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# MPE MYELOMA PATIENTS EUROPE **CONFERENCE REPORT**

European Hematology Association (EHA)

2022 Annual Congress

# European Hematology Association (EHA) 2022 Annual Congress

The European Hematology Association (EHA) annual meeting is the most important haematology scientific congresses in Europe. This year, it was held both virtually and in person in Vienna, Austria, on June 9th - 12th. This report summarises the most important updates presented in this congress around myeloma, AL amyloidosis and patient advocacy.

Please refer to the end of this document, as it contains a glossary of useful terms to help you understand some of the words used to explain each study.

This is not intended to be medical advice. Please speak with your clinician, if you have any questions or concerns about treatment options.



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# **1. MYELOMA UPDATES**

## 1.1. Transplant-Eligible Newly Diagnosed Patients

#### **Current Options in Therapy**

#### Induction

Triplet induction regimens are the current standard of care for most transplant eligible patients. The use of these regimens has doubled between 2011 and 2019. However, the use of monoclonal antibodies (mAbs) as a fourth agent has been shown to be beneficial to patient outcomes. The clinical studies GMMH-HD6, GMMG-HD7, PERSEUS and CASSIOPEIA provide evidence this is the case.

GMMG-HD7 compared isatuximab plus bortezomib-lenalidomidedexamethasone (VRd) versus VRd alone. Results indicate that the addition of isatuximab induced a greater post-induction response, including consistent Minimal Residual Disease (MRD) negativity benefit. Of note, VRd is the preferred regimen by the US National Comprehensive Cancer Network (NCCN) and EHA-ESMO guidelines.

Similarly, the CASSIOPEIA trial showed how the addition of daratumumab to bortezomib-thalidomide-dexamethasone (VTd) achieved a deeper response after transplant. Furthermore, results from these trials suggest that mAbs confer minimal additional toxicity with no increase in serious infections. However, evidence suggests that the use of mAbs may reduce the yield of stem cells, though not the feasibility of a transplant.

The trials IsKia, MIDAS and DSMM XVII are currently ongoing to investigate the addition of mAbs to carfilzomib-lenalidomide-dexamethasone (KRd) to transplant-eligible patients.

A high proportion of patients are unable to swiftly receive several lines of therapy (e.g., they drop out or die). Thus, Enrique Ocio, from the University of Cantabria (Spain), defended his perspective of using the most active treatment regimens up front to maximise treatment benefits. María-Victoria Mateos from the University of Salamanca (Spain) and Fredrik Schjesvold from Oslo University Hospital (Norway) also acknowledged the importance of using the most effective treatment regimens in first line treatment, especially in high-risk patients.

It must be highlighted that quadruplet combinations increase regimen complexity, therefore individual patient factors need to be considered, including disease risk, frailty, comorbidities, quality of life and treatment tolerability.

#### **First line treatment**

Upfront high-dose melphalan plus transplant (HDM-ASCT) has shown consistent beneficial results compared with non-transplant approaches based on lenalidomide or bortezomib-containing regimens. However, the toxicity of

melphalan has put into question whether this is the most appropriate first line regimen for newly-diagnosed patients. Several trials that have been conducted for this purpose indeed suggest that HDM-ASCT provides superior benefits to patients. Examples of these trials are RV-MM-EMM-441, EMN02/HO95, IFM 2009/DETERMINATION and FORTE. Their results indicate that HDM-ASCT significantly increases the rate of 12-month sustained MRD negativity compared to immunomodulatory agents (e.g., lenalidomide) and proteasome inhibitor (e.g. bortezomib) triplets. Furthermore, based on the data from these studies, delayed HDM-ASCT could be an option in selected patients.

Beyond these results for current first line therapy, investigators are now studying the potential role of CAR-T cell therapy in newly-diagnosed patients in trials such as the CARTITUDE-6 study.

#### **Ongoing Clinical Trials**

#### IFM 2018-04 study

IFM 2018-04 is an ongoing phase 2 study in newly-diagnosed high-risk multiple myeloma patients eligible for stem-cell transplant (SCT), which examines the feasibility of daratumumab, carfilzomib, lenalidomide, and dexamethasone (dara-KRd) induction, autologous SCT followed by dara-KRd consolidation and a second round of SCT followed by daratumumab and lenalidomide (dara-R) maintenance. The results of the study thus far suggest that this approach is feasible, in case the dara-KRd induction phase is no longer than 3-4 treatment cycles. The initial protocol contained six cycles of dara-KRd, however, this led to stem-cell collection failure in six patients, hence the protocol was amended. Promisingly, dara-KRd induction led to a deep response rate in patients with 91% achieving a very good partial response (VGPR). The MRD negativity rate was also high (62%). These results are in accordance with the GMMG CONCEPT trial. However, at the end of his presentation, Cyrille Touzeau from the University Hospital of Nantes (France), concluded that a longer follow-up is necessary to safely determine the efficacy and feasibility of this treatment approach.

#### ATLAS study

ATLAS is an ongoing, phase 3, randomised trial of 180 newly-diagnosed patients who received induction therapy followed by a stem-cell transplant (SCT). This study compares the benefit of carfilzomib, lenalidomide and dexamethasone (KRd) with lenalidomide (R) alone after SCT. At data cut-off, 92 patients from the group receiving KRd and 86 patients from the R-only group were evaluable. The primary objective of the study is to compare progression-free survival between the two groups. The results at the time of data cut-off suggests that KRd serves as a superior maintenance therapy after SCT, with a median progression-free survival (PFS) of 59 months, compared to a median PFS of 41.1 months when R alone was administered. Furthermore, at treatment cycle six, MRD negativity rates were significantly higher in patients receiving KRd (44% by the definition of the International Myeloma Working Group (IMWG)) in comparison to R (27% by IMWG definition). The toxicity profiles of the two treatment approaches did

not seem to differ significantly. Based on the results, Dominik Dytfeld from the Medical University of Poznan (Poland) suggested that KRd is a superior form of maintenance therapy following SCT in newly-diagnosed myeloma patients.

# 1.2. Transplant-Ineligible Patients

#### **Current Options in Therapy**

Fredrik Schjesvold from Oslo University Hospital (Norway) reviewed the first-, second- and third-treatment line options for patients who are not eligible for a stem cell transplant. Schiesvold showed how, specifically, the addition of daratumumab to current therapeutic combinations was beneficial. This has been seen in phase 3 of the MAIA study that compared daratumumab-lenalidomidedexamethasone (DRd) to lenalidomide-dexamethasone alone. Preliminary results indicated that median progression-free survival is approaching 60 months and it is statistically and significantly different to lenalidomide-dexamethasone alone (Rd). Similarly, the addition of daratumumab to bortezomib-melphalanprednisone (D-VMP) has been shown to provide median progression-free survival of approximately 36 months compared to the combination therapy without daratumumab, where progression-free survival results were under 20 months. Conclusively, for patients who are ineligible for transplant, Schjesvold defended DRd as the first choice of therapy followed by D-VMP and VRd. Similarly, Jesús San Miguel from the University of Navarra (Spain) also argued in his talk that the addition of daratumumab or another anti-CD38 antibody to VRd or carfilzomib. lenalidomide and dexamethasone (KRd) significantly increases PFS.

In second line treatment after relapse, Schjesvold argued for a therapy that strategically takes into consideration the prior line of therapy so that a change in type of pharmacological agents is made. In this way, a proteasome inhibitor (PI), e.g., bortezomib, should follow DRd and an immummodulatory agent (e.g., lenalidomide) should follow failed treatment with D-VMP. Similarly, patients who received VRd or Rd as the first choice should move to a PI or a monoclonal antibody treatment (e.g., daratumumab).

According to Schjesvold, other combinations are also of interest. Based on the OPTIMISMM clinical trial results, the addition of pomalidomide to bortezomib and dexamethasone (PVd) shows greater efficacy than bortezomib-dexamethasone (Vd) alone. Alternatively, there is also evidence from the BOSTON clinical trial that the addition of selinexor to Vd may be beneficial to patients.

Compelled by this evidence and the results of other trials (e.g. CASTOR, CANDOR, IKEMA), as well as recommending a change in type of pharmacological agent, Schjesvold concludes that the addition of a third agent is beneficial overall. However, an exemption must still be made in frail patients.

Schjesvold also drew attention to the importance of starting a new treatment line as soon as a biochemical relapse was detected, e.g., when a rise in M-protein in the blood or urine is seen during monitoring, instead of waiting for further clinical signs.

#### **Ongoing Clinical Trials**

#### BelaRd study

An ongoing phase 1/2 study is examining the safety and efficacy of belantamab mafodotin (belamaf) in combination with lenalidomide and dexamethasone (Rd) in newly-diagnosed, transplant-ineligible, multiple-myeloma patients. Belantamab mafodotin is an antibody-drug conjugate made of a B-cell maturation antigen (BCMA)-targeting monoclonal antibody and a cytotoxic (cell-destroying) agent, maleimidocaproyl monomethyl auristatin F. The primary goal of the study is to evaluate the safety, tolerability and recommended dose of this combination. The secondary goal is to investigate the occurrence of ocular toxicities (known to occur with belamaf), pharmacological profile and the efficacy of the triplet combination. Three doses (2.5 mg/kg, 1.9 mg/kg, 1.4 mg/kg) of belamaf were administered to three patient cohorts (12 patients in each cohort) every eight weeks. The results obtained to date suggest that the safety profile of the combination is manageable. Ocular toxicities were common (between 83.3-100% of patients experienced them). However, these were all grade 1-2 (except in one patient) and did not seem to significantly impact day-to-day functioning. Other treatment-related adverse events were skin rash, diarrhoea, neutropenia and leukopenia. The overall response rate (ORR) was high (91.7-100%). The researchers chose the recommended dose of 1.9 mg/kg for further studies.

#### AGMT-MM02 study

The AGMT-MM02 study compares carfilzomib, lenalidomide and dexamethasone (KRd), and carfilzomib, thalidomide, and dexamethasone (KTd) induction, followed by K maintenance or observation in transplant, non-eligible patients. Nine cycles of KTd or KRd were administered to 123 patients randomised to two groups, followed by 12 cycles of K or observation-only in 79 patients, again, randomised to two groups. The overall response rate in the KTd group was 93.3% and in the KRd group it was 88.1%. Most treatment-related adverse events were grade 1-2. The toxicity profiles of KTd and KRd differed. KTd resulted in more events of thrombocytopenia, cardiac and neurologic events. With KRd neutropenia, diarrhoea and rash were more common. For comparing observation with K maintenance, the researchers looked at progression-free survival (PFS) rates. In the group receiving K, it was 25.2 months and in the group not receiving medication, it was 13.8 months. The researchers also found that a high immune score correlated with worse treatment outcomes.

# 1.3. Relapsed/Refractory Myeloma

In myeloma, relapses - despite technological advances - are common. At present, we have three key studies that report on the suboptimal outcomes of patients with myeloma refractory to the anti-CD38 antibody. These are: MAMMOTH (275 patients); LocoMMotion (248 patients) and the Connect MM Disease Registry (240 patients). According to the Connect MM Disease Registry, the median overall survival (OS) for all triple-class refractory was 8.9 months and the one-year survival probability was 38%.

Currently, approved therapies endorsed by EHA and ESMO guidelines include selinexor, belantamab mafodotin (belamaf) and two BCMA Chimeric antigen receptor (CAR)- modified T cell products named idecabtagene vicleucel (idecel) and ciltacabtagene autoleucel (cilta-cel). Selinexor is approved by the FDA (US), EMA (European Union) and TGA (Australia); belamaf is approved by the FDA (conditional approval) and the EMA; ide-cel is approved by the FDA, EMA (conditional approval) and in Japan; and cilta-cel is approved by the FDA and EMA (conditional approval).

There is no standard of care for triple-class refractory patients. Up to 92 combinations of different treatments were reported by the patients enrolled in the LocoMMotion trial. Considering the prior therapy is "the most critical factor towards decision making on the face of relapse", said Fredrik Schjesvold from the Oslo Myeloma Center (Norway). However, what treatment is available remains key in this process.

## 1.4. EHA-ESMO Treatment Guidelines

The clinical practice guidelines for diagnosis, treatment and follow-up issued by EHA and ESMO in collaboration were approved in November 2020 and then published early in 2021. An interdisciplinary panel of clinical experts on myeloma, members of ESMO, EHA and of the European Myeloma Network (EMN), selected the relevant literature. Levels of evidence and grades of recommendations were assigned according to the adapted Infectious Diseases Society of America-United States Public Health Service Grading System. Recommendations are given distinctively for frontline therapy, relapsed/refractory patients and plasma cell leukaemia. An overview of frontline treatments and first relapse treatment guidelines is provided here (no review date is stated):

#### **Smouldering Multiple Myeloma (SMM)**

'Watch and Wait'. High-risk patients are encouraged to participate in randomised phase 3 studies, which include overall survival as a primary endpoint in their analysis.

#### Myeloma Patients < Than 70 Years Old

If they have no other medical conditions, induction therapy followed by high-dose melphalan, then followed by autologous transplantation (ASCT) is recommended. The recommended induction therapy for these is bortezomib, lenalidomide and dexamethasone (VRd) or daratumumab-bortezomib-thalidomide-dexamethasone (DaraVTD) as the first option when available.

#### **Transplant Ineligible Myeloma Patients**

Patients are recommended to take VRd; or a combination of daratumumab with lenalidomide-dexamethasone (DaraRd) or with bortezomib-melphalanprednisone (DaraVMP).

#### **Consolidation Therapy After ASCT**

It has not been established to date as standard therapy. Allogeneic SCT from a healthy donor following ASCT has not shown to offer a survival benefit even in high-risk disease compared with tandem ASCT.

#### Maintenance

After transplant, maintenance with lenalidomide is considered the standard of care for all myeloma patients. However, bortezomib may be considered for patients with high-risk disease.

#### **Relapse/Refractory Patients**

The treatment of relapsed/refractory patients takes into consideration the previous line and the refractoriness to previous agents. For patients who had received VRd as frontline, second line therapy is dependent on whether they are sensitive or resistant to lenalidomide or bortezomib. Patients who are refractory to both lenalidomide and bortezomide are recommended daratumumab-carfilzomib-dexamethasone (DaraKd) or isatuximab-carfilzomib-dexamethasone (DaraKd) or isatuximab-carfilzomib-dexamethasone (IsaKd). For patients who had received DaraRd as first line, the next option includes several regimens such as pomalidomide-bortezomib-dexamethasone (PomVd) or carfilzomib-dexamethasone (Kd). Patients who had been treated with DaraVMP are recommended to switch to a regimen containing elotuzumab-lenalidomide-dexamethasone (EloRd) or, if they are sensitive to bortezomib, other regimens can also be considered.

## 1.5. Personalised Treatments

#### High-Risk Myeloma Profile

The definition of high-risk in myeloma is not uniform across clinical trials and accounts for a small subgroup of the population understudy. Several factors which define high-risk have been suggested:

- The genetic acquisition of deletion 17p
- Early relapse after prior therapy. Early relapse occurs less than 12 months after autologous stem cell transplant or less than 18 months after the initial line of therapy
- Observable clinical relapse
- Detectable disease outside the bone marrow

Challenges in this population come from potential organ damage and that the patient is likely to be refractory to lenalidomide and a proteasome inhibitor at first relapse. NCCN guidelines state the importance of performing a bone marrow biopsy at the time of relapse and a reassessment of the genetic profile. The GMMG CONCEPT study has shown that the quadruplet isatuximab-carfilzomib-lenalidomide-dexamethasone provides encouraging rates of rapid and deep remissions for these high-risk patients; 20 out of 31 patients analysed achieved negative MRD.

#### **Cytogenetic Profile**

Treatment can also be adapted to a patient's cytogenetic profile: Venetoclax, a Bcl2 inhibitor, is given to patients with the genetic abnormality t(11;14). The IMWG and EHA-ESMO provided guidelines and recommendations on cytogenetic testing to detect of del17p, t(4;14), t(14;16), ampl 1q/ gain 1q, and t(11;14)<sup>1</sup>. In the past decade, many targets have been identified and led to drug discovery, and there is still a lot to do to better understand which patients can benefit the most from each compound, and to better define the best treatment sequence for a given patient. There is also potential for biomarker-driven strategies at prognosis and predictive levels. To conclude, when making a treatment decision, not only should efficacy be considered, but also quality of life and treatment burden.

#### **Other Factors: Age and Distance**

Treatment can be adjusted according to patients' characteristics: for example, aged patients and/or who live far away from the hospital can take Carfilzomib once a week at a higher dose, instead of twice a week at the normal dose. However, Carfilzomib has been linked to a significant number of cardiovascular events, and these adjustments are therefore not recommended for patients who have high cardiac involvement.

# **2. LATEST THERAPIES**

1. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-u. Dimopoulos, M.A. et al. Annals of Oncology, Volume 32, Issue 3, 309 - 322. https://www.annalsofoncology.org/article/S0923-7534(20)43169-2/fulltext The targeted therapeutic approaches, which emerged in the past two decades in the treatment of myeloma, have significantly improved disease prognosis. Most targeted therapeutic approaches involve immunotherapeutic agents, which utilise the cells of the body's immune system to fight diseases such as cancer. These play a vital role in effective myeloma treatment. Types of immunotherapy medications used for the treatment of myeloma include monoclonal antibodies; immunomodulators, such as proteasome inhibitors and immunomodulatory imide drugs (IMiDs); and cell therapies, such as chimeric antigen receptor T-cell (CAR-T) and bispecific antibodies. Upon reviewing the history of myeloma treatment starting from the 1960s, Jesús San-Miguel from the University of Navarra (Spain) pointed out the importance of individualised approaches, as each patient will benefit from different treatments based on the genetic nature of their myeloma, their overall health and fitness, and as their co-occurring conditions. The following section reviews the data presented on emerging therapeutic approaches that allow for the targeted treatment of myeloma.

# 2.1. Small Molecules

#### Selinexor

The mode of action of selinexor is the inhibition of exportin 1 (XPO1), a nuclear exporter for tumour suppressor proteins that contribute to nine out of 10 cancer hallmark processes. The STORM trial studied the combination of selinexor plus dexamethasone in patients who had a median of seven prior regimens. The results of the trial showed an overall response rate (ORR) of 26.2% and an overall survival (OS) of 8.6 months. Common, serious side effects were thrombocytopenia, pneumonia and sepsis. In terms of health-related quality of life, most patients were reported to have maintained a steady level during the first six cycles of treatment.

The BOSTON clinical study compared Selinexor with bortezomib and dexamethasone vs bortezomib and dexamethasone alone. The median progression-free survival (PFS) was reported to be statistically and significantly superior (13.93 versus 9.46 months). Results from exploratory analyses outside the study's objectives were shown to be less favourable for the subgroup of patients with the specific genetic translocation t(4;16).

Selinexor is approved by the EMA for triple-class refractory patients who have received at least four prior lines of therapy including two immunomodulatory agents, two proteasome inhibitors and one anti-CD38 antibody. It is of particular interest because in vitro studies showed that it can overcome acquired resistance to proteasome inhibitors.

#### Venetoclax

This agent targets patients with a genetic t(11;14) translocation via the B Cell leukaemia/lymphoma-2 (BCL-2) protein. The phase 1 trial M13-367, which

enrolled 66 patients, showed that most responses (12/14 [86%]) were reported in patients with the specific genetic t(11;14) translocation. In this group, the overall response rate was 40% with 27% of patients achieving a very good partial response or better. According to the BELLINI trial, only patients with t(11;14) or high BCL2 gene expression could benefit from venetoclax without an increased risk of death.

#### **Cereblon E3 Ligase Modulating Drugs (CELMoDs)**

#### Iberdomide (CC-2020)

Iberdomide's mode of action is the inhibition of cereblon E3 ligase modulator (CelMoD), causing the degradation of target proteins, including Ikaros and Aiolos. It is active in lenalidomide- and pomalidomide-resistant myeloma cell lines in vitro. This agent is being investigated in relapse/refractory patients who have received at least three lines of therapy, including lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid and a CD38 monoclonal antibody. The CC-220-MM-001 phase 1b/2a trial enrolled patients who had shown progressive disease within 60 days of their last myeloma therapy, with the goal to evaluate the maximum tolerated dose. Results in 107 patients indicated an ORR of 28% and a median PFS of 13.1 weeks. A further interesting finding from this study is that upon examining the tumour micro-environment, researchers saw an increased activation of T-cells and NK cells (immune cells that play a vital role in the destruction of cancer cells). Based on the clinical data, Sagar Lonial from Emory University, Atlanta (USA) argued for the consideration of iberdomide in first line myeloma treatment.

#### Mezigdomide (CC-92480)

Similarly to iberdomide, mezigdomide has shown to provide immunostimulatory stimulus and anticancerous effects in myeloma cells in vitro, including those resistant to lenalidomide and pomalidomide. In combination with dexamethasone, it has demonstrated acceptable safety and encouraging efficacy. Its effectiveness has been evaluated in the trial CC-92480-MM-002. This is an ongoing phase 1/2 study evaluating mezigdomide in combination with standard treatments in patients with relapse/refractory myeloma. Results currently remain preliminary.



# 2.2. Antibody Drug Conjugates

Antibody drug conjugates (ADCs) provide a convenient therapy as they are available off-the-shelf (and therefore do not require personalised manufacturing) and can be administered outside the hospital. Anti-CD38 monoclonal antibodies synergise with IMiDs and with proteasome inhibitors.

A number of ADCs targeting different cell surface antigens are currently under evaluation. Some examples are shown here:

Belantamab mafodotin (belamaf) is an ADC now approved by the EMA for triple-class refractory patients, who have received at least four prior lines of therapy, including one immunomodulatory agent, one proteasome inhibitors and one anti-CD38 antibody.

A pivotal efficacy study was the phase 2 DREAMM-2 Study, designed to investigate belamaf in patients who had three or more prior lines of treatment. The primary efficacy point was an overall response rate that was achieved by 32% patients. In terms of safety, grade 3-4 adverse events were observed in 83% of patients, with keratopathy (31% of patients), thrombocytopenia (22%), anaemia (21%), lymphopenia (17%) and neutropenia (11%) occurring in more than 10% of patients.

Further trials for belamaf in multiple myeloma are currently ongoing, such as the series named as DREAMM (DRiving Excellence in Approaches to Multiple Myeloma). In the DREAMM-5 study, belamaf is being evaluated in combination with nirogacestat to determine if the combination can result in similar efficacy and an improved ocular safety profile compared to the currently approved belamaf schedule. It has shown a 31% overall response rate (ORR), however, 44.5% of patients experienced grade 3-4 keratopathy. Other reported common, serious side effects are pneumonia, pyrexia and infusion-related reactions. The median OS is 13.7 but data is still immature and a longer follow-up is required.

In addition to this, latest updates from the DREAMM-6 trial have reported positive outcomes for belamaf in combination with lenalidomide and dexamethasone (Rd) in relapse/refractory patients who have received one or more prior lines of treatment.

DREAMM-9, evaluates a quadruplet combination treatment regimen of belantamab mafodotin with standard of care (bortezomib, lenalidomide and dexamethasone or VRd) in 36 patients with newly-diagnosed multiple myeloma who are transplant-ineligible. Preliminary data suggests the addition of belamaf to VRd did not reveal new safety signals, as compared to VRd or belamaf alone, and seems to lead to high response rates. More than half of the patients achieved VGPR or better. A longer follow-up is needed to confirm safety and evaluate the efficacy of this quadruplet.

# 2.3. Modakafusp Alfa (Tak-573)

Modakafusp alfa is a first-in-class immunocytokine (an antibody-cytokine fusion protein) designed to deliver interferon alpha-2b (IFN $\alpha$ 2b) to CD38+ cells. CD38 is present on the surface of myeloma cells. Interferon alpha-2b is a cytokine protein that activates the body's immune cells so they can destroy the cancer cells. Modakafusp alfa is currently being tested in a phase 1/2 trial in relapsed/ refractory patients who received at least three previous lines of therapy. The primary goal of the study is to test the safety and tolerability of the drug. In a group of 30 patients receiving 1.4 mg/kg modakafusp alfa every four weeks, an ORR of 43% was reported. The median PFS was 5.7 months and the response rate in patients who were refractory to anti-CD38 antibodies was 39%. The most common treatment-related adverse events were haematological; these included thrombocytopenia, neutropenia, anaemia, leukopenia and fatigue.

## 2.4. CAR-T therapy

Chimeric antigen receptor (CAR) T-cell therapy is one of the rapidly-emerging and highly-promising immunotherapeutic options in myeloma. This form of therapy has already shown unprecedented results in B-cell malignancies. In essence, CAR T-cell therapy works by reprogramming the patient's immune system to directly attack tumour cells. During a highly complex manufacturing process, T lymphocytes are biologically engineered to express monoclonal antibodies recognising tumour-associated proteins in the surface of tumorous cells.

After the identification of eligible patients, their journey will follow a number of steps:

- 1. Leukapheresis. Also simply called apheresis, this is the process by which white blood cells are removed from the patient's sample of blood. The number and quality of T cells obtained determine the success of the treatment. All treatments must be stopped one week in advance.
- 2. Bridging therapy. This may include treatment with a number of agents such as glucocorticoids, proteasome inhibitors, alkylating and other antineoplastic agents. This therapy must be stopped two weeks prior to the future CAR T-cell infusion.
- **3.** Lymphodepletion therapy. These are three consecutive injections given 3-5 days before CAR T-cell infusion.
- **4.** CAR T-cell infusion. Cells are given back to the patient. According to the KarMMA trial and CARTITUDE-1 trial, an estimated 10-15% of patients cannot be infused after apheresis.
- **5.** Monitoring. Patients require close monitoring as they are at risk of developing serious adverse events. This observation is variable and depends on several factors. This is critical to the overall success of the treatment.

If you would like to find out more details about how CAR-T therapy works and what side effects it may have, please take a look at MPE's publications: 4th *European CAR-T cell meeting conference report* and the Q&A on CAR-T therapy.

#### **Available CAR-T Agents**

Data from phase 3 trials are pending, but BCMA-targeted CAR-T cells are showing response rates and durability in heavily pre-treated patients. There are two therapies that currently receive FDA and EMA approval: idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel).

#### Ide-cel (BCMA-CAR-T)

Evidence for the effectiveness of this agent has been provided by the KarMMa trial, a pivotal phase 2 study. Results indicate that 78% of all ide-cel treated patients were event-free at 12 months. The reported median OS is 24.8 months. Common, serious side effects include Cytokine Release Syndrome (CRS), infections, febrile neutropenia and fever. It is now approved by the EMA for patients who have received at least three prior lines of therapy, including one immunomodulatory agent, one proteasome inhibitor and one anti-CD38 antibody.

#### Cilta-cel (BCMA-CAR-T)

The effectiveness of cilta-cel is based on the results of the CARTITUDE-1 clinical trials. This is a phase 1b/2 trial, which has been conducted in patients with at least three prior therapies. The reported median OS is 27 months. Further evidence has been made available from the CARTITUDE-2 trial Cohort B, of which the results were presented by Niels van de Donk from Amsterdam UMC (The Netherlands). In this cohort, all eligible patients had received one line of prior therapy prior to cilta-cel, including a PI and an IMiD, and had an early relapse (within 12 months) after this first line.

The main goal of this study was to reach MRD negativity after at least one year after cilta-cel administration (at the level of  $10^{-5}$ , which is one cell among 100000). Bridging therapy was possible and 60% of patients needed it. Among them, 40% of patients progressed during the bridging therapy, highlighting the fast-progressing feature of their disease. After 12 months, 89.5% of patients were still stable or in remission. This is a very good result, knowing the profile of these patients. In terms of safety and tolerability, 84% of those patients experienced CRS (5% at a grade of three or four, severe or life-threatening), and 5% experienced neurotoxicity (ICANS) of grade 1-2. Of those treated patients, 80% were lenalidomide refractory. Future data should tell if this population has different outcomes. Conclusively, Cilta-cel is a promising treatment for patients who experience early relapse.

#### Safety Of CAR-T Therapy

Christian Chabannon from Aix Marseille Université School of Medicine (France) pointed out that clinical trials have different designs and patient populations, hence direct comparison of the safety profiles is not yet possible and only real-world data in the future will enable this.

The most common short- and mid-term side effects of CAR-T therapy can be summarised as follows: the short-term side effects are CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) and the mid-term effects are cytopenia and neutropenia, infections and hypogammaglobulinemia. The accurate assessment of long-term side effects is not yet possible, since the longest follow-up after CAR-T treatment was 10 years (in other disease areas). More data would be necessary to investigate long-term side effects and to determine if the short- and mid-term side effects have a far-reaching impact on the health of patients. As the short- and mid-term toxicity profiles are well-known, risk mitigation plans must include specific training of healthcare professionals and specific and tight hospital organisation to accommodate for patients receiving CAR-T therapy.

Early and late infections may follow this line of therapy. This is because CAR-T cells are exposed to short- and long-lasting immune suppression. Most infections are seen before the end of the first month after CAR-T administration. It must be noted that the prevention of infection with prophylactics is often centredependent and can occur at different strategic time points of the CAR-T process. Levofloxacin, acyclovir or valacyclovir, fluconazole or micafungin and trimethoprim-sulfamethoxazole are some of the treatments used. Bacterial infections are the most common, but viral and fungal infections can also occur. Viral infections are seen at later stages, with respiratory viruses being the most prevalent. In the case of myeloma, fungal infections were more frequent after 100 days. Infection rates are higher in patients with poor physical health (high ECOG score) and 60% of patients who received BCMA CAR-T products contracted infection(s) during the first month. There is also the risk of cumulative infections that could occur in the long term. In addition, the risk of developing COVID-19 is higher in this population. Conclusively, efforts need to be made to better understand the timeline of these infections in order to escalate/de-escalate different kinds of prophylactic treatments at the right time. Notably, it is currently difficult to discriminate between CRS and infections. New techniques are being developed, but will need to be validated.

Nikhil Munshi from the Harvard Medical School (USA) briefly reviewed the factors influencing CAR-T therapy outcomes and risk of toxicities. He suggested that patients on immunosuppressants should also be considered for CAR-T. Patients on anticoagulation medicines should have no active bleeding, and that adequate bone marrow function is not a prerequisite for CAR-T. However, very low blood counts (absolute neutrophil count below 1000 cells/mm<sup>3</sup>) may impact the production of adequate CAR-T cells and increase the risk of cytopenia after treatment.

#### **Current CAR-T Research**

At present there are a number of clinical trials on novel CAR-T therapy taking place. Examples of these are: ARI0002h (phase 1/2); P-BCMA-101 PRIME, which evaluates an alternative manufacturing process; CT053 LUMMICAR and ALLO-715 UNIVERSAL (allogeneic CAR-T). Two clinical studies on specific novel agents, which are in their very early stages, are the following:

#### Fast CAR-T GC012F (BCMA/CD19 CAR-T)

Juan Du from the Shanghai Changzheng Hospital (China) presented the results of a first-in-human study of BCMA/CD19 dual-targeting fast CAR-T GC012F, conducted in China. CD19 is expressed in both myeloma cells and their progenitor cells, which makes it a good target for new therapies. This new CAR-T has been designed to improve the depth of response and efficacy. The study includes patients refractory to anti-CD38, PI and IMIDs. The median follow-up was 6.3 months (28 patients so far) with the CAR-T manufacturing process taking two days followed by seven days for testing. MRD negativity was achieved for 100% of patients at a level of  $10^{-6}$ , with an ORR of 93% in a mostly high-risk population that had 4-5 median lines of therapy. CRS (grade 1-2) was experienced by 93% of patients, and while longer follow-up analyses are required to confirm these results, GC012F in earlier lines of therapy as well as additional indications is currently being studied.

#### CT103A (Human BCMA-targeting CAR-T)

Chunrui Li from the Tongji Medical College of Huazhong University of Science & Technology (China) presented the results of the phase 1/2 FUMANBA trial. It is a human BCMA CAR-T conducted in 14 sites in China. The ORR is currently 95%, including 90% of patients who achieved a VGPR or better. The CAR-T cells were still detected in 53% of the patients 12 months after infusion, showing a long-term persistency. CRS was experienced in 94% of patients (no higher than grade two) and some patients had prior CAR-T therapy. They showed lower responses but still benefited from the therapy.

#### **Future CAR-T Research**

Some of the main questions with this therapy are: how can we prevent relapse after one or two years? Is maintenance the solution? What kind of treatment or therapy can come next? Claire Roddie from UCL (UK) presented on the dual targeting of CAR-T cells. Dual targeted, or bispecific CAR-T cells, have binding sites for two different targets that can be found on the tumour cells. This approach may reduce the frequency of relapse, increase CAR-T cell therapeutic efficacy and lead to higher specificity towards the tumour cells. Michel Sadelaine from the Memorial Sloan Kettering Cancer Center (USA) talked about epigenetic programming of CAR-T cells. Research findings show that this approach increases CAR-T cell potency and efficacy. It may also decrease the severity of CRS and improve cell metabolic fitness, which leads to CAR-T cells being able to better function.

# 2.5. Bispecific Antibodies

Bispecific antibodies (bispecifics) to BCMA, as well as to other cell surface targets (e.g. GPRC5D, FCRH5, FCRL5) are showing promising response rates and durability. This form of therapy can be available off-the-shelf.

#### **Current research on bispecifics**

Here is a summary of the currently explored bispecifics in myeloma:

Agent name	Product	Targets	Phase
n/a	AMG420	BCMAxCD3	1
Pavurutamab	AMG701	BCMAxCD3	2
Alnuctamab	CC93269	BCMAxCD3	1
Elranatamab	PF06863135	BCMAxCD3	3
Linvoseltamab	REGN5458	BCMAxCD3	2
Teclistamab	JNJ64007957	BCMAxCD3	3
n/a	TNB-383B	BCMAxCD3	1
n/a	EMB-06	BCMAxCD3	2
Talquetamab	JNJ64407564	GPRC5DxCD3	2
Cevostamab	BFCR4350A	FCRH5xCD3	1
n/a	GBR1342	CD38xCD3	1

#### Teclistamab (BCMA-CD3 bispecific antibody) + daratumumab

Paula Rodríguez-Otero, from the University of Navarra (Spain) presented the results from the phase 1b TRIMM-2 study: 64 relapse refractory myeloma patients were treated with teclistamab and daratumumab subcutaneously. The hope is that this combination will show improved efficacy. During this study, premedication, including steroids, was limited to step-up doses and prior exposure to CD38 antibodies was allowed. 63% of patients were refractory to prior CD38 antibodies such as daratumumab or isatuximab. During the treatment, 63% of the patients experienced CRS (24% of CRS events were grade 2 (moderate) and 0% were grades 3-4). Among other adverse events, diarrhoea was reported by 32% of patients. No new safety signals or overlapping toxicities were observed, as compared to what has been previously reported with teclistamab and daratumumab taken separately. This combination is promising for heavily pre-treated patients with relapse/refractory myeloma, who have been exposed to CD38 antibodies. More data is needed to confirm these results and determine the appropriate doses.

#### **REGN5458 (BCMA-CD3 bispecific antibody)**

The last results from this phase 1/2 study, which included patients who had prior BCMA antibody drug conjugates such as belantamab mafodotin (but no BCMA bispecifics or CAR-T) showed an ORR of 51%. This included 58% patients achieving VGPR or better. 4/10 patients achieved MRD negativity at the level of  $10^{-5}$ . 38% of the patients experienced CRS (< grade 3).

# 2.6. Treatment Choice

#### **CAR-T Versus Bispecifics**

Ajai Chari from Mount Sinai - New York (USA) and Kwee Yong from University College London (UK) debated the topic of how to choose between CAR-T and bispecifics. Between ide-cel and cilta-cel, the toxicity is not significantly different, however cilta-cel is more efficient. We need more data to identify which patients will benefit the most from each therapy to guide treatment choice. Between CAR-T and bispecifics, several parameters can play a role: toxicity (neurotoxicity is higher with CAR-T), potential for advancement (to improve effector activity for CAR-T, combinations with other therapiess (multiple combinations are currently under investigation for bispecifics), and also availability and access. A true debate should be based on a randomised study where patients receive either CAR-T or bispecifics after randomisation. However, such a trial does not yet exist.

It is certain that the manufacturing process of CAR-T is a true limitation. Access and choice matter, and we need a therapy that will reach the highest number of patients, and fast. CAR-T takes time to be manufactured and can only be administered in a limited number of centres - both of these factors make the number of slots limited. On the other hand, bispecifics are off-the-shelf, less toxic (at least in the short-term), and could be given anywhere. However, toxicity has been tested only until progression of the disease, not after, so the long-term toxicity of bispecifics is still uncertain and needs to be documented. Attention should be given to the possibility of stopping treatment to limit long-term toxicity.

It is also important to find a treatment for everyone, not just fit patients. There is currently no data on CAR-T in unfit patients. How many myeloma patients would be able to get CAR-T at accredited centres? The extremely high price is also a limiting factor. More competition between CAR-T products, publicfunded academic CAR-T and better price negotiation with the industry could help decrease these prices in future.

#### Safety of CAR-T and bispecifics

Cytokine Release Syndrome (CRS), Immune effector-cell associated neurotoxicity syndrome (ICANS) and hemophagocytic lymphohistiocytosis (HLH) are specifically associated with both of these therapies. High grade CRS are risk factors of ICANS. It must be noted that CRS are less frequent and less severe

with bispecifics than CAR-T cells, and therefore, may be given in the outpatient setting in future. The American Society for Transplantation and Cellular Therapy (ASTCT) has graded CRS and ICANS. This is based on a number of symptoms and patients' responses such as the immune effector cell encephalopathy (ICE) score in the grading of ICANS. The ICE score includes questions on the ability of the patient in terms of orientation, naming, following commands, writing and attention (e.g. ability to count backwards from 100 by 10). The management of CRS may require fluids for hypotension, supplemental oxygen and tocilizumab. The management of ICANS will be based on avoiding sedating medications, the prevention of seizures and tocilizumab, amongst other potential interventions. In case of no response, immune suppression must be considered with anakinra, antithymocyte globulin or cyclophosphamide.

Available evidence indicates that priming the dose and premedication for the first doses of bispecific antibodies decreases the incidence of CRS. In the case of high tumour burden and severe CRS, debulking strategies are of interest prior to the administration of bispecific antibodies. Effective bridging therapy to reduce tumour burden is highly desirable before infusion with CAR-T cells.

Other important side effects that are shared with different therapies are cytopenia, hypogammaglobulinemia and infections. The risk of infections in relapse/refractory patients is due to several factors. The management of these infections will require the treatment with antibiotics and close monitoring of viral and fungal infections.

#### **Overview: ADCs, CAR-T And Bispecifics**

The table below provides an overall comparison ADCs, bispecific antibodies and CAR-T.

	ADCs	Bispecifics	CAR-T
Availability	Off-the-shelf	Off-the-shelf	Need manufacturing (treatment delay, bridging therapy needed in most patients)
Additional Treatment	Not needed	Not needed	Lymphodepletion
Dosing	Continuous treatment	Continuous treatment	One cycle then off therapy
Treatment delivery setting	Outpatient	Inpatient for first dosing, then outpatient	Inpatient
Main toxicities	Keratopathy	CRS (initial dosing) Cytopenia	CRS Neurotoxicity Cytopenia

# **3. REAL WORLD CLINICAL EVIDENCE**

## 3.1. Introduction

The evidence presented by clinical trials presents a number of challenges. Many myeloma patients are not judged non-eligible for inclusion in clinical trials. As an example, it has been estimated that approximately 40% of relapse/refractory patients do not meet the inclusion criteria for phase 3 clinical trials. In addition, trials often investigate complex novel regimens, which do not translate well to real clinical practice. Moreover, relevant data on patient outcomes resulting from therapies after the clinical trial protocol is often not collected. These issues highlight the need for gathering evidence in the real world of clinical practice. This setting allows a better understanding of the effectiveness of novel treatments in the broader population as well as how these vary between countries and regions. More importantly, only real-world clinical evidence can provide us with details on the treatment burden and the impact on the quality of life of patients.

As a result of the limitations of clinical trials and the challenges in collecting real world clinical evidence, Katja Weisel from the University Medical Center in Hamburg (Germany), suggested some strategies to enhance future data collection in research to facilitate the regulatory process. In Weisel's opinion, efforts must be made to clearly define the inclusion criteria for real world studies. In addition to this, a collective aim must direct the collaboration to gather data from trials and real-world evidence in parallel. Furthermore, it is also necessary to improve the dissemination of up-to-date information to myeloma specialists. Lastly, decision-making analysis needs to incorporate patient-reported outcomes in order to issue clinical guidance for therapies which result in actual patients' benefits.

A number of real-world studies in myeloma need to be highlighted:

Study	Country	N° of patients	Period	Reference
Not-treatment spec	ific			
LocoMMotion prospective study	EU & US	248	Ongoing	Mateos MV, et al. Leukemia 2022
Multicenter, retrospective analysis	Germany	911	2012-2018	Weide R, et al. Oncol Res Treat
Myriam registry	Germany	NR	2017-2021	Engelhardt M, et al. Poster presented at DGHO 2020
Treatment specific				
KRd	Italy	197	2016-2018	Rochhi S, et al. Hematol Oncol
IxaRd (INSIGHT-RMG)	13 countries	263	Ongoing	Hajek R, et al. Future Oncol 2021
Selinexor- containing regimens	US	34	Ongoing	Restrepo P, ASH 2021
SVd Case Series	Belgium	7	Ongoing	Delforge M, et al. Onco Targets Ther 2022
DGHO, Deutsche Gesellschaft für Hämatologie und Onkologie. IxaRd, ixazomib-lenalidomide-dexamethasone.				

KRd, carfilzomib-lenalidomide-dexamethasone

SVd. Selinexor-bortezomib-dexamethasone.

## 3.2. Age and Frailty

The effects of ageing on the immune system, both innate and adaptive, are evident in myeloma patients. Therefore, the differences between the older and younger population in the management of myeloma need to be noted. For a start, treatment aims can often be different. Older patients demand a finely tuned balance between efficacy and quality of life. Yet, achieving the greatest possible progression-free survival at first line is a key driver for overall survival. Because of this, it is important to provide realistic outcomes for informed decision making upfront.

Critically, older patients are under-represented in clinical trials. Therefore, clinical trial results may not represent real-life results where patients are subject to a number of challenges such as logistics, co-morbidities and poor compliance.

In terms of CAR-T therapy, at present there appears to be a greater incidence of CAR-T related toxicities in the older population, particularly ICANS. Available evidence indicates that after apheresis, older patients are, statistically, significantly less likely to be infused and more likely to receive safer agents. This produces bias in the research that needs to be overcome. CAR-T fitness in the elderly should be assessed early, e.g., to avoid highly toxic bendamustinecontaining therapies that can impair future success.

The limitations of clinical trials make real-world evidence studies, such as data gained from the International Myeloma Foundation (IFM) registry, particularly valuable. This registry contains data for 1,890 newly-diagnosed patients older than 75, whose genetic profiles via Fluorescence In Situ Hybridization (FISH) is available. Other notable studies are the UK NCRI Myeloma XI, CoMMpass and HOVON studies. Data for these studies was presented by Yaek Cohen, Director of the Myeloma Unit at the Tel Aviv Sourasky Medical Center (Israel).

In addition to age, frailty is an important factor to take into account when tailoring a pharmacological regimen to a specific myeloma patient. Frailty is defined as an ageing-related syndrome of physiological decline, characterised by marked vulnerability to adverse health outcomes (disability, hospitalisation and death). The gold-standard indicator of frailty in myeloma is given by the IMWG score, which factors in the Katz's activities of daily living and the Charlson Comorbidity Index. Yet, the prognostic accuracy of this score has been put into question and refining the evaluation of ultra-frail patients appears pertinent for elderly patients. In this regard, Sonja Zweegman, from the UMC Cancer Center

Patient status Patient	Deffect to me	Risk assessment	Recommended treatments	
			Preferred	Alternative
Newly diagnosed	Patients without significant neuropathy	Cardiac Stage I-IIIa	Dara-CyBorD	CyBorD VMDex
		Cardiac Stage IIIb	Dose modified dara-CyBorD Dara	CyBorD VMDex
	Patients without significant neuropathy	All stages	Rd (+/- cyclophosphamide)	Dara MelDex Carfilzomib-Dex

Dara= daratumumab, Cy/cyclo= cyclophosphamide, V/Bor= bortezomib, D/d/Dex=dexamethasone, M/Mel=melphalan, R=lenalidomide.

in Amsterdam (The Netherlands) argued for the use of objective biomarkers that are measurable, reliable and reproducible. Moreover, Zweegman put forward the strategic reversal of frailty by 3S: Sport (creates muscle); Senolytics and Senomorphics (novel anti-aging agents).

Studies conducted in the UK and in Germany, in other pathologies different from myeloma, showed that different CAR-T products led to various outcomes in frail patients. An upper age limit for the standard of care with CAR-T treatment in large B cell lymphoma (LBCL) could not be identified. Available evidence from studies carried out in Spain on relapsed LBCL suggests that patients over 70 years old can benefit from CAR-T cell agents similarly to younger patients. These results are promising, if confirmed in myeloma.



# 4. AL AMYLOIDOSIS - TREATMENT GUIDELINES

Ashutosh Wechalekar from University College London (UK) presented the newest treatment guidelines from the International Society of Amyloidosis (ISA) and the EHA.

## 4.1. Transplant-ineligible patients



Dara= daratumumab, Cy= cyclophosphamide, V/Bor= bortezomib, D/d/Dex=dexame thas one, M=melphalan, R=lenalidomide, I=lxazomib, Pom=pomalidomide.

The goal of therapy is to achieve a complete haematological response. Patients achieving less than VGPR by cycle three, or less than a partial response by cycle two, should be considered for treatment modification. Supportive care and multidisciplinary team involvement are key (cardiologists, neurologists, nephrologists and gastroenterologists) during the course of the treatment.

#### First line of therapy

Regarding consolidation and maintenance, there is not enough data on their relevance. Routine consolidation and maintenance are not recommended, because of the very high toxicity of treatment in AL amyloidosis patients. Consolidation may be considered for patients with VGPR or CR with persistent MRD and no organ response.

#### Special case - IgM related AL Amyloidosis

Patients with IgM monoclonal protein and lymphoproliferative disorders require different treatments:

#### Relapse

Treatment should occur when the disease progresses as per ISA criteria (VGPR or less with organ progression, and maybe CR with MRD positivity and no organ response or progression, or high-risk abnormal concentrations of free light chains).

To choose the drug regimen, Wechalekar recommends considering drugs used as first line, the depth and duration of response obtained, the extent of organ damage and, of course, funding and availability of these drugs.

## 4.2. Transplant-eligible patients

Vaishali Sanchorawaia from the Boston Medical Center (USA) presented the ISA-EHA guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis, according to the best available data at present.

Eligibility criteria for stem cell transplant depends on major health issues and varies for centres depending on experience, local policies and standard operating procedures. However, careful patient selection is critical for the success of stem cell transplant. Appropriate supportive care and the experience of the treatment centre are also key to SCT success.

#### Induction therapy

Bortezomib-based induction therapy (2-4 cycles) prior to transplant is recommended for patients with bone marrow plasmacytosis >10%. Induction therapy prior to transplant is not recommended for other patients.

#### **Conditioning regimen**

High-dose melphalan remains the standard regimen. A multidisciplinary discussion is recommended to determine melphalan dosing, depending on age, cardiac stage and kidney function.

#### **Consolidation and maintenance**

Maintenance therapy is not recommended after SCT. Consolidation therapy may be considered for patients who achieve less than VGPR and who did not receive induction therapy. Potential benefits must be balanced with toxicity risks. However, low dose lenalidomide can be considered as consolidation therapy for myeloma-associated AL amyloidosis.

#### Special cases - SCT after organ transplantation

Patients with end-stage renal disease on dialysis can undergo SCT, if other eligibility criteria are met. SCT is also feasible after renal transplantation, but the renal transplantation needs to be performed in haematological CR or VGPR to achieve prolonged, overall and renal survival. For SCT following heart transplantation, a coordinated team of cardiologists and haematologists is needed to avoid reappearance of amyloid in the transplanted heart.

## **5. MINIMAL RESIDUAL DISEASE**

Minimal residual disease (MRD) is a term used to describe the number of cancer cells that remain in the body during or after treatment. If positive, it means we can find low-level malignant cells that persist even after a complete response has been achieved. In this sense, MRD may be depicted at the bottom of the imaginary iceberg that represents the disease burden and what we can detect or see.

Technically, MRD negativity is defined by the IMWG as the absence of clonal malignant plasma cells in patients with a suspected complete response, assessed by next-generation flow cytometry (NGF) or next-generation sequencing (NGS) with a sensitivity of at least one in 100,000 cells.

The use of MRD negativity as a primary endpoint has been studied in several clinical trials. However, FDA and EMA guidance on using MRD negativity as a primary endpoint is subject to caveats. The EMA states that early approval based on MRD negativity as an intermediate endpoint may be considered due to medical need with confirmatory comprehensive data on other endpoints at a later stage. The call for validation of MRD negativity as a necessary surrogate endpoint to PFS is ongoing with the International Independent Team for Endpoint Approval of Myeloma MRD Initiative (i<sup>2</sup>TEAMM).

Juan Flores-Montero, from the University of Salamanca (Spain), argued for the

use of MRD negativity as an endpoint in clinical practice. This was supported by 20 years' experience with MRD in myeloma; the clear and reproducible relationship of MRD status with other traditional clinical endpoints; the consistent inclusion of MRD negativity as endpoint in clinical trials and the available mature MRD methodologies. Polling results showed that approximately 80% of attendees agreed that MRD negativity was a valid endpoint in clinical practice.

Noopur Raje, from the Center for Multiple Myeloma in Massachusetts General Hospital (USA), also spoke of the utility of MRD negativity as an endpoint for newly-diagnosed patients that require especially sensitive tools. For these patients, sustained MRD negativity has been associated with the best survival outcomes. The evidence of MRD as a prognostic tool in newly-diagnosed patients has been gained in the three PETHEMA/GEM trials where MRD status was compared to other endpoints, namely complete response and partial response. According to these trials, patients with a high-risk genetic profile (when MRD negative) were shown to have similar outcomes to patients of a standard risk. This confirms the validity of MRD as a prognostic tool in newly-diagnosed patients.

Notwithstanding, some limitations must be observed in the use of MRD status as a prognostic marker. Conflicting results exist between the achievement of complete response and MRD negativity, because of the biochemical detection of the persistent M-protein. Others are the variability in laboratory protocols and the lack of guidance on the optimal time for assessment. Jesús San Miguel from the University of Navarra (Spain) argued that achieving MRD negativity is the best way to avoid a poor outcome in patients with high-risk cytogenetics. Furthermore, when outlining the treatment journey of transplant-eligible patients, María-Victoria Mateos from the University of Salamanca (Spain) suggested that MRD is one of the most important prognostic factors in myeloma. However, she also pointed out that for MRD measurement to serve as a more accurate prognostic marker, increasing measurement sensitivity in the future would be vital.

# 6. COVID-19

Jamie Maddox from South Tees Hospitals NHS Foundation Trust (UK) presented how mortality among patients who have haematological malignancies has changed since the beginning of the COVID-19 pandemic. They captured the outcome of all patients with a haematological malignancy and COVID-19 in a region in the north of the UK, including 60 myeloma patients. They found that during the first wave, survival was around 40%, then 70% during the second wave and 90% during the third wave (with no difference between the Omicron and Delta variants during this third wave). The reason for this survival improvement could be due to different factors, including vaccination. The highest mortality risk factor was age, but not diagnosis or treatment. Myelodysplastic syndrome (MDS) and chronic lymphocytic leukaemia (CLL) patients had a higher mortality rate, but also the highest median age. The current mortality rate is 6-8%, which is much less than during the first wave. However, this is still higher than in the general population. This high death rate continues until 7-8 weeks after infection.

Patients with haematological malignancy suffering from severe COVID-19 disease

benefit from treatment with the plasma of healthy vaccinated individuals donated after COVID-19 convalescence, and who present high levels of neutralising antibodies important to fight the infection. Maike Janssen presented the results of the RECOVER study performed in Germany, where high-risk patients with confirmed severe COVID-19 disease were randomised to receive either the standard of care (SOC), or the SOC, plus this plasma. The goal of this approach was to compensate for the lack of antibody response, which might have been linked to the poor outcomes in these patients. This is a great need, as there are currently limited options for severe cases, especially when oxygenation is already required. One group in the study comprised patients with haematological diseases and/or who received cancer therapy in the past 24 months. The neutralising antibody levels of these patients increased after SOC plus plasma treatment. The time needed to see a health improvement was also shorter in this group, but not in the other groups. Similarly, these patients had a better survival rate with the addition of the plasma to the SOC, while there was no benefit in immunocompetent patients. This provides hope for patients who do not respond to the vaccine due to their disease and/or treatment.

# 7. PROs AND QUALITY OF LIFE

An Italian team conducted an analysis of Patient Reported Outcomes (PROs) to compare health- related quality of life (HRQoL) differences associated with VMP vs Rd treatment in an unselected real-life, transplant-ineligible myeloma patient population. Of the 104 patients who participated, 46% were over 75 years old. The median follow-up for all patients was just over a year (14 months). Mattia D'Agostino from the University of Turin (Italy) presented these results obtained as part of the phase 4 Real MM Trial. The measurement of HRQoL was determined using validated questionnaires for this condition namely EORTC QLO-C30, EO-5D-5L and QLO-MY20. PROs were collected as baseline, then every three months during the first year and, later, every six months. The analysis was adjusted for the IMWG frailty score and cytogenetic risk, so that these two factors could not confound actual results. They show that VMP is associated with transitory HROoL decrement, as compared to Rd, with more fatigue, appetite loss, nausea and worse physical functioning within the first three months. After these three months, HROoL improved. The depth of response had no impact on HRQoL, however, the frailty status (as defined by IMWG) at baseline could predict lower HRQoL. A longer follow-up will address the impact of VMP discontinuation vs continuous Rd on quality of life in the long-term. Of note, the response rate to the PRO questionnaires was only 50%, and differences were site-specific, not patient-specific. This means efforts should be made to improve the systematic collection of the data, and to train the clinical teams at trial sites to make sure everyone understands how important guality of life measures are, and how to explain it to patients.

Interestingly, Eva Telzerow from the University Hospital, LMU Munich (Germany), who presented HRQoL data from the German Acute Myeloid Leukaemia Cooperative Group (AMLCG) trial on long term AML survivors, mentioned that patients with children had better HRQoL. She thinks that this could be explained by the fact that people with children tend to have more social support. Such a link

between social support and HRQoL could also be studied in myeloma. Moreover, evidence suggested that lower levels of education and a worse financial status were associated with a higher risk of poor HRQoL. Furthermore, the association of age, gender, allogeneic stem cell transplant or relapse with poor HRQoL was not statistically significant.

# 8. ADVOCACY AND PATIENT SESSIONS

## 8.1. The patients' perspective

#### **Patient-centric clinical trials**

The President of Myeloma Patients Europe (MPE), Hans Scheurer (The Netherlands), was chairing a session on patient centric clinical trials. During this session, we heard about EU-PEARL, which is a strategic alliance between the public and private sectors to transform the way clinical trials are conducted, to improve and accelerate drug development processes and to place patients at the centre. EU-PEARL promotes a new paradigm of collaborative platform trials, where patients – represented by patient organisations – play a bigger role in trial designs and outcomes.

Several messages were also sent to trial sponsors: a good treatment is not just an efficient one. Quality of life and quality of care are also highly important. Therefore, clinical trial sponsors need to collect patient-reported experience measures (PREMs) to understand a patient's satisfaction with care and a patient's reported outcome measures (PROMs) to understand their quality of life during the treatment. Interviews, focus group discussion and survey measures, such as preferences studies and questionnaires, are other ways to gather patient feedback and allow future patients to make informed treatment decisions. Sponsors are also encouraged to develop audio and visual materials to communicate scientific concepts and to engage with the patient community.

#### **Patients' emotions**

Androulla Eleftheriou, Executive Director for the Thalassaemia International Federation, later gave us her findings of how patients feel regarding their condition and their care. Sentiments appear common to all patients, irrespective of their eligibility for genetic therapy. Some statements capture their thoughts: '(...) hooked to regular life-long transfusions'; '(...) iron overload complications and medications that I cannot afford'; '(...) frequent monitoring tests'; '(...) daily chelation adherence is difficult to keep up with'; '(...) sometimes I feel that I spend all of my time at transfusion units'. These feelings need to be understood in the context of a great number of personal challenges, such as the development of complications, the need for extra care and hospital days. In addition to this, patients talk about their extensive and life-long intrusion in their personal,

professional, social and family life. Like Eleftheriou, Raffaela Origa, Paediatrician and President of the Italian Society of Thalassaemia & Haemoglobinopathies (Italy), told us of her experiences listening to patients. Patients reported feeling highly insecure and unable to make plans. This was aggravated with the initial withdrawal of the medicine Zinteglo, which left them feeling "being used" and "betrayed" after providing their time and contribution to research. Zynteglo is a genetic therapy based on betiglogene autotemcel, which at present holds an EMA conditional marketing authorisation for Transfusion-Dependent Beta-Thalassaemia.

## 8.2. European projects in haematology

Helen Papadaki from the University of Crete, School of Medicine (Greece) introduced us to EuNET-INNOCHRON, the European Network for Innovative Diagnosis and Treatment of Chronic Neutropenias (CNPs). It is part of an umbrella of initiatives directed by the EU Cooperation in Science and Technology (COST). The principal remit of EuNET-INNOCHRON is to create a wide network of researchers with a special interest in CNPs and facilitate interactions from different scientific areas. Three main goals lead their operations:

- The promotion of science, training and education for the accurate diagnosis and treatment of patients with different forms of CNPs
- The expansion of neutropenia networks for a more multidisciplinary approach towards the development of individualised precision medicine
- The organisation of CNPs patient Registries and Biobanks using homogeneous protocols in line with the European legal framework

Michael Hudecek, from the University of Würzburg (Germany), gave an overview of the T2EVOLVE project, which he coordinates together with Hélène Negre at Servier. The T2EVOLVE is a new alliance of academic and industry leaders in cancer immunotherapy under the European Union's Innovative Medicines Initiative (IMI). This initiative aims to accelerate the development and access of cancer patients to immunotherapy with cells that contain a genetically engineered T-cell receptor or synthetic chimeric antigen receptor (CAR). T2EVOLVE does so while providing guidance on sustainable integration of these therapies into the EU healthcare system.

The T2EVOLVE project contains two key avenues for patient involvement. One of these is an educational hub that has been launched for patients, allowing for workshops with patients, patient associations and healthcare professionals. The second of these patient engagement avenues is a survey, which will be launched this year. This survey is directed to European adult patients who have received a CAR-T therapy for blood cancer. The objectives of this survey are as follows:

- To evaluate the experiences and challenges of receiving CAR-T cell therapy
- To evaluate the impact of receiving CAR-T cell therapy on quality of life
- To identify information needs and gaps
- To produce recommendations for more patient-friendly, informed consent forms

- To develop new educational materials to address unmet needs
- To ensure the patient's perspective is included in the reimbursement decision process

Christian Chabannon provided us with an update on the GoCART coalition. This association is a collaboration of patient representatives, healthcare professionals, pharmaceutical companies, regulators, Health Technology Assessment bodies, reimbursement agencies and medical organisations. The GoCART coalition was funded by the EHA in partnership with EBMT, a non-profit medical and scientific organisation that hosts a unique patient registry. The key objective is to maximise the potential of cellular therapies manufactured from cells and tissues of hematopoietic origin. Their mission is to promote patient access to novel cellular therapies and to contribute to health and well-being through innovation by multistakeholder collaboration on clinical data, standards of care, centre qualification, education and policy. In March 2022, the coalition published a multi-stakeholder revision of the EBMT Cellular Therapies data collection. This project addressed the challenges that resulted from the data that manufacturers and regulators want and the data that can reasonably be reported by the relevant clinical centres in a timely manner.

### 8.3. Inequities in Europe: lessons from Ukraine

A session on the challenges that current political conflicts present to the care of patients with myeloma was presented as part of the virtual workshops held at the EHA 2022. The panellists verbally explained their interpretation of the main issues and how these could be addressed. The session was chaired by Natacha Bolaños (Spain) on behalf of the Lymphoma Coalition. The panel was formed by Richard Sullivan, King's College London (UK); Anita Kienesberger, Chair of Childhood Cancer International (CCI) Europe Committee; Ewa Lech-Marańda, Director of the Institute of Haematology in Warsaw (Poland) and Andrés José María Ferreri, Director of the Lymphoma Unit of the IRCCS San Raffaele Hospital (Italy).

The panel explained how, at present, cancer patients are seen being sent from centre to centre, from Ukraine to neighbouring countries, and back again. Following their journey can be complex, and it is difficult to have the full picture of the current situation, but what must be understood is that refugees and internally displaced people don't just have cancer. The impact of the political conflict has resulted in important psychological stress and a decompensation of other non-communicable diseases, which is aggravated from the interruption of their therapy and issues in the supply of pharmaceuticals.

One of the most notable and specific challenges resulting from the displacement of cancer patients is the enormous variation in the radiotherapy protocols. An additional challenge that these patients present is the lack of full reports on their medical history compounded with treatment plans which vary enormously. Inequalities between patients of the same origin and with patients of different origins create issues which are often difficult to overcome, particularly when it comes to reimbursement. In the opinion of Sullivan, engaging with organisations working at grassroots level and that can be sufficiently agile to deal with the changing kinetics of the conflict, is required. This needs to be done in an environment riddled by a vast number of competing priorities. Because of the urgency of these issues, it is therefore paramount to start recovery planning as soon as possible, potentially anticipating for the conflict to remain long-term.

The consequences of the political conflict in Ukraine on healthcare must also be seen from the capacity perspective in terms of human resources. A great number of clinicians are leaving or have left Ukraine. This creates a requirement for equal standards and harmonised clinical guidelines.



## **GLOSSARY OF TERMS**

- Adverse event (AE) or side-effects: any unfavourable event and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medical treatment or procedure; in the context of clinical trials, adverse events are given a specific grade in severity based on specific criteria:
  - Grade 1: mild
  - Grade 2: moderate
  - Grade 3: severe
  - Grade 4: life-threatening
  - Grade 5: death
- AL amyloidosis: also referred to as light chain amyloidosis- is a rare disease that arises due to abnormal plasma cells, which are a type of immune cell. These abnormal plasma cells produce abnormal antibodies that serve no purpose in the body and deposit in organs and tissues where they disrupt normal function
- Allogeneic stem cell transplant (Allo-SCT): a type of stem cell transplant where cells that are genetically different are taken from someone other than the patient (usually a close relative or match)
- Anaemia: low levels of red blood cells in the body
- Antibodies: proteins that the body creates to fight infection
- Antibody drug conjugates (ADCs): drugs that are monoclonal antibodies attached to a chemotherapy agent, which binds to a protein on the surface of myeloma cells. The drug is then taken into the cell, releases the chemotherapy agent and causes myeloma cells to die. Example: belantamab mafodotin (Blenrep)
- Antigen: Protein on the cell surface
- Autologous stem cell transplant (ASCT): a type of stem cell transplant where a patient's own stem cells are taken out of their body, processed and reinfused after a patient receives chemo with the goal to replace damaged cells
- Bispecific antibodies (bispecifics) or Bi-specific T-cell engagers (BiTEs): drugs that are monoclonal antibodies, designed to bind both a target on the malignant plasma cells and on immune cells (T cells) to create an immune response, leading to the activation and the destruction of myeloma cells. Examples: talquetamab, teclistamab, elranatamab, cevostamab
- Bone marrow: spongy material in the centre of large bones in the body. This is where many cells are produced, including white blood cells (also called plasma cells) and red blood cells

- Bone marrow biopsy: a procedure that uses a large needle to take a sample of bone marrow (spongy tissue within the long bones), often from a patient's hip
- CELMoDs: (cereblon E3 ligase modulators): a new class of drug that degrades a specific set of proteins, stimulates the immune system and directly kills myeloma cells. It binds to the cereblon molecule, which plays a role in cancer cells, and which is also the main target of IMiDs. They are thought to induce degradation more efficiently, and to better induce myeloma cells death, as compared to IMiDs. Examples: Iberdomide, Mezigdomide
- Chemotherapy: a therapy that prevents myeloma cell division and replication, and induces cell death. Examples: cyclophosphamide, doxorubicin, melphalan, bendamustine (Levact), panabinostat (Farydak)
- Chimeric antigen receptor (CAR T) cell therapy: a type of immunotherapy treatment where T cells are genetically modified in a laboratory to enable them to find myeloma cells more easily. CAR-T cells are then infused in a patient, which then bind to myeloma cells and stimulate the immune system to kill the cancer cells. When the original T cells come from the patient him/herself, it is called autologous CAR-T, as opposed to allogeneic CAR-T cells. Examples: Idecabtagene vicleucel or ide-cel (Abecma), ciltacabtagene autoleucel or cilta. cel (Carvykti)
- Clinical trial protocol: a document or study plan that details all aspects of a clinical trial
- **CNPs:** Chronic Neutropenias (see: Neutropenia)
- Complete response (CR): a treatment response type where less than 5% of plasma cells can be found in the bone marrow and no paraproteins are detectable in blood or urine
- Consolidation therapy: a treatment given following a stem cell transplant or initial therapy once cancer can no longer be detected. This works to kill any remaining cancer cells that may be left in the body
- Cycles: administration of treatment followed by a 'time-off' treatment (or rest period); often occurs at the beginning of the month followed by 21 or 28 days
- Cytokines: proteins released by cells throughout the body to stimulate cell growth and kill target cells and microbes, which is part of the immune response
- Cytokine release syndrome (CRS): a side effect characterised as a systemic inflammatory response causing flu-like symptoms such as fever, body aches and fatigue, and, in severe cases, can be life-threatening
- Drug class: a set of medicines or therapies that have similar chemical structures, the same mechanism of action, or that target the same antigen. Examples: PIs, IMiDs, chemotherapy, IMiDs, mAb or moAb, steroids, BiTEs, trispecific antibodies, ADCs, CAR-T etc.

- Eastern Cooperative Oncology Group (ECOG): a measurement that describes a patient's mobility or ability to complete daily activities (a lower ECOG score means a better level of functioning)
- **EBMT:** The European Society for Blood and Marrow Transplantation
- **EMA:** European Medicines Agency. This oreganisation guarantees the scientific evaluation, supervision and safety monitoring of medicines in the European Union. It is equivalent to the U.S. Food and Drug Administration (FDA), and the Therapeutic Goods Administration (TGA) in Australia
- **EMN:** The European Myeloma Network
- **Endpoint:** an outcome or result measured in a clinical trial, such as survival, decreased pain, or the absence of disease
- **ESMO:** European Society for Medical Oncology
- **FISH:** Fluorescence in situ hybridization
- High-risk myeloma: a risk category, which includes patient-specific factors such as old age, poor performance status and comorbidities; clinical factors such as primary plasma cell leukaemia and extramedullary disease or plasmacytoma; disease-specific biologic factors such as deletion 17p, t(4;14) and high-risk gene expression profiling signatures. High-risk myeloma is associated with lower life expectancy. The definition of high-risk myeloma is continuously evolving, following new scientific discoveries
- HRQoL: Health Related Quality of Life
- Hypogammaglobulinemia: an immune system problem that prevents it from producing enough immunoglobulins (type of antibodies)
- Immunomodulatory imide drugs (IMiDs): drugs that prevent cell growth and blood supply formation to cells. These drugs g,enerate an anti-inflammatory response and stimulate an immune system response to kill cancer cells. Examples: thalidomide, lenalidomide (Revlimid), pomalidomide (Imnovid)
- Immune effector cell-associated, neurotoxicity syndrome (ICANS): a clinical and neuropsychiatric syndrome that can occur in the days to weeks following administration of certain types of immunotherapy (e.g. CAR-T, BiTEs). Symptoms can include delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, headache, and, rarely, cerebral oedema
- Inclusion criteria: characteristics study participants must have if they are to be included in a clinical trial
- Induction: initial treatment therapy for myeloma patients who are transplanteligible

- Informed consent: a patient's voluntary agreement, based on an understanding of the relevant information, to participate in a clinical trial
- Infusion-related reactions: adverse reactions to the infusion of pharmacological or biological substances. Symptoms can be pruritus, urticaria, fever, rigors/chills, diaphoresis (excessive sweating), bronchospasms (difficulty breathing, wheezing, coughing), cardiovascular collapse (severe hypotension resulting in loss of consciousness)
- **Keratopathy:** blurred vision, dry eyes, photophobia (very sensitive to light), eye irritation
- **Leukopenia:** low levels of leukocytes, a type of white blood cell that fights infections
- Lines of treatment: the order in which different treatments are given to patients as their disease progresses
- Lymphodepletion: a therapy given before stem cell transplant, which is usually high-dose chemotherapy to kill remaining cancer cells and remove any blood-producing cells that are left in the bone marrow
- Lymphopenia: low levels of lymphocytes, a type of white blood cell that fights infections
- Maintenance therapy: usually given after a stem cell transplant or after stem cell transplant plus consolidation therapy. It might also be used after induction therapy in patients who will not receive a stem cell transplant. The maintenance therapy drug is usually given in a low dose over a long time to reduce the risk of relapse in patients in remission
- Mean: average of data/numbers
- Median: middle value in a list of data/numbers
- Monoclonal gammopathy of undetermined significance (MGUS): condition in which an abnormal protein (monoclonal protein or M protein) is found in the blood after formation in the bone marrow. It does not usually cause any symptoms and does not require treatment, as only 1% of people with MGUS further develop multiple myeloma each year
- Minimal residual disease (MRD): use of specialised testing to test for microscopic levels of cancerous plasma cells in a patient that has had a complete response to treatment
- Monoclonal antibodies (mAb or moAb): antibodies engineered to mimic human antibodies that bind to specific targets on cancer cells to recruit the body's immune system to kill the cancer cells. Examples: daratumumab (Darzalex), isatuximab (Sarclisa), elotuzumab (Empliciti), magrolimab

- **Neuropathy:** Nerve damage. When the neuropathy is mild and happens peripherally, it can cause tingling in the hands and feet
- Neurotoxicity: a side effect of some myeloma treatments that is characterised by confusion, lethargy, inability to speak, tremor and, in severe cases, can progress to seizures and a coma
- Neutropenia: low levels of neutrophils, a type of white blood cell that fights infections
- Overall response rate /objective response rate (ORR): the percentage of patients with a partial response or better
- Overall survival (OS): number of individuals in a group that are alive after a duration of time
- Outcome: a clinical outcome or result is a measurable change in health, function or quality of life that results from an intervention/treatment or care (e.g. survival, decrease of pain etc.). It is also known as 'endpoint'
- M-protein / Paraprotein: an abnormal protein found in the blood that is formed by abnormal myeloma cancerous cells; paraprotein levels are often measured to assess myeloma disease states
- Patient Reported Outcomes (PRO): health outcome directly reported by the patient who experiences it, as compared to health outcomes reported by healthcare professionals. PRO measurement tools are often questionnaires used in clinical trials to help better understand a treatment's impact on a patient's quality of life (or QoL) and ePROs (electronic patient-reported outcomes) are becoming more frequent
- Peptide drug conjugates (PDCs): drugs that transport inactive anti-tumour agents to myeloma cells, which are then cleaved to an active toxic drug for myeloma cells. This aims to minimise the effect on healthy cells and therefore reduce adverse effects
- Phases (of a clinical trial): the parts of the investigative process that determine the safety, efficacy and tolerability of a treatment or procedure (see clinical trial phases section)
- Placebo: a 'dummy' pill that appears similar to the study drug but has no active ingredients
- Plasma cell: a type of cell found in the bone marrow that produces antibodies
- **Pneumonia:** infection of the lungs
- Plasmacytoma (extramedullary disease): a condition where cancerous myeloma plasma cells are found outside of the bone marrow, usually in the form of a tumour

- Progressive disease (PD): a treatment response type that shows an increase by 25% of urine or blood paraprotein levels
- Proteasomes: a protein complex in the body that degrades and removes damaged proteins
- Proteasome inhibitors (PIs): drugs that block proteasomes; this results in the build-up of proteins inside myeloma cells to toxic levels, causing cancer cells to die. Examples: bortezomib (Velcade), carfilzomib (Kyprolis), Ixazomib (Ninlaro)
- Pyrexia: fever
- Randomisation: the process of assigning study participants into the treatment versus placebo arm (a dummy treatment) of a study at random (using computer programs, random numbers, etc.)
- Red blood cells: blood cells that circulate oxygen to our vital organs and tissues
- Refractory: when the number of myeloma cells and paraproteins continues to increase despite someone receiving treatment
- Relapse: myeloma that initially responded to therapy but, after some time, myeloma plasma cell levels continue to increase
- Remission: classified as partial (some cancer cells or symptoms are present but at lower levels) or complete (cancer cells or symptoms are undetectable)
- Sepsis: life-threatening reaction to an infection
- SINE XPOI inhibitors: drugs that block the production of a certain protein (XPOI, or exportin), thus blocking the transport from the cell nucleus to the cytoplasm of several proteins involved in myeloma cell growth. This stops the cell cycle and leads to myeloma cell death. Example: Selinexor (Nexpovio)
- Smouldering multiple myeloma (SMM): asymptomatic clonal plasma cell disorder similar to MGUS but SMM patients have a much higher risk of progression to multiple myeloma. It is considered an early form of multiple myeloma with high numbers of plasma cells in the bone marrow and a high level of M protein in blood and urine. Nowadays, SMM patients do not need any treatment, but are monitored to see if the disease progresses to multiple myeloma. This might change in the future as SMM treatments are currently under investigation
- Stable disease: no worsening or improvement of myeloma after treatment; also, disease that has previously responded to therapy and paraproteins levels have not increased
- Step-up dosing: drugs are given at low doses that are progressively increased to measure their safety, efficacy and tolerance

- **Steroids:** drugs that reduce inflammation to relieve pain. Examples: dexamethasone, prednisone, prednisolone
- Subcutaneous: a drug or treatment that is given through a needle underneath the skin
- **Tachycardia:** increased heart rate
- **Transplant eligible:** patients considered good candidates for a stem cell transplant, usually younger than 65 years old. Patients between 65 and 75 years old may be eligible, depending on factors such as overall health and cancer stage
- **Transplant ineligible:** patients not considered good candidates for a stem cell transplant, because of factors such as age, health status, physical status and cancer stage
- Triple class refractory: patients who have previously been treated with a combination of three drugs, such as an immunomodulatory drug, proteasome inhibitor and a monoclonal antibody, and are no longer responding to therapy
- Thrombocytopenia: low levels of platelets in the blood; platelets are used by the body to stop bleeding
- Very good partial response (VGPR): a treatment response type that shows a greater than 90% decrease in paraproteins in blood and a paraprotein level in urine of <100 mg/24 h</p>
- White blood cells: cells of the immune system that fight infections



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