The American Society of Clinical Oncology (ASCO) and European Hematology Association (EHA) Annual Congresses conference report
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The American Society of Clinical Oncology Annual Meeting (ASCO2020) is the largest and one of the most important congresses for the oncology community. Many myeloma and AL amyloidosis updates were presented at this congress which was held from 29 to 31 May 2020. Two weeks later, the 25th edition of the European Hematology Association’s annual congress (EHA25 Virtual), one of the most important haematology congresses here in Europe, was held from 11 June to 21 June 2020.

Due to the COVID-19 outbreak, for the first time, both congresses were held virtually and included poster, oral presentations, and live sessions with relevant experts.

Myeloma Patients Europe (MPE) attended both ASCO2020 and EHA25 Virtual and interviewed relevant myeloma and AL amyloidosis specialists to provide an overview of the key highlights in both diseases presented during these meetings.
**CAR T TREATMENTS TARGETING BCMA**

Dr Maria Victoria Mateos, Director of the Myeloma Unit at the University Hospital of Salamanca-IBSAL in Spain, commented on the trials of CAR T cells presented at EHA 25: the pivotal KarMMA trial, the EVOLVE trial, and the CARTITUDE trial.

“These trials were conducted in patients with myeloma after at least 5 or 6 previous lines of therapy and a significant proportion of patients presenting with extramedullary disease and high tumour burden. Definitely, the overall response rate, the complete response rate, and the minimal residual disease negativity rate have been impressive from my point of view for all of them if we consider that the population included in these studies started at an overall response rate of 30% with conventional agents. In these studies, the overall response rate was over 80% with all of them, with a complete response rate from 30% up to 45%. These results are impressive. The only problem is the duration of response after CAR T therapy, which is not very long, and more scientific research is needed to extend the durability of the response. From a safety perspective, the side-effects of CAR T therapy were manageable with cytokine release syndrome occurring in almost all patients, as well as neurotoxicity in some patients, and haematological toxicity.”

**Idecabtagene vicleucel: the KarMMA trial 1-3**

Results of the largest trial ever conducted studying CAR T treatment for myeloma, the KarMMA trial, were presented at EHA25. Patients who took part in the KarMMA trial had relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment). On average, they had received 6 prior lines of treatment, including immunomodulatory drugs (IMiDs, such as lenalidomide and pomalidomide), proteasome inhibitors (such as bortezomib), and anti-CD38 antibodies (such as daratumumab).

The KarMMA trial assessed a new experimental CAR T treatment called idecabtagene vicleucel, also known as ide-cel or bb2121. Ide-cel recognizes a protein commonly found on the surface of myeloma cells, called B-cell maturation antigen (BCMA), so that the body’s immune system can attack the myeloma cell. In total, 128 patients were given ide-cel and followed up for 11 months on average. Three doses of ide-cel were tested: 150 million CAR T cells, 300 million CAR T cells, and 450 million CAR T cells.

Fifty-four patients received the highest dose, 450 million CAR T cells. The overall response rate was 82%, meaning that a small amount or no myeloma cells were found in 44 patients. Nineteen patients had a complete response, meaning that no myeloma cells could be found in their blood, bone marrow, or urine. In the patients receiving the highest dose, the myeloma did not progress for 11 months on average.

With lower doses of ide-cel, at least half of all patients had a complete or partial response.

Describing the results, Dr Hermann Einsele, Director of the Department of Internal Medicine II at the Würzburg University Hospital in Germany, said, “If we consider these extremely heavily pre-treated patients, and the options we have, this is an exceptional treatment and outcome.”
Most patients were able to tolerate the treatment well. The following side-effects occurred:

- Most patients who received the highest dose had cytokine-release syndrome (CRS). For most patients, CRS was not severe. However, CRS was severe in 5% of patients.
- In the highest dose group, 1 in 5 patients developed neurotoxicity, a side effect seen in patients who are treated with CAR T. These symptoms are confusion, headache, and delirium, but this was usually not severe.
- Most patients experienced some reduction in blood cells, which may increase their risk for infections or bleeding.
- CRS and neurotoxicity were less common with lower doses of CAR T treatment.

Dr Einsele said of ide-cel, “It is a fairly safe treatment. It requires 14 days of treatment in the hospital, and it is very effective in patients with very fast developing myeloma.”

It is important to remember that this was a small trial. A larger confirmatory trial (known as a ‘Phase 3’ trial) is underway to compare the effectiveness and side-effects of ide-cel with standard treatment.

JNJ-4528: the CARTITUDE-1 trial

At ASH 2019, early results of the CARTITUDE-1 trial studying JNJ-4528 were presented and showed promising response rates. Patients have now been followed up for an average of 9 months (ranging from 3 to 17 months) and follow-up results were presented at ASCO 2020.

In the CARTITUDE-1 trial, the side-effects and dosing of JNJ-4528 were assessed. JNJ-4528 is a new experimental CAR T treatment for myeloma in which 2 proteins are added to T cells to recognise an antigen protein. This antigen protein can be found on the surface of myeloma cells and is called B-cell maturation antigen. This allows the body’s immune system to find and attack the myeloma cells.

Patients in the CARTITUDE-1 trial received a single infusion of JNJ-4528 of about 730,000 CAR T cells per kg of body weight. All 29 patients had received at least 3 different treatments before the trial, with most patients having received 5 or more treatments. Patients in the CARTITUDE-1 study were relapsed/refractory myeloma patients whose disease was not responding to immunomodulatory drugs (IMiDs, such as lenalidomide and pomalidomide) or proteasome inhibitors (such as bortezomib and carfilzomib) and they had all received anti-CD38 antibodies (such as daratumumab).

All patients completely or partly responded to JNJ-4528:

- In 22 patients (76%), sensitive tests found no myeloma proteins or cells in patients’ blood, urine, or bone marrow, which is called a ‘complete response’.
- The other 7 patients had a ‘partial response’, meaning that their levels of myeloma were lower but had not gone away completely.
- Sixteen patients had their bone marrow sample checked for low
levels of myeloma (known as ‘minimal residual disease’). In all 16, fewer than 1 in every million bone marrow cells was a myeloma cell, meaning they had a deep and significant response to treatment.

In most patients (93%), the myeloma had not progressed after 6 months. So far, 1 patient has experienced 15 months without progression of the myeloma.

The following side-effects occurred:

- Most patients (93%) experienced cytokine-release syndrome (CRS). In most patients, CRS was not severe. However, 1 patient had severe CRS, and 1 died of CRS.

- It was common for patients to have lower levels of white blood cells (neutrophils and leukocytes) and blood platelets, which can increase the risk of infections or bleeding.

- 14% of patients had neurotoxicity which is confusion, delirium, or headache; but this was usually not severe.

The researchers concluded that responses to JNJ-4528 were early, deep, and durable. Side-effects like CRS were manageable in most patients. It is important to remember that this was a small trial. A larger trial (known as a ‘Phase 3 trial’) is needed to confirm the findings.

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Orvacabtagene autoleucel: the EVOLVE trial

EVOLVE is a study assessing the side-effects and dosing of orvacabtagene autoleucel (orva-cel), a CAR T treatment for myeloma. These CAR T cells recognize a protein called BCMA which is commonly found on the surface of myeloma cells. In the EVOLVE trial, increasingly higher doses of orva-cel are being tested in patients with relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment).

Early results of the EVOLVE trial for the first 8 patients in the study who had received 50 million or 150 million CAR T cells, presented in previous scientific meetings, showed that the side-effects of orva-cel were acceptable. The benefits of treatment appeared to outweigh the risks. The trial therefore continued with higher doses of orva-cel.

At ASCO 2020, the results for 51 patients receiving 300 million, 450 million, or 600 million CAR T cells were presented. All patients had received 3 or more prior treatments (6 treatments on average) including a proteasome inhibitor (such as bortezomib and carfilzomib), an immunomodulatory drug (IMiD, such as lenalidomide or pomalidomide), and anti-CD38 antibodies (such as daratumumab). Patients had now been followed up for between 1 and 9 months (6 months on average).

The effectiveness of the treatment was measured in 44 patients. The overall response rate was 91%,
meaning that fewer or no myeloma cells were found in 40 patients. Seventeen patients (39%) had a complete response, meaning that myeloma could not be detected in their blood, bone marrow, or urine. The remaining 23 patients had a partial response, meaning that their levels of myeloma were lower but had not gone away completely.

Following orva-cel treatment, 2 of 51 patients experienced side-effects that were so severe that the dose of orva-cel could not be further increased.

- One of these patients received 300 million CAR T cells and had a side-effect on their nerves that was severe for more than a week.

- Another patient who received 450 million CAR T cells experienced a life-threatening decrease in the number of white blood cells lasting more than 28 days.

Some patients developed cytokine-release syndrome (CRS), which was severe in 1 patient. In total, 2 patients experienced severe neurological problems, including the patient already mentioned before.

The researchers concluded that, at the doses tested, the side-effects of orva-cel were manageable. In patients with relapsed and/or refractory myeloma who had received many previous treatments, orva-cel had compelling effectiveness. It is important to remember that this was a small trial. A larger trial (known as a 'Phase 3 trial') is needed to confirm the findings.

ANTIBODIES AGAINST BCMA

Dr Maria Victoria Mateos, Director of the Myeloma Unit at the University Hospital of Salamanca-IBSAL in Spain, paid special attention to trials of antibodies against B-cell maturation antigen (BCMA), a protein on the surface of myeloma cells. This new type of anti-myeloma treatment was presented at EHA 25 Virtual. In this report, we highlight 2 trials of anti-BCMA antibodies that have different mechanisms: bispecific monoclonal antibodies (also called T-cell engagers) and conjugated monoclonal antibodies.

Dr Mateos also mentioned ongoing research about "tri-specific antibodies targeting not only BCMA but also CD38, and together they improve bringing the T lymphocytes to the tumour. So I definitely think the development plans for these BCMA-engagers is very exciting."

We asked Dr Mateos how she would choose between CAR T treatments, bispecific antibodies, and conjugated monoclonal antibodies, since all of these treatments target BCMA.

She responded that "disease-related factors as well as patient-related factors have to be considered in order to make the right choice. CAR T cells are very attractive, but of course patients need to wait approximately 6 to 7 weeks between the selection of the patient for CAR T and the moment when the patient finally received the CAR T, because the T lymphocytes have to be modified and this takes approximately 5 weeks. T-cell engagers or bispecific monoclonal antibodies and belantamab mafodotin are off-the-shelf drugs. This means that these drugs are going to be in the pharmaceutic hospital and maybe
some patients with a very aggressive relapse cannot wait for CAR T and it is possible to select the T-cell engagers or the conjugated monoclonal antibodies. But also travel, patient preferences, and hospital availability need to be considered.” She also expects that all patients with myeloma will receive treatments that target BCMA in the future.

### Bispecific antibodies: teclistamab

Dr Mateos explained how teclistamab works, since it has a different mechanism than the CAR T cell treatments that target BCMA. “Teclistamab is a bispecific monoclonal antibody targeted at BCMA but at the same time redirects the T lymphocytes to the tumour. This means that this bispecific antibody is going to induce cytotoxicity through the activation of the T lymphocytes.”

In this trial, teclistamab was tested in 66 patients with myeloma who did not respond to standard treatments or lost their response. Dr Mateos emphasized that “Patients had received an average of 6 prior treatments and 84% of patients had triple-refractory myeloma, meaning that their myeloma did not respond to proteasome inhibitors, immunomodulatory drugs (IMiDs), and anti-CD38 antibodies. A significant proportion of patients had extramedullary disease as well as high-risk cytogenetic abnormalities.” This means that the myeloma of these patients is difficult to treat.

The most common side-effects related to teclistamab were mild or moderate cytokine release syndrome (CRS), low levels of white and red blood cells, and infections. In 2 patients, teclistamab doses could not be increased due to severe side-effects (delirium in 1 patient and low blood platelet levels in the other patient).

Teclistamab was active at doses of 38.4 µg per kg and higher. At this dose, 20 out of 52 patients (38%) had a response to teclistamab. Seven out of nine patients (78%) had a response to the highest weekly treatment dose, with more than 50% of patients achieving a very good partial response. Dr Mateos also reported that a substantial proportion of these patients had been difficult to treat before this study, because their myeloma had been refractory to 3 or more treatments or because of high-risk genetic changes. Some patients achieved a complete response or even minimal residual disease (MRD) negativity, meaning they had a deep and significant response to treatment.

Few patients took part in this study and the follow-up duration has been short. Since teclistamab was generally tolerated well by patients and was effective in treating myeloma in this phase 1 study, larger trials will be performed.

### Conjugated monoclonal antibodies: belantamab mafodotin (belmaf): the DREAMM-6 trial

The DREAMM-6 trial looks at the side-effects of belantamab mafodotin (belmaf) in patients with myeloma that has not responded to treatment.
with an anti-CD38 antibody such as daratumumab (refractory myeloma). Belmaf is a conjugated monoclonal antibody consisting of 2 parts: an antibody that helps the immune system identify and attack myeloma cells that have BCMA (B-cell maturation antigen); and MMAF (monomethyl auristatin F) which disrupts the microtubules in myeloma cells so that they cannot divide anymore.

Dr Katja Weisel from the University Medical Centre Hamburg-Eppendorf in Germany explains that “this is the first trial of belmaf in combination with bortezomib and dexamethasone. This combination is especially promising since it provides deep responses in many patients with a late stage of myeloma.”

Bortezomib (Velcade®) 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 by the European Medicines Agency (EMA). The combination of bortezomib and dexamethasone is generally well tolerated by patients and had some positive effects against myeloma.

The 52 patients in the DREAMM-6 trial received belmaf with bortezomib and dexamethasone. They received belmaf in 1 of 4 ways: 2.5 mg per kg on day 1 only or split between day 1 and day 8; or 3.4 mg per kg on day 1 only or split between day 1 and day 8. Patients did not have intolerable side-effects with these doses.

The most common side-effects were low levels of blood platelets and eye problems (blurred vision, cornea problems, and dry eyes). Dr Weisel mentioned that belmaf has a unique safety profile, since most other medications against myeloma do not cause eye problems.

She also explained that each patient was affected differently by the side-effects. “Patients may not experience any problems even if their eye doctor can see side-effects. Other patients experience more severe symptoms. Belmaf can be paused or the dose can be lowered if the side-effects are too severe for the patient. However, patients usually handle it very well with eye drops and supportive care.”

**ANTIBODIES AGAINST CD38**

Treatment of relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment) has greatly improved. However, even in this population, patients will eventually have disease progression. Therefore, more effective treatments are needed. At ASCO 2020 and EHA 25 Virtual, the results of 2 studies about isatuximab were presented.

**Isatuximab with carfilzomib and dexamethasone**

Isatuximab (Sarclisa®, Isa) is a monoclonal antibody that helps the immune system to recognize CD38 antigens on myeloma cells so that the cancer cells can be killed by the immune system. Isa has got a positive review from the European Medicines Agency (EMA) and has been approved by the US FDA to be used
in combination with pomalidomide (Imnovid®) and dexamethasone to treat patients with relapsed and/or refractory myeloma. In the IKEMA study, Isa was tested with another combination: carfilzomib (Kyprolis®) and dexamethasone (Kd).

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.

At EHA 25 Virtual, the results from the IKEMA study were presented by Professor Philippe Moreau from the University Hospital Hôtel-Dieu in Nantes, France. All 302 patients received Kd twice a week. Of these patients, 179 also received Isa infusions (10 mg per kg) weekly for 4 weeks, then every 2 weeks.

The 2 treatment groups were similar in average age, disease stage, and genetic risk profile. Most patients had stage 1 (26%) or stage 2 (60%) disease. Overall, 77% had had 1 or 2 prior myeloma treatments, most often proteasome inhibitors (such as bortezomib or carfilzomib) and immunomodulatory drugs (IMiDs, such as lenalidomide or pomalidomide).

After an average follow-up period of 21 months, more patients did not have myeloma progression after taking Isa-Kd than patients who received Kd only. The benefit of adding Isa was seen in all subgroups. Most patients had a partial or complete response to Isa-Kd (87%) and to Kd only (83%). Responses were generally deeper in patients who received Isa-Kd. Since the trial is still ongoing, researchers do not yet know if patients generally live longer after taking Isa-Kd compared with Kd only.

In both groups, 3% of patients died during the trial. Most patients experienced severe side-effects related to treatment: 59% of patients taking Isa-Kd and 57% of patients on Kd only. The most common side-effects were infusion reactions, respiratory problems, heart failure, low blood platelet levels, and low white blood cell levels. Except for heart failure, these side-effects happened more often in patients who received Isa-Kd.

The researchers conclude that adding Isa to Kd led to deeper responses and fewer myeloma progressions. The side-effects of Isa-Kd were manageable with medical treatment. According to Dr Maria Victoria Mateos, Director of the Myeloma Unit at the University Hospital of Salamanca-IBSAL in Spain, “this means that Isa-Kd will maybe become a new standard of care for patients with relapsed and/or refractory myeloma.”

Isatuximab: the GMMG-CONCEPT trial

Patients with high-risk myeloma have specific genetic changes that result in a worse prognosis. The current standard treatment for these patients is high-dose chemotherapy, autologous stem cell transplant, and consolidation. In earlier studies, isatuximab (Sarclisa®, Isa) led to significantly better responses and outcomes in patients with newly diagnosed myeloma and patients with insufficient responses to treatments. The GMMG-CONCEPT trial is testing Isa-KRd, which is Isa in combination...
with 3 other myeloma treatments: carfilzomib (Kyprolis®), lenalidomide (Revlimid®), and dexamethasone in patients with high risk disease.

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. Lenalidomide is licensed by the EMA for patients with myeloma who have had a stem cell transplant, have newly diagnosed myeloma, or have had at least 1 previous myeloma treatment.

At ASCO 2020, the first results of the GMMG-CONCEPT trial were presented by Dr Katja Weisel from the University Medical Center Hamburg-Eppendorf in Germany. A few weeks later, the results were also presented at EHA 25 Virtual. Up until now, 50 patients with newly diagnosed high-risk myeloma have taken part in the GMMG-CONCEPT trial, which is still ongoing and recruiting patients.


All patients had a response to Isa-KRd. Most patients had a complete response (46%) or a very good partial response (44%). The 4 patients who could not undergo transplant all had a very good partial response. More sensitive tests (called minimal residual disease or MRD testing) showed that no traces of myeloma could be found in the bone marrow samples of 20 out of 30 patients (67%) with a very good partial response or a complete response. This is an important finding, since patients with MRD-negativity are thought to have better outcomes, such as lower risks of disease progression and improved survival.

The most common side-effects during the GMMG-CONCEPT trial were low white blood cell levels, low blood platelet levels, high blood pressure, and infections. Also, 16% of patients had nerve damage (peripheral neuropathy). No patients died during the study.

According to Dr Weisel, this is the first time that a trial has focused on patients with newly diagnosed high-risk myeloma, as well as the first time that this combination of 4 medicines (Isa-KRd) has been tested in patients with myeloma. Dr Maria Victoria Mateos, Director of the Myeloma Unit at the University Hospital of Salamanca-IBSAL in Spain, named the GMMG-CONCEPT trial as one of the main myeloma highlights presented at EHA 25 virtual. In her interview with us, she said: “Although the sample size is rather small right now, the results were quite promising and maybe this quadruple combination can potentially overcome the poor prognosis of the patients with high-risk cytogenetic abnormalities.”

When asked whether the cost of a quadruple combination would be a barrier to accessing this treatment, Dr Weisel responded: “We don’t know. Personally, I think that all the data now coming out on quadruple treatment are really showing that it should be the standard of care. We see that we can induce high rates of MRD-negativity and we know that we can translate MRD-
negativity into a better progression-free survival and what’s more, a better overall survival in our myeloma patients. I think we have the elements needed to establish this treatment as the standard of care and hopefully it also justifies the effort.”

SELECTIVE INHIBITORS OF NUCLEAR TRANSPORT

Recently, a new type of myeloma treatment has been studied: selective inhibitors of nuclear transport. These medicines work by blocking the transport of proteins that are involved in the growth of myeloma cells, which results in death of the cells. One of these treatments is selinexor, which has been studied in the phase 3 BOSTON study. The results of the BOSTON study were presented at ASCO 2020.

Selinexor: the BOSTON study

Selinexor (Xpovio®) is a new, once-weekly treatment for myeloma that is taken orally (by mouth). Selinexor has already been tested in combination with bortezomib (Velcade®) and dexamethasone.

Bortezomib is a proteasome inhibitor, which works by blocking the actions of cellular proteasomes, causing the build-up of proteins leading to myeloma cell death. It is an effective myeloma drug that is already approved by the European Medicines Agency (EMA). The combination of bortezomib and dexamethasone (Vd) is generally well tolerated by patients and has had some positive effects against myeloma.

Unfortunately, peripheral neuropathy, which is nerve damage that causes numbness, tingling, and pain mostly in the hands and feet, is a common side-effect of bortezomib. The combination of selinexor and Vd (SVd) is now being tested in the BOSTON study to see if the addition of selinexor will result in reduced rates of peripheral neuropathy and improvement in outcomes for patients when compared to Vd alone.

In the BOSTON study, 195 patients received SVd once a week. Their results were compared to those of 207 patients who received Vd twice weekly. All 402 patients had relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment). Their average age was 67 years (ranging between 38 and 90 years) and 57% were men.

The first results from the study showed that in patients taking SVd, the length of time before myeloma returns (progression-free survival) was significantly longer (average 14 months) than in patients taking Vd (9 months). Responses to treatment were seen in significantly more patients taking SVd (overall response rate: 75%) than with Vd (62%). Patients taking Vd survived an average of 25 months. Because patients taking SVd are surviving longer in this study, their average survival duration cannot yet be calculated.

Dr Maria Victoria Mateos, Director of the Myeloma Unit at the University Hospital of Salamanca-IBSAL in Spain, mentioned that “the better outcomes seen with SVd were sustainable, also
in patients who have high-risk genetic changes, who are older (above 65 years), or were treated with immunomodulatory drugs (IMiDs) as part of their induction treatment.”

The most common severe side-effects were low blood platelet levels (in 36% of patients taking SVd and 15% of patients taking Vd), fatigue (11% for SVd and 0.5% for Vd), and nausea (in 8% of patients taking SVd and no patients on Vd). Significantly fewer patients taking SVd (21%) had moderate or severe nerve damage than patients taking Vd (34%). As time progresses and doctors gain more experience with selinexor, the lead researcher of the BOSTON study, Prof Dr Meletios A. Dimopoulos of the National and Kapodistrian University of Athens School of Medicine in Greece, expects that they will find better ways of reducing its side-effects.

According to Prof Dr Dimopoulos, “there was a higher incidence of adverse events in the SVd arm; however, the occurrence of really severe adverse events that necessitated treatment discontinuation was low. This is why we have approximately the same rate of treatment discontinuation in both arms.”

The BOSTON study has thus shown that once-weekly selinexor with bortezomib and dexamethasone is better than twice-weekly bortezomib and dexamethasone, without selinexor, in terms of effect (i.e. longer time before myeloma returns, more patients having a response, and longer survival) and the risk of nerve damage.

Prof Dr Dimopoulos highlighted that “we know that there is less peripheral neuropathy associated with once-weekly bortezomib, and less frequent hospital visits, so this is associated with improved quality of life for patients.” In the near future, selinexor will be tested in combination with other anti-myeloma treatments to see which combinations work best.

**PROTEASOME INHIBITORS**

Proteasome inhibitors work by blocking the actions of proteasomes, leading to myeloma cell death. Many patients with myeloma already receive proteasome inhibitors, such as bortezomib (Velcade®) and carfilzomib (Kyprolis®). At ASCO 2020 and EHA 25 Virtual, researchers presented the results of a phase 3 trial for a new proteasome inhibitor: ixazomib.

Ixazomib: the TOURMALINE-MM4 trial 12,13

Not all patients with newly diagnosed myeloma can safely undergo stem cell transplant. For those who do not undergo transplant, long-term maintenance treatment after induction treatment can delay the progression of the myeloma. In the TOURMALINE-MM4 trial, ixazomib (Ninlaro®) was tested as a maintenance treatment after standard induction.

Ixazomib is a proteasome inhibitor that is taken orally (by mouth), making it more convenient for patients to take for maintenance treatment. Ixazomib is already approved by the European Medicines Agency (EMA) and the US
FDA for patients with relapsed and/or refractory myeloma (myeloma that is no longer responding to previous treatment). In the TOURMALINE-MM4 trial, researchers compared ixazomib against a placebo to determine if it is also effective and safe in patients who did respond to induction treatment.

In total, 706 patients with newly diagnosed myeloma took part in the TOURMALINE-MM4 trial. They all had a partial or complete response to 6–12 months of standard induction treatment with chemotherapy and immunotherapy. Ixazomib was given to 425 patients, and 281 patients received a placebo; both groups were treated for up to 2 years. The groups were very similar in characteristics such as age, disease stage, genetic risk profile, and induction treatment.

Patients who received ixazomib had better results than patients who received a placebo. Better results were seen regardless of age, disease stage, response to induction treatment, and having received a proteasome inhibitor before the trial.

The length of time before myeloma returns (progression-free survival) was longer for patients receiving ixazomib compared with placebo. The average time to progression of the myeloma was 18 months for ixazomib and 10 months for placebo.

Three patients taking ixazomib and 2 patients on placebo died during the trial. Since the trial is still ongoing, researchers do not know yet if patients who received ixazomib will generally live longer than patients who received a placebo.

Most patients in the TOURMALINE-MM4 trial had side-effects: 91% of patients on ixazomib and 82% of patients on placebo. The most common side-effects were nausea, vomiting, and diarrhoea. Few patients had another cancer during the trial: 5% of patients on ixazomib and 6% of patients on placebo. Serious side-effects occurred slightly more often in patients receiving ixazomib (22%) than in patients taking placebo (17%). Some patients stopped with the trial because of side-effects: 13% with ixazomib and 8% with placebo.

The researchers conclude that ixazomib is a good maintenance treatment option for patients with newly diagnosed myeloma who had a complete or partial response to standard induction treatment. It is the first oral maintenance treatment for these patients. These results were also recognised as one of the main myeloma highlights at EHA 25 Virtual, according to Dr Maria Victoria Mateos, Director of the Myeloma Unit at the University Hospital of Salamanca-IBSAL in Spain, who said that “from my personal point of view, I think that this is an excellent opportunity to extend the duration of response in this population through proteasome inhibition with ixazomib. Also, this drug opens the door to be combined with monoclonal antibodies or immunomodulatory drugs (IMiDs).”

Ixazomib is expensive and needs to be taken for a long time (2 years). Dr Katja Weisel from the University Medical Center Hamburg-Eppendorf in Germany said that she does not know if ixazomib will become available to patients in Europe. “In transplant-eligible patients, it seems to be less effective than lenalidomide maintenance. However, not all patients tolerate lenalidomide and there are countries where lenalidomide is not available. Ixazomib could be a good alternative for these patients.” She explained that it is up to the EMA and national authorities to decide whether ixazomib will become available.
**CELMOD AGENTS**

An interesting new group of medicines called CELMoD medicines is being tested in patients with myeloma and was presented at ASCO 2020 as well as EHA 25 virtual.

**CC-92480**

CELMoD medicines such as CC-92480 lead to the destruction of Ikaros and Aiolos, proteins that help myeloma cells survive. In cell tests, CC-92480 killed myeloma cells that did not respond to lenalidomide (Revlimid®) and pomalidomide (Imnovid®) and prevented the myeloma cells from growing, which led researchers to test it in patients with myeloma for the first time.

Lenalidomide and pomalidomide are immunomodulatory drugs (IMiDs), which work by directly killing or stopping the growth of myeloma cells. Lenalidomide is licensed by the European Medicines Agency (EMA) for patients with myeloma who have had a stem cell transplant, have newly diagnosed myeloma, or have had at least 1 previous myeloma treatment. Pomalidomide is licensed by the EMA and is available in many European countries for the treatment of patients with relapsed myeloma.

CC-92480 was tested in 66 patients with myeloma that did not respond to current treatments or had progression of myeloma within 2 months of their last treatment (relapsed and/or refractory myeloma). The researchers tested different doses of CC-92480 together with dexamethasone to see if patients developed side-effects and whether the side-effects were tolerable.

Patients in the trial had received an average of 6 previous treatments for myeloma, such as stem cell transplant, proteasome inhibitors (such as bortezomib or carfilzomib), immunomodulatory drugs (IMiDs, such as lenalidomide or pomalidomide), and anti-CD38 antibodies such as daratumumab.

The maximum dose of CC-92480 that was tolerated by patients was 1.0 mg taken once per day on 10 out of 14 days or on 21 out of 28 days. Different doses led to intolerable side-effects in 10 patients, mostly low white blood cell levels. Most patients (88%) had severe side-effects, including low white and red blood cell levels, low blood platelet levels, infections, and fatigue.

Overall, 14 out of 66 patients (21%) had a response to CC-92480. In the groups that received 1.0 mg CC-92480 per day, 10 of 21 patients (48%) had a partial or very good partial response. Additional tests showed good responses to CC-92480 in blood and bone marrow of patients who did not respond to lenalidomide or pomalidomide before the trial.

CC-92480 will now be tested in trials with more patients and in combination with other treatments.

**AL AMYLOIDOSIS**

**Daratumumab: the ANDROMEDA study**

As of June 2020, there are no approved treatments for amyloid light chain (AL) amyloidosis. The plasma cells that make the amyloid depositions have
CD38. Daratumumab (Darzalex®) is an antibody against CD38 that is used to treat myeloma and is now being studied in the treatment for AL amyloidosis.

In the ANDROMEDA trial, researchers compared the current standard treatment CyBorD (cyclophosphamide, bortezomib, and dexamethasone) to CyBorD plus daratumumab in patients with newly diagnosed AL amyloidosis in 1 or more organs. All 388 patients received 6 cycles of CyBorD. Of these patients, 195 also received daratumumab (once per week in cycles 1 and 2, every 2 weeks in cycles 3 through 6, and every 4 weeks thereafter for up to 24 cycles). Each treatment cycle lasted 4 weeks.

Patients in the 2 groups were similar. The average age was 64 years. Most patients (65%) had AL amyloidosis in 2 or more organs, most often in the heart (71%) and kidneys (59%) and according to Dr Moshe Gatt of the Hadassah Hebrew University Medical Center in Jerusalem, Israel, “this makes them a more difficult patient group to treat.”

On average, the treatment duration was 10 months for daratumumab plus CyBorD and 5 months for CyBorD only. Nineteen patients treated with daratumumab plus CyBorD and 79 patients on CyBorD needed more treatment. Of the patients treated with CyBorD only, 48 received daratumumab afterwards.

After an average follow-up time of 11 months, responses were better in patients on CyBorD plus daratumumab. The complete response rate was 53% for daratumumab plus CyBorD and 18% for CyBorD only. Dr Gatt explains that complete responses are so important because patients with a higher complete response rate generally maintain good organ function and live longer.

Also, 79% of patients on daratumumab plus CyBorD had a very good partial response or even a complete response, compared with 49% for CyBorD only. These patients also achieved their response faster: on average 17 days for daratumumab plus CyBorD and 25 days for CyBorD. Responses in blood, heart, and kidneys also happened more often in the patients who had received daratumumab plus CyBorD.

The risk of amyloidosis progression in important organs was almost twice as low in patients on daratumumab plus CyBorD compared to CyBorD only.

A total of 56 patients died during the ANDROMEDA trial: 27 on daratumumab plus CyBorD and 29 on CyBorD only. The most common severe side-effects were low white blood cell levels, pneumonia, diarrhoea, heart failure, fainting, and swelling of the feet (known as peripheral oedema). Fourteen patients (7%) treated with daratumumab plus CyBorD had some infusion-related reactions, generally during the first infusion.

Dr Gatt highlighted the encouraging results of the ANDROMEDA trial, emphasising that adding daratumumab to CyBorD led to deeper and faster responses and maintaining the function of important organs. This combination treatment improved patient outcomes, with acceptable side-effects. During his interview with Myeloma Patients Europe, Dr Gatt said that daratumumab plus CyBorD has also been tested in patients who did not respond well to their first, second, or even third AL amyloidosis treatment, with very impressive results.
Adverse event: a side-effect of treatment

Antibody: a protein that sticks to a specific protein on a myeloma cell (an antigen)

Anti-CD38 antibodies: myeloma treatment that recognizes CD38, a protein that is mostly present on the surface of myeloma cells. The immune cells are then sent to kill the myeloma cells in different ways. An example of an anti-CD38 antibody used for myeloma treatment is daratumumab (Darzalex®)

B-cell maturation antigen (BCMA): a protein on the surface of myeloma cells that is used as a target for myeloma treatments, such as CAR T treatment and other immunotherapies

Bispecific monoclonal antibodies (T-cell engagers): myeloma treatment that targets the myeloma cells in 2 ways: by recognising a protein on the myeloma cell and by directly attracting immune cells (T cells) to the myeloma cell

Bortezomib (Velcade®): a proteasome inhibitor, which works by blocking the actions of proteasomes. Proteasomes are proteins in cells that break down damaged proteins; by blocking the proteasomes in the myeloma cells, it causes the build-up of toxic levels of proteins in the myeloma cell, causing it to die. Bortezomib is an effective myeloma drug that is already approved by the European Medicines Agency (EMA)

Carfilzomib (Kyprolis®): Carfilzomib is a proteasome inhibitor, which works by blocking the actions of proteasomes. Proteasomes are proteins in cells that break down damaged proteins; blocking the proteasomes in the myeloma cells causes the cells to die. Carfilzomib is an effective myeloma drug that is already approved in combination with dexamethasone by the European Medicines Agency (EMA) and is available in some European countries

CAR T treatment (chimeric-antigen receptor T-cell therapy): a new experimental myeloma treatment. For this treatment, healthy white blood cells (known as T cells) are collected from a patient and a special protein is added to them that helps them to identify myeloma cells. The cells are then put back into the patient’s body, where they find and destroy myeloma cells.

CELMoD: myeloma treatment that works by destroying proteins that help myeloma cells survive

Complete response (CR): no myeloma proteins or cells in patients’ blood, urine, or bone marrow after treatment

Conjugated monoclonal antibodies: antibodies that are attached to other treatments, such as chemotherapy or radiation therapy
Cytokine release syndrome (CRS): an inflammation reaction to myeloma treatment that causes flu-like symptoms such as fever, body aches, and fatigue, and in severe cases can be life-threatening. CRS is a common side-effect of CAR T treatment

Daratumumab (Darzalex®): an antibody against CD38 that is used to treat myeloma and AL amyloidosis

European Medicines Agency (EMA): the European medicines licensing body

Extramedullary disease: myeloma outside of the bone marrow

Food and Drug Authority (FDA): the US medicines licensing body

Haematological toxicity: lower numbers of blood cells (red blood cells, white blood cells, and/or blood platelets) caused by myeloma treatment

High-risk cytogenetic abnormalities: genetic changes in the DNA of the myeloma cell that increase the risk of relapsed and refractory myeloma and shorter survival

Immunomodulatory drugs (IMiDs): myeloma treatment that works by directly killing or stopping the growth of myeloma cells. Examples of IMiDs are lenalidomide (Revlimid®) and pomalidomide (Imnovid®)

Lenalidomide (Revlimid®): an immunomodulatory drug (IMiD). Lenalidomide is licensed by the European Medicines Agency (EMA) for patients with myeloma who have had a stem cell transplant, have newly diagnosed myeloma, or have had at least 1 previous myeloma treatment.

Minimal residual disease (MRD): very low number of myeloma cells in the bone marrow, usually less than 1 myeloma cell in every million bone marrow cells. This can be tested with extra sensitive tests. If no MRD is found (MRD-negativity), the risks of disease progression and early death are lower

Neurotoxicity: nerve damage caused by myeloma treatment

Overall response rate (ORR): the percentage of patients whose myeloma is completely or partially gone after treatment. The ORR is calculated by adding up the number of patients with a complete response, a partial response, or a very good partial response divided by the total number of patients

Partial response (PR): treatment response with a 50% DECREASE in myeloma proteins or cells in patients’ blood, urine, or bone marrow

Pomalidomide (Imnovid®): an immunomodulatory drug (IMiD). Pomalidomide is licensed by the European Medicines Agency (EMA) and is available in many European countries for the treatment of patients with relapsed myeloma

Progression-free survival (PFS): time before the myeloma returns after treatment
Proteasome inhibitors: myeloma treatment that works by blocking the actions of proteasomes. Proteasomes are proteins in cells that break down damaged proteins; blocking the proteasomes in the myeloma cells causes them to die. Examples of proteasome inhibitors are bortezomib (Velcade®) and carfilzomib (Kyprolis®)

Relapsed myeloma: myeloma that is no longer responding to previous treatment

Refractory myeloma: myeloma that is not responding to treatment

Selective inhibitors of nuclear transport: myeloma treatment that works by blocking the transport of proteins that are involved in the growth of myeloma cells, which results in death of the cells. An example of these treatments is selinexor (Xpovio®)

Trial: a study in which medicines are tested in people. In a phase 1 trial, a treatment is tested in a small group of healthy volunteers or patients for safety; multiple doses are tested. In a phase 2 trial, a treatment is tested in a slightly larger group of patients to find out if it works and what the side-effects are. In a phase 3 trial, the treatment is tested in a large group of patients to determine if it works and if it is safe. In most phase 3 trials, the treatment is compared with another treatment or a fake treatment (placebo) to see if it is better

Tumour burden: how much myeloma protein and/or myeloma cells a patient has in their body

Very good partial response (VGPR): treatment response with a 90% DECREASE in myeloma proteins or cells in patients' blood, urine, or bone marrow (VGPR is a better outcome when compared to partial response)
REFERENCES

Conference abstracts


Video interviews


MPE is a network of European myeloma patient organisations. It supports national patient organisations to improve treatment and access for patients in their countries and helps inform and raise awareness on a European level through its educational programmes. Please note, this information does not replace the information provided by your doctor. If there is anything that is not clear to you, please always ask your clinical team.

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