 (13%) were further relapsed MM. Forty-eight patients (88.9%) were under treatments including dexamethasone (64.8%), proteosome inhibitors (25.9%), IMiDs (75.9%), anti-CD38 monoclonal antibodies (44.4%) or other

therapies (7.4%). Six patients (11.1%) in complete response, three of whom after autologous transplantation and one after CAR-T treatment, were in follow-up, without active therapy. Infection was symptomatic in 35 patients (64.8%) and the most common symptoms were fever, cough, sore throat and runny nose. Overall, 4 patients (7.4%) were hospitalized: among them, 1 (1.8%) was admitted to an intensive care unit (ICU) due to respiratory distress. Fourteen patients (25.9%) received specific anti-SARS-CoV-2 treatment: 7molnupivar, 5 PF-07321332/ritonavir, 1 PF-07321332/ritonavir + sotrovimab, 1 sotrovimab. After a median follow-up of 258 days (IQR: 181-294; range: 43-356), 3 patients (5.6%) had died and no patient reported long-lasting symptoms. Our data indicate that SARS-CoV-2 infection remains frequent even in "triple vaccinated" MM patients, but also that the clinical outcome of COVID-19 appears to be significantly improved by a "booster" dose of vaccine with respect to pre-vaccination era in this high risk population exposed to novel Omicron variants. The role of new antiviral agents and monoclonal antibodies, currently used to reduce the risk of progression of COVID-19 to severe disease, warrants to be further investigated in larger series.

Table 1

Characteristics of 54 full vaccinated MM patients with SARS-CoV-2 infection

Age, years	
Median (IQR)	65 (60-76)
Range	39-84
Sex, n. (%)	
Male	32 (59.3)
Female	22 (40.7)
Comorbidities, n. (%)	
0	27 (50)
1	16 (29.7)
2	5 (9.2)
≥3	6 (11.1)
MM subtype, n. (%)	
IgG	33 (61.1)
IgA	12 (22.2)
Light chain	7 (13)
Non-secreting	2 (3.7)
Days from last vaccine dose to SARS-CoV-2 infection	136.5 (89-199.2)
Median (IQR)	11-381
Range	
Disease status, n. (%)	
Newly diagnosed/First line	27 (50)
1st Relapse	20 (37)
Relapse-Refractory	7 (13)
Current MM treatment, n. (%)	**48 (88.9)**
Dexamethasone	35 (64.8)
Contains Proteosome inhibitor	14 (25.9)
Bortezomib	9
Carfilzomib	3
Ixazomib	2
Contains IMiD (including maintenance therapy)	41 (75.9)
Thalidomide	6
Lenalidomide	32
Pomalidomide	3
Contains CD38 mAb	24 (44.4)
Daratumumab	22
Isatuximab	2
Contains other	1
Elotuzumab, Belantamab Mafodotin Melphalan	1
No therapies	**6 (11.1)**

(*Continued*)

Table 1

(***Continued***)

Age, years	
COVID-19 outcome, n. (%)	
Presence of symptoms	35 (64.8)
Hospitalization	4 (7.4)
Hospitalization in ICU	1 (1.8)
Death to COVID-19	3 (5.6)
COVID-19 symptoms, n. (%)	28 (80)
Fever	14 (40)
Cough	11 (31.4)
Sore throat	11 (31.4)
Runny nose	6 (11.1)
Fatigue	3 (8.6)
Diarrhea	
Treatment, n. (%)	
Molnupiravir	7 (13)
PF-07321332/Ritonavir	5 (9.3)
PF-07321332/Ritonavir +	1 (1.8)
Sotrovimab	1 (1.8)
Sotrovimab	40 (74.1)
None	

P64 A CASE OF COVID-19 PNEUMONIA AFTER CAR T-CELL THERAPY IN A PATIENT AFFECTED BY RELAPSED/ REFRACTORY MULTIPLE MYELOMA

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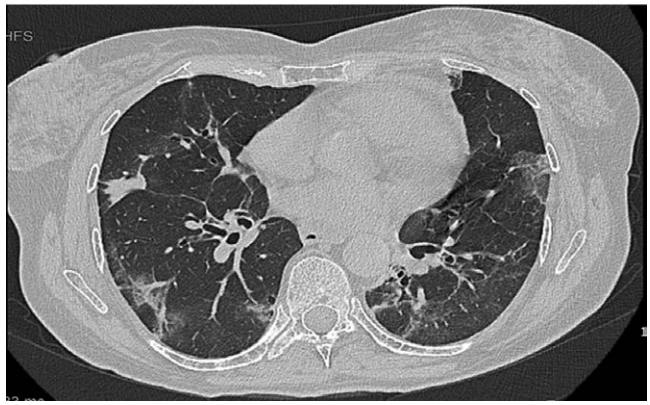
BCMA-targeting chimeric antigen receptor (CAR) T cells proved extremely effective in the treatment of relapsed/refractory (RR) multiple myeloma (MM). Nevertheless, their impact on immune system along with immune impairment induced by previous treatments and MM itself could determine vulnerability to infectious events. COVID-19 could evolve into a life-threating infection in MM patients especially in those with RR disease. Moreover, immune response to SARS-CoV-2 vaccines in this patient population could be suboptimal preventing adequate protection against COVID-19 complications. We report a case of a 51-year-old woman with anaemia and rib fractures diagnosed with IgG-k MM in 2012. Serum monoclonal component was 6.3 g/dl and Bence Jones proteinuria was 2.3 g/24h. Cytogenetic analysis showed amplification of 1q21 and, according to the International Staging System (ISS) and Revised-ISS, the disease was classified as stage I and I, respectively. After taking part in the EMN02 trial, the patient received 4 induction cycles with bortezomib, cyclophosphamide and dexamethasone, followed by tandem autologous stem cell transplantation and 2 consolidation cycles with bortezomib, lenalidomide and dexamethasone. Complete remission was achieved at the end of consolidation and maintained with lenalidomide until 2020 when she experienced clinical relapse. Subsequent treatment consisted of 8 cycles of induction therapy with carfilzomib, pomalidomide and dexamethasone followed by maintenance with pomalidomide within the EMN11 trial and led to partial remission. After a few months, the patient experienced biochemical relapse and third line therapy with daratumumab, lenalidomide and dexamethasone was started. Due to refractoriness to the last therapy, the patient was enrolled in the CARTITUDE-4 trial and randomized to receive CAR T- cell therapy in December 2021. On third day post-infusion, grade 2 cytokine release syndrome developed and resolved with tocilizumab and steroids. Minimal residual disease (MRD) negativity has been achieved 6 months after infusion. In July 2022 the patient contracted SARS-CoV-2 infection. She had been vaccinated against COVID-19 and received a third boost in March 2022. Despite antiviral therapy with molnupiravir, cough worsened, and bilateral interstitial pneumonia was detected by CT scan (Fig.1) on admission to hospital. Blood tests showed lymphopenia (800

cells/µl), severe hypogammaglobulinemia (200 mg/dl) and high levels of inflammatory markers (CRP 38000 µgr/l and IL-6 38 pg/ml). Remdesivir and tixagevimab-cilgavimab did not improve the clinical condition which was exacerbated by pulmonary embolism and required high-flow oxygen therapy. Viral genotyping revealed non BA.2 omicron variant, viremia resulted positive and antinucleocapsid antibodies were not identified. Analysis of lymphocyte subpopulation displayed B-cell aplasia (10 cells/µl), CD4+ T cells (200 cells/µl) and NK cells (37 cells/µl) deficiency. Hyper immune plasma was administered obtaining resolution of opacities and improvement of respiratory failure. Soon after pulmonary aspergillosis superimposed and resolved with isavuconazole. Viral clearance has been obtained 5 months after initial infection and the patient is still in complete remission with MRD negativity one year after CAR-T infusion. Long-term infectious complications in MM CAR-T recipients should be taken into consideration as they could counteract the efficacy of this treatment.

Fig.1



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