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Myeloma Patients Europe

CONFERENCE REPORT

American Society of Hematology (ASH) Annual Meeting 2019

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Myeloma Patients Europe

American Society Hematology 2019 Conference Report

The American Society of Hematology (ASH) Annual Meeting is the largest haematology conference in the world. More than 25,000 people attended ASH 2019 from 7 to 10 December in the Orange County Convention Center, Orlando, Florida, USA.

Of the nearly 5,000 abstracts presented during the conference, more than 900 were myeloma and AL amyloidosis presentations (posters and oral sessions) explaining the most important updates in these disease areas. Clinical trials exploring novel immunotherapies, new drug combinations and CAR-T cell therapy in myeloma and AL amyloidosis were some of the topics covered.

Myeloma Patients Europe (MPE) attended ASH 2019 and we provide an overview of the key highlights from the conference below.

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Myeloma updates

Immunotherapy

Treatment approaches that use the immune system (how the body responds to infection), known as immunotherapies, are promising for a wide range of cancers and related conditions, including myeloma and AL amyloidosis. Some immunotherapies such as monoclonal antibodies (i.e. drugs which target one protein expressed on the surface of cancer cells) are now a reality among treatment options for myeloma. Myeloma drugs daratumumab and elotuzumab are examples of monoclonal antibodies which have been approved by the European Medicines Agency [EMA] (the European medicines licensing body) in recent years.

There are now other immunotherapies, providing promising and innovative approaches for the treatment of myeloma, that are becoming a reality little by little. A good demonstration of this is the large number of presentations focused on myeloma immunotherapies at ASH 2019. Data on monoclonal antibodies, chimeric antigen receptor T-cell (CAR-T) therapies and bispecific antibodies were all presented at the conference.

Monoclonal antibody combinations – the CANDOR clinical trial

On the final day of every ASH meeting, the "late-breaking" news is delivered in a plenary session involving presentations from key researchers across different haematological cancers. These presentations are very prestigious and often provide the most compelling data at ASH.

The late-breaking myeloma presentation at ASH 2019 covered the results of the Phase III CANDOR clinical trial. This global trial looked at carfilzomib (Kyprolis®) in combination with dexamethasone and daratumumab (Darzalex®) (KdD) compared to carfilzomib and dexamethasone alone (Kd) in 466 patients with relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment).

Carfilzomib is a proteasome inhibitor, which works by blocking the actions of proteasomes, leading to cell death. It is an effective myeloma drug that is already approved in combination with dexamethasone by the EMA and is available in some European countries.

The data presented during the late-breaking session found a "significant survival benefit" by adding daratumumab, a monoclonal antibody targeting a protein expressed on the surface of myeloma cells called CD38, to the existing Kd combination. Monoclonal antibodies work by targeting a protein and attaching to the cancer cell. Once attached they can recruit other parts of the immune system to come and destroy that particular cell. The data presented at ASH showed a 37% reduction in the risk of disease progression or death in patients receiving KdD compared with patients taking Kd alone. Further survival data, including progression-free survival (i.e. the length of time before myeloma returns) and overall survival from the trial, is still pending.

Side-effects reported by patients in the trial were generally manageable and the incidence of stopping treatment due to these events was similar in both trial groups. The most common adverse events were thrombocytopenia (low white blood counts), anaemia (low red cell counts), diarrhoea, hypertension, upper respiratory tract infection, fatigue, and shortness of breath. There was a high incidence of cardiac (heart-related) events, occurring in 5-8% of

patients, which has been reported in prior studies involving carfilzomib; heart failure was lower in patients receiving the three-drug combination.

Lead researchers involved in the trial argued that these results support the KdD combination as an effective new regimen for this patient population, including for patients previously treated with the immunomodulatory drug lenalidomide. As increasing numbers of patients have received prior treatment with backbone drugs bortezomib (Velcade® - the first proteasome inhibitor) and lenalidomide (Revlimid®) and may no longer respond, it is important that new combinations are developed which are suitable for this population. Of those in the trial, 42.3% and 90.3% had previously received lenalidomide- or bortezomib-containing regimens, respectively. Roughly one out of three patients were no longer responding to lenalidomide.

"The majority of patients have disease progression on lenalidomide and, of the six treatment combinations that are currently approved in this setting, four have lenalidomide as part of their treatment combination. It makes little sense to re-challenge a patient with something they are progressing on just by adding other drugs," said lead study author Saad Z. Usmani, MD, of Atrium Health. *"So, there is a need for novel therapeutic options for patients with multiple myeloma who have relapsed or are refractory to lenalidomide-based treatments."*

According to Dr Katja Weisel, University Medical Center Hamburg-Eppendorf in Germany, *"more and more patients are refractory to lenalidomide when they go to second or third line treatment and for those patients, this combination is a very important treatment option and I hope this will very rapidly translate in a standard of care."*

Monoclonal antibody combinations – the ICARIA-MM clinical trial

Isatuximab is another monoclonal antibody indicated for the treatment of myeloma. Like daratumumab, it targets the CD38 protein expressed on the surface of myeloma cells. The Phase III ICARIA-MM clinical trial is assessing isatuximab in combination with pomalidomide (Imnovid®) and dexamethasone (IPd), compared to pomalidomide and dexamethasone (Pd) alone in 307 patients with relapsed and refractory myeloma who have received at least two or more prior lines of therapy. Pomalidomide is an immunomodulatory drug (similar to lenalidomide), which works by directly killing or stopping the growth of myeloma cells. Pomalidomide is licensed by the EMA and is available in many European countries for the treatment of patients in the relapsed setting. Researchers wanted to understand the anti-myeloma effect and efficacy of the combination with the addition of isatuximab.

An update was presented on the ICARIA-MM trial results at ASH 2019, which showed that the IPd combination induced deeper, more frequent and faster responses in this group of patients. The results also showed a survival benefit for the IPd arm compared to Pd. The median progression-free survival was 11.53 months in the IPd arm and 6.47 months in the Pd arm. In addition, overall response in patients was 60.4% in the IPd arm compared to 35.5%.

The data presented at ASH continues to show isatuximab as a promising new treatment option for relapsed myeloma patients.

Anti-body drug conjugate - DREAMM-3 clinical trial

A new category of immunotherapy related to monoclonal antibodies is called antibody-drug conjugates (ADCs). ADCs work by linking a chemotherapy agent with a monoclonal antibody. The ADC searches for the protein expressed on the surface of the myeloma cell. Once it finds the protein, it delivers the chemotherapy directly into the cell.

A new ADC being explored in myeloma by the company GlaxoSmithKline (GSK) is called belantamab mafodotin (hereafter belantamab), which targets a protein on myeloma cells called BCMA. Upon binding to BCMA on the surface of myeloma cells, it is rapidly internalised, and cytotoxic moiety is released, killing the myeloma cells.

Belantamab is being explored in a range of clinical trials, known as the DREAMM trials. Ongoing trials DREAMM-1 and DREAMM-2 have highlighted positive results in heavily pre-treated myeloma patients.

During ASH 2019, plans for the upcoming DREAMM-3 trial were presented. DREAMM-3 will be a Phase III clinical trial looking at efficacy and safety of belantamab monotherapy (i.e. when given to patients on its own). It will be compared with pomalidomide and low-dose dexamethasone (Pd) in patients with relapsed and/or refractory myeloma. The study is planned to start in late 2019.

In ongoing clinical trials looking at belantamab, the main side-effects have included thrombocytopenia, anaemia and keratopathy. Keratopathy is characterised as changes in the corneal epithelium (i.e. tissue which covers the front of the cornea in the eye) as seen on eye examinations which can manifest with or without symptoms. In simple terms, the drug can impact on a patient's eyes causing varying degrees of "blurry" vision. In an interview, Dr Katja Weisel, who is leading DREAMM-3, commented *"the blurry vision is a unique side-effect of this drug class caused by a corneal ulceration. This side-effect can be handled with prophylaxis, with therapeutic eye drops. It affects around one third of the patients, so it is significant, and it is completely reversible… We learn together about this side-effect. There are now well established protocols to manage the side-effect. It is a new toxicity, but we currently know we can manage it well"*. Health related quality of life (HRQOL) will be a secondary endpoint in DREAMM-3. Measuring HRQOL will allow researchers to better understand the impact of side-effects, including the keratopathy, on patients' lives.

CAR-T cell therapy – CARTITUDE-1 clinical trial

At ASH 2019 an important topic of conversation was chimeric-antigen receptor T cell (CAR-T) therapy. In CAR-T, a type of white blood cell which makes up part of the immune system (T-cells) is collected from patients and equipped with a chimeric antigen receptor or "CAR". When reintroduced into patients' bodies, it acts like a sensor boosting the ability of the immune T-cells to find and destroy the myeloma cells. Most clinical trials looking at CAR-T in myeloma are in the early phases, involving very small groups of patients. Early data presented at ASH on the CARTITUDE-1 clinical trial showed promising results in heavily pre-treated patients.

CARTITUDE-1 is a Phase Ib/II clinical trial of a new CAR-T being developed by Janssen called JNJ-4528. The trial involved 29 patients with relapsed and refractory myeloma. These patients had received a median of five prior lines of therapy and were no longer responding to the standard of care in the disease. The primary aims of the Phase Ib trial were to assess the

therapy's safety and to confirm the dose to be tested in a larger, phase II trial.

JNJ-4528 is a CAR-T targeted against the BCMA protein which is commonly found on the surface of myeloma cells. Researchers involved in the trial outlined that JNJ-4528 is a novel CAR T-cell therapy featuring two molecules that bind to the BCMA. In a press release issued at ASH 2019, lead researcher Dr Madduri from Mount Sinai Hospital, New York commented "*We are learning that every CAR T-cell therapy is different. JNJ-4528 has a unique CAR T-cell composition in patients, preferentially enriched in CD8 T-cells, which are believed to be one of the most important T-cells in killing cancer cells."*

The results of CARTITUDE-1, analysed after six months, demonstrated that all 29 patients achieved a response to the JNJ-4528 CAR-T. 66% of patients achieved a stringent complete response, meaning that sensitive laboratory and microscopic tests found no evidence of myeloma proteins or cells in blood, urine, or bone marrow, 3% achieved a complete remission, 17% a very good partial response and 14% a partial response, meaning that the level of M-protein (an abnormal protein produced by the cancerous plasma cells) in the blood or urine was reduced but still detectable. In the analysis at six months, all but two patients remained progression free. All 17 patients evaluable for minimal-residual disease (MRD) were MRD-negative. MRD is a sensitive measure designed to assess the very small amounts of myeloma left in the bone marrow after treatment. MRD negativity means that patients did not have any detectable myeloma in the bone marrow.

Most patients in the trial (93%) experienced cytokine release syndrome (CRS), a known side-effect caused by an immune response in the body to the activated T-cells that are attacking the cancer. CRS causes flu-like symptoms such as fever, body aches, and fatigue, and in severe cases can be life-threatening. One patient had severe (grade 3) CRS, and one patient died from its complications 99 days after the CAR T-cell infusion. In 76% of patients, CRS was treated with tocilizumab.

Whilst the results of CARTITUDE-1 are promising, it is important to bear in mind the results are early and immature. The trial results show data in a very small group of patients, with a short follow-up time of six months. Further analysis, clinical research and trials are therefore important to better understand the anti-myeloma impact of JNJ-4528 and whether these promising results are long-lasting in myeloma patients. To address this, the phase II portion of this study is ongoing to evaluate the overall response rate of patients treated with JNJ-4528. Researchers reported that this trial is now fully recruited. Additional clinical studies are planned to evaluate the safety and efficacy of JNJ-4528 in different myeloma treatment settings.

Bi-specific CAR-T cell therapy

Another approach being explored is bi-specific CAR-T therapy. With other CAR-Ts in myeloma, they are programmes to locate one protein expressed on the surface of myeloma cells. A bispecific drug can target two proteins at the same time. The hypothesis is that bispecific CAR-T may increase the efficacy of CAR-T and overcome something called antigen-loss, where the myeloma cells effectively "hide" from the CAR-T cells.

Researchers in China presented on a bispecific CAR T-cell therapy targeting both BCMA and CD38. An author of the study, Yu Hu, MD from Union Hospital, Huazhong University of Science and Technology in Wuhan, China commented *"Our thinking was that targeting both of these proteins would improve treatment efficacy without increasing toxicity, and induce deeper, more durable remissions."*

The Phase I, dose-escalation trial, explored the bi-specific CAR-T cell product in 22 patients with relapsed and/or refractory myeloma. The study aimed to determine the safest and most effective dose of the dual-targeted CAR T-cell therapy as well as to initially evaluate its effectiveness. To do this, patients were divided into five groups, with each group receiving a higher dose than the previous one. Depending on the cell dose, patients received either one or two infusions.

Patients participating had received at least two prior treatment regimens, including a proteasome inhibitor (such as bortezomib or carfilzomib) and an immunomodulatory agent (such as lenalidomide or pomalidomide). Nine of the 22 patients had extramedullary tumours. This occurs when myeloma cells form tumours outside the bone marrow in the soft tissues or organs of the body. It occurs in roughly one-in-ten myeloma patients and research has shown that patients may have a poorer prognosis.

Of the 22 patients receiving the treatment, 20 responded, including 12 stringent complete responses. At data cut-off, 19 patients remained alive, with 10 still in stringent complete response (i.e. a very deep response to treatment). Of nine patients with extramedullary disease, eight achieved a complete or partial response. A total of 18 patients became MRD-negative. The median progression-free survival had not been reached, with 78.9% of patients still progression-free at nine months. In eight of the nine patients with extramedullary lesions, these tumours were undetectable on their computed tomography scans.

As in other CAR-T studies, researchers found 20 patients experienced CRS, of whom six needed treatment. They reported that no serious adverse neurological effects such as seizures, movement impairment, difficulty speaking or understanding speech, or fatal swelling in the brain were reported.

Dr Hu further commented: *"Our results show that this CAR T-cell product can effectively achieve elimination of extramedullary tumours. Although these are preliminary data, they are encouraging for patients with myeloma who have not responded to other therapies."*

Like in the CARTITUDE-1 study, the data is very early phase and in a small group of patients. In addition, the cut-off time was short. Researchers involved in the study will continue to follow the patients for two years to better understand the safety and efficacy of the treatment. They are also planning to conduct a phase II trial in both China and the United States to test the treatment's effectiveness in a larger number of patients.

Bi-specific T-cell engagers – CC-93269

Bi-specific T-cell engagers are artificial bispecific antibodies which go after two targets – one on the T-cell and one on the cancer cell. The antibody directs a patient's immune system to link their T-cells to the cancer cell, killing it. BiTE drugs can be likened to CAR-T but without the need to programme T-cells in a lab, which has benefits in time and cost.

Data was presented during ASH 2019 on a Phase I clinical trial investigating a drug known as CC-93269, which specifically binds to the BCMA protein, expressed on myeloma cells and to CD3 expressed on T-cells.

This was a first-in-human, dose-finding trial, involving 30 patients with heavily pre-treated myeloma. Patients had received a median of five prior lines of therapy, with 77% being refractory (i.e. no longer responding) to daratumumab. Extramedullary disease and high-risk cytogenetics were present in 26.7% and 30.0% of patients, respectively. These are populations of patients who typically have a poorer prognosis and are often more difficult to treat.

Patients involved in the study were divided into cohorts, all receiving different doses of CC-93269. For all study patients, across all cohorts, the overall response rate was 43.3%, with a stringent complete response and complete response rate of 16.7%, and MRD negativity in 92.3% of patients who responded. Of the nine patients treated with an initial dose of the study drug of at least 6mg, the overall response rate was 88.9%, with 44.4% and 33.3% of them achieving a stringent complete, complete or very good partial response, respectively. The median time to response was 4.1 weeks, and 11 of 13 responses were ongoing at the time of analysis.

The most common side-effects across all patients were neutropenia, anaemia, infections, and thrombocytopenia. Three quarters of patients developed some level of CRS, which was most frequently associated with the first dose of CC-93269. CRS was managed in patients with dexamethasone and tocilizumab. Four deaths occurred during study follow-up, one of which was attributed to CRS. The other three causes of death (sepsis, sudden cardiac death, and general health deterioration due to progressive myeloma) were not thought to be related to the study drug.

The results of this early-phase clinical trial have highlighted that CC-93269 works in the treatment of heavily pre-treated myeloma. Further clinical research in Phase II clinical trials is required to better understand the optimum dose of the treatment, the safety and efficacy of the drug and the impact that the drug has on patient quality of life.

Novel agents

As well as research on immunotherapy, a range of data was presented on ongoing clinical trials of different categories of new and existing novel drugs used to treat myeloma. Updates were provided on drugs / drug combinations including proteasome inhibitors (PIs), such as ixazomib and carfilzomib and immunomodulatory agents (IMiDs), such as pomalidomide and the new CC-220 drug. You can find all relevant abstracts on the ASH website.

SINE Inhibitor - Selinexor

Key data to highlight on novel agents from ASH 2019 relate to a drug called selinexor, which is also referred to as XPOVIO®. Selinexor is a treatment being explored by the pharmaceutical company Karyopharm in a range of clinical trials involving myeloma patients. It is a first-in-class drug known as a Selective Inhibitor of Nuclear Export (SINE) compounds. Selinexor works by blocking the action of a protein called XPO1 within the nucleus (cell centre) of myeloma cells.

In total there were nine presentations at ASH on selinexor in myeloma, including an oral presentation providing updated data from the Phase Ib/II STOMP trial.

STOMP stands for Selinexor and Backbone Treatments of Multiple Myeloma Patients, which means that the trial is looking at selinexor in combination with other standard therapies for the disease. The oral presentation focused on the arm of STOMP looking at selinexor in combination with pomalidomide and low-dose dexamethasone (SPd) in patients with relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment) who received at least three prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or patients with myeloma refractory to both a proteasome inhibitor and an immunomodulatory drug.

The results found that in relapsed and/or refractory myeloma patients who had not previously received pomalidomide and were no longer responding to lenalidomide (n=32), the median progression free survival was 12.2 months. For patients who had previously been treated with pomalidomide and were no longer responding to lenalidomide (N=14), the median progression free survival was 5.6 months.

At the time of analysis, the most common treatment-related side-effects patients experienced were cytopenias (i.e. reduction in the number of one or more normal blood cell types), along with gastrointestinal and constitutional symptoms; most were manageable with dose modifications and/or standard supportive care. The most common non-haematologic treatment-related side-effects were nausea (52%), fatigue (52%) and weight loss (39%). The most common treatment-related Grade 3 and 4 AEs were neutropenia (58%), thrombocytopenia (27%) and anaemia (27%).

Based on these Phase II results, a Phase III study investigating the SPd combination is planned. This will further explore the safety and efficacy of the drug in myeloma.

Disease monitoring in myeloma

CASSIOPET - Prognostic value of PET-CT scanning

CASSIOPEIA is a Phase III clinical trial in which newly-diagnosed transplant-eligible myeloma patients were randomised to receive treatment with four pre-transplant induction cycles (i.e. treatment to get rid of myeloma before an autologous stem cell transplant) and two post-transplant consolidation cycles (i.e. treatment to reinforce the response to induction treatment and stem cell transplant) with either bortezomib, thalidomide and dexamethasone (VTD) alone or in combination with daratumumab (D-VTd). The results showed that D-VTd induction and consolidation significantly reduced the risk of disease progression and death compared to VTd. D-VTd also improved the rates of stringent complete response, complete and very good partial responses, and MRD-negativity vs VTd.

Whilst MRD-negativity is associated with improved outcomes, relapse still occurs in MRD negative patients. Researchers think this might be due to the presence of focal (very specified/focused) bone disease, which might not be picked up through bone-marrow biopsy. The role of imaging is therefore being explored to understand its role in determining whether patients are truly MRD negative.

To address this question, a "companion" study was run alongside the CASSIOPEIA clinical trial to assess the role of a scanning technique called Positron Emission Tomography-Computed Tomography (PET-CT) in understanding patient prognosis (i.e. the course of the disease in a patient) and the length of time a patient will remain progression free. The study aimed to compare the treatment response of patients who had achieved MRD negativity and PET-CT negativity (i.e. no presence of disease in both tests) post consolidation vs. those who did not have MRD and PET-CT negativity. Researchers hypothesised that patients in the CASSIOPEIA trial who achieved MRD negativity and had a negative PET/CT scan would have better outcomes than patients that did not.

In the CASSIOPEIA study, PET/CT scans were performed in patients at the start of the study (prior to first dose) and post-consolidation (Day 100 post stem cell transplant).

The results presented at ASH highlighted that PET-CT is a viable prognostic tool in myeloma. The study showed that newly diagnosed patients with PET-negative findings prior to treatment had a more favourable prognosis. Patients who had both PET and MRD double negativity post-consolidation after D-VTd and transplantation also had better outcomes.

The researchers concluded that through longer-term assessment of findings, and further exploration, PET-CT and MRD negativity alignment could provide more insight into using both methods as predictors of patient outcomes.

QIP - Mass Spectrometry

GEM-CESAR is a clinical trial exploring treatment approaches for high-risk smouldering myeloma. These are patients who have "asymptomatic" myeloma but have a higher risk of progressing to active myeloma.

In the trial, 90 high-risk smouldering myeloma patients received six cycles of carfilzomib, lenalidomide and dexamethasone (KRd) followed by high-dose melphalan and an autologous stem-cell transplant and two further cycles of consolidation with KRd. All patients received maintenance with lenalidomide for up to two years. The primary end-point of the GEM-CESAR trial is bone-marrow MRD negativity, which is measured using a technique called "next generation flow cytometry" (NGF).

Another sensitive test developed to understand the level of myeloma in a patient is known as Quantitative Immunoprecipitation Mass Spectrometry (QIP-MS). In GEM-CESAR, researchers wanted to explore whether there is an alignment between MRD negativity in patients assessed by NGF and the measurement of QIP-MS in patients. They wanted to understand how specific the QIP-MS test is and whether it aligns/complements MRD negativity in terms of measuring very precise levels of disease.

The results of the trial found that disease monitoring through QIP-MS shows a moderate concordance with MRD assessment in this group of patients. There were a number of cases that did not align, which will be followed up by researchers in the longer term.

Explaining the implications of the findings for patients, Prof Faith Davies from NYU Langone Health commented: *"A highlight of ASH is a presentation on a new blood test called Mass Spectrometry to look at the level of a patient's myeloma. This test seems more sensitive than*

the regular blood test that we currently do, the measure of the M component of the paraprotein, but also may be more sensitive than the bone marrow test we do. At the moment for the bone marrow test we do a test called flow cytometry and we can measure one myeloma cell in a hundred thousand normal cells and this new test looks like it may be more sensitive. This is important because it may mean that in some patients we don't need to do the bone marrow."

Real-world evidence

A very important topic in the myeloma field is real-world evidence. As well as understanding how treatments work in a very controlled clinical trial setting, it is also important to understand whether they work that way in the real world. In clinical trials, patients are often selected according to something called "eligibility criteria", which can be very strict and can prevent patients from participating if they have concurrent conditions, have experienced specific complications and side-effects or are frail. The reason for this is so researchers can understand the safety and effectiveness of the treatment in a controlled way.

In the real world, however, patients are likely to be different to those selected in clinical trials. They may be older, frailer and have more concurrent conditions. Real-world data can therefore help us understand whether treatments work in all patients, the same way they do in those patients who are selected for clinical trials.

Observational study - INSIGHT-MM

One of the biggest ongoing global studies in the real world, known in this case as an "observational study", is INSIGHT-MM. Run by the pharmaceutical company Takeda, it is observing real-world patients who have newly diagnosed and relapsed and/or refractory myeloma.

Data was presented from the INSIGHT-MM study at ASH 2019. In this data, researchers analysed whether patients being observed in the INSIGHT-MM trial would meet the eligibility criteria to participate in clinical trials.

Within INSIGHT-MM, patient demographics and disease characteristics are collected using electronic case report forms. For the analysis presented at ASH, researchers assessed this patient data against 20 standard eligibility criteria used in clinical trials. In total, 3,201 patients (1,761 newly diagnosed and 1,400 relapsed patients) were analysed.

Results from the analysis showed that 39.2% of the patients would have been ineligible to participate in a clinical trial (38.8% of newly diagnosed patients and 39.7% of relapsed patients). A prior diagnosis of cancer, heart problems and low platelet (blood cells which form clots and stop bleeding) counts were issues commonly found to prevent patients participating in a clinical trial. The results also showed that frail patients, categorised by IMWG frailty index, were more likely to be ineligible for trial participation. Frail patients are therefore likely to be

under-represented in clinical trials.

These new findings from INSIGHT-MM emphasise the discrepancy between real-world populations and clinical trial populations. They support the need for real-world evidence to evaluate the effectiveness of treatment options and to further explore whether there is a need for clinical trials with wider eligibility criteria, where appropriate.

AL amyloidosis updates

Ixazomib - Tourmaline AL-1 clincial trial
During ASH 2019, there was a limited amount of data presented on AL amyloidosis. The main clinical trial data was presented from Takeda on their Phase III Tourmaline AL-1 clinical trial. This clinical trial was assessing the safety and efficacy of the oral proteasome inhibitor ixazomib (Ninlaro®) in combination with dexamethasone compared to physician's choice of the following: dexamethasone plus melphalan; dexamethasone plus cyclophosphamide; dexamethasone plus thalidomide; dexamethasone plus lenalidomide; or dexamethasone alone. In total, 168 patients participated in the clinical trial.

Earlier on in 2019, Takeda reported that the AL-1 trial was being discontinued as it had failed to meet two primary end-points of haematologic response. Haematologic responses were seen in 53% versus 51% of patients receiving ixazomib plus dexamethasone versus physician's choice. Complete response (CR) rate was 26% in the ixazomib plus dexamethasone arm versus 18% in the physician's choice arm. This means they were very similar for both arms.

Haematologic response in AL amyloidosis refers to a reduction in light chains, in the plasma cells in bone marrow and in serum monoclonal protein levels.

Dr Moshe Gatt, Hadessah Medical Center, Jerusalem – a myeloma and AL amyloidosis expert – commented: *"We know that light chains themselves are toxic to the organs. Meaning when the response isn't good enough the light chains don't go as low as we'd like and this becomes toxic to the organs. Our goal in treatment is to lower the light chains as much as possible. If we don't do that it means we do not achieve a haematologic response and this is correlated to worse outcomes."*

Whilst the ixazomib arm failed to show a significant improvement in response, compared to the physician's choice, the depth of response was better for the ixazomib arm in terms of progression free survival and vital organ progression free survival. The haematologic progression free survival was 20.1 months in the ixazomib arm and 16.7 months in the physician's choice arm. Vital organ progression free survival was 18.0 months in the ixazomib plus dexamethasone arm and 11.0 months in the physician's choice arm.

Other data showed that in patients' time to treatment failure was 10.1 months in the ixazomib plus dexamethasone arm and 5.2 months in the physician's choice arm. Time to subsequent therapy was 26.5 months in the ixazomib plus dexamethasone arm and 12.5 months in the physician's choice arm.

Common any grade side-effects in both the ixazomib plus and physician's choice arms included fatigue (45% and 43%), peripheral edema (46% and 32%), diarrhea (34% and 30%), insomnia

(38% and 17%), rash (33% and 20%), constipation (21% and 26%), dyspnea (24% and 19%), upper respiratory tract infection (24% versus 16%), nausea (24% versus 14%) and peripheral neuropathy (19% versus 15%). Discontinuation of treatment due to side-effects was 26% in the NINLARO plus dexamethasone arm compared to 20% in the physician's choice arm.

On the topic of whether ixazomib is likely to become a standard of care in AL amyloidosis, on the basis of this data, Dr Gatt commented: *"The trial was designed six or seven years ago. Six or seven years ago we had not too many options. As more options come to the myeloma field, more options come to the AL amyloidosis field. In a way, ixazomib will become a very good treatment to use in AL amyloidosis but nowadays we also have other medications like daratumumab and other novel agents. So we might use these and new combinations of drugs for patients because of the good results we get from it."*

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