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CONFERENCE REPORT

The American Society of Hematology (ASH) Annual Congress 2020 conference report

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The American Society of Hematology (ASH) Annual Meeting took place virtually in 2020, between the 5th and the 8th of December. The ASH Annual Meeting is the largest haematology conference in the world, and despite its unusual format this year, it has brought together an impressive number of researchers, clinicians and patient advocates working in the field of haematological malignancies.

Myeloma Patients Europe (MPE) attended the virtual ASH 2020 meeting. This report provides an overview of the key highlights from the conference, selected by the MPE team. Information about further sessions can be found on the ASH website (https://www.hematology.org/meetings/annual-meeting/schedule-and-program).

A glossary section with relevant scientific terms can be found at the end of the report.

MYELOMA UPDATES

Immunotherapy highlights

Immunotherapy drugs utilise the cells of the body's immune system to fight diseases such as cancer. The use of immunotherapy drugs is now widespread in the treatment of cancers and related conditions (including myeloma and AL amyloidosis). Types of immunotherapy used for the treatment of cancer 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. Examples of immunotherapy drugs that have been approved by the European Medicines Agency (EMA) for the treatment of myeloma are daratumumab, isatuximab, lenalidomide and bortezomib.

Over recent years, several other types of immunotherapies have emerged and many of these show very promising results in the treatment of myeloma. In an interview on the highlights from ASH 2020, Dr. Pieter Sonneveld, president of the European Myeloma Network (EMN), remarked "We are at the brink of entering a new era in immune therapies for multiple myeloma".

Bispecific antibodies, CAR-T therapy and antibody-drug conjugates are examples of such therapeutic approaches. Examples of these three classes of therapy were discussed during the ASH 2020 conference.

T-cell engaging bispecific antibodies

Antibodies are molecules made by the body that can bind to specific proteins on the surface of cancer cells, thus tagging them for destruction by the immune system. T-cell engaging bispecific antibodies are designed to recognise and bind to two targets at the same time: one target is a T-cell (patient's immune cell) while the other target is the myeloma cancer cells. Once this binding occurs, the T-cells are activated, and the immune system is then recruited to kill the myeloma cancer cells. By killing the myeloma cells, the patient's immune system is also activated to search for further myeloma cells and destroy them. Several presentations and updates relating to the various T-cell engaging bispecific antibodies which are currently being investigated for the treatment of myeloma were provided at the ASH Annual Meeting, and summaries of these are presented below:

Talquetamab

Talquetamab (JNJ-64407564) is a T-cell engaging bispecific antibody that binds to the activating receptor CD3 on T-cells and to GPRC5D, which is commonly present on the surface of myeloma cells. This antibody is being investigated in an ongoing phase 1 dose finding study (NCT03399799). So far, 157 myeloma patients have been enrolled in this study. All patients were refractory to or could not tolerate traditional therapies: 82% of them were triple class refractory and 33% were penta drug refractory (median prior lines of therapy: 6). Talquetamab was administered either subcutaneously (sc) or intravenously (iv). Both formulations were evaluated with step-up dosing and were administered weekly or every 2 weeks with iv doses ranging from 0.5-3.38 micrograms/kg to 180 micrograms/kg and sc doses ranging from 5 micrograms/kg to 800micrograms/kg.

At the most active iv (20 - 180 µg/kg) and sc dose (135 - 800 µg/kg), the overall response rate was 67% and 66% respectively. Median time to response was 1 month. Median duration of response is not yet determinable as most patients were still in response at the time of data collection.

Most frequently reported haematologic adverse events were anaemia or low red blood cells (48%), neutropenia or low white blood cells (47%) and lymphopenia or low lymphocytes a type of immune cell (40%). Cytokine release syndrome (CRS) occurred in 54% of patients; only 3% of patients had grade 3 CRS. CRS is a common side-effect of some immunotherapies, which involves a systemic inflammatory response causing flu-like symptoms such as fever, body aches and fatigue, and, in severe cases, can be life-threatening. Notably, on sc dosing, all CRS events were grade 1-2. Dysgeusia (distortion of sense of taste or lack of taste) was reported in 38% of patients. Treatment-related neurotoxicity occurred in 6% of patients (all resolved/resolving). Infections occurred in 37% of patients. Other, less frequent adverse events were infusion related reactions and injection site reactions, fever and diarrhoea.

Based on the results obtained in this study so far, the researchers selected a recommended phase 2 dose of 405 µg/kg to be administered subcutaneously.

Cevostamab

Cevostamab is another T-cell engaging bispecific antibody currently being investigated in an ongoing phase 1 dose finding study (NCT03275103). Cevostamab binds CD3 on T-cells and to the FcRH5 molecule on myeloma cells. Fifty-three heavily pre-treated myeloma patients had been enrolled so far. Ninety-four per cent (94%) of them were refractory to last prior therapy, 72% were triple class refractory, 45% were penta drug refractory (Median prior lines: 6). Cevostamab was administered as an iv formulation, doses were administered every 3 weeks. A step-up dosing schedule was applied to decrease the likelihood of severe CRS events. At doses of 3.6/20mg or higher, the overall response rate was 53%; no response was observed in patients receiving a lower dose. Median time to first response was 29.5 days. Duration of response cannot be accurately determined at this stage, as several patients were still in response at the date cut-off.

Adverse events were most commonly haematologic with decreased platelet counts and anaemia being the most common. Over two thirds of patients (76%) experienced CRS with 1 patient experiencing grade 3 CRS. Other side-effects were diarrhoea, infection related reactions, electrolyte abnormalities, nausea, fatigue, elevated liver enzyme levels.

Teclistamab

An update on an ongoing phase 1 clinical trial (NCT03145181) investigating the safety and

effective dosing of Teclistamab (JNJ-64007957). This antibody directs T-cells to attack cells expressing B-cell maturation antigen (BCMA), a protein widely expressed on the surface of cancerous plasma cells in multiple myeloma.

As of data cut-off, doses between 0.3–720 µg/kg of Teclistamab were administered to 84 patients intravenously (iv) and 80–3000 µg/kg Teclistamab was received by 44 patients subcutaneously (sc). In the 47 patients treated with the two highest, most active dose levels of 270 µg/kg and 720 µg/kg weekly for iv and 720 µg/kg and 1500 µg/kg weekly for sc, the overall response rate was 63.8%.

The most common adverse events included anaemia (low red blood cell count), neutropenia (low neutrophil count, a type of immune cell), thrombocytopenia (low white blood cell count, a type of immune cell), and leukopenia (low leukocyte count, types of immune cells), fever, diarrhoea, cough, fatigue, nausea, back pain and headache. Approximately half of the patients (53%) experienced CRS. During this trial, CRS events were grade 1-2. Neurotoxicity was observed in 5% of patients (all iv) and 15% of patients experienced infection-related grade 3 or higher adverse events.

These results support progression to the planned phase 2 trial where Teclistamab will be administered sc at a dose of 1500 µg/kg, as well as the launch of future combination studies.

AMG 701

A phase 1, first in human study of AMG 701, an anti-B-Cell Maturation Antigen (BCMA) bispecific T-cell engager (BiTE) was discussed. Relapsed/refractory myeloma patients who received or were intolerant to at least 3 prior lines of therapy were administered weekly AMG 701 iv infusions in 4-week cycles until their disease progressed. As of July 2020, 75 patients had received AMG 701. An initial step dose (0.8 mg) was administered to prevent severe CRS.

The response rate was 36% at doses of 3-12 mg. Notably, the response rate was 83% in the cohort (5 patients) with earlier dose escalation. Four out of these 5 responders were refractory to 3 lines of treatment. Median response duration was 3.8 months, the maximum duration was 26 months, with ongoing response in 14 patients at the point of data collection.

The most common adverse events were anaemia, neutropenia, thrombocytopenia, CRS, diarrhoea, fatigue, and fever. CRS was mostly grade 1 or 2, 5 patients had severe CRS, which was reversible with corticosteroids and tocilizumab in all cases. Neurotoxicity was seen in 6 patients; this was also reversible with treatment. Four patients died due to adverse events (sepsis, bleeding in a part of the stomach called the retroperitoneum, hematoma).

REGN5458

REGN5458 is another anti-BCMA bispecific T-cell engager, currently being tested in a phase 1 study that aims to determine its safety, efficacy, tolerability and recommended dose. As of data cut-off, 49 patients had enrolled, with 15 of these patients still receiving treatment, and 2 patients having completed REGN5458 therapy. The treatment of 32 patients was discontinued due to disease progression (24 patients), adverse events (2 patients), patient/physician decision (3 patients) or death (3 patients). Patients were heavily pretreated, (a median of 5 prior lines of therapy). All patients were triple-refractory, 57% were penta-refractory and 61% were refractory to last line of therapy. Patients with non-secretory myeloma or who had plasmacytoma were also allowed to enrol in the trial.

REGN5458 was administered as an intravenous formulation, the dose was escalated from 3–96 mg over six dose levels, with initial weekly split dosing, followed by administration of a single dose every other week. The overall response rate at the lowest doses (dose level 1-3) was 29.2%, at the dose level 4-5, it was 41.2% and at the highest dose level (dose level 6), it was 62.5%.

The most frequent adverse events were haematological with anaemia being the most common (37%, any grade). CRS was a common non-haematological adverse event with 39% experiencing any grade; no patients experienced higher than grade 3 CRS. Neurotoxicity was observed in 12% of patients, with no events being higher than grade 3. Other side effects were fatigue, nausea, fever, back pain, pneumonia, and upper respiratory tract infections.

Notably, quality of life data was also collected. It showed meaningful improvement in global health status at week 4, which was maintained throughout weeks 8-24 (taken from EORTC QLQ-C30 questionnaire). Patients are currently being recruited for a phase 2 study of REGN5458.

TNB-383B

TNB-383B is a further BCMA targeting, bispecific T-cell engaging antibody. A phase 1 dose escalation and cohort expansion first-in-human study of TNB-383B (NCT03933735) is currently being carried out. The initial results of this study were shared during ASH2020. Relapsed/refractory myeloma patients who have been exposed to at least 3 prior lines of therapy can enrol in the study. As of July 2020, 38 patients have been treated with escalating doses of intravenous TNB-383B every 3 weeks. Patients only had to be hospitalised for the first dose. The overall response rate was 52% at doses 5.4 – 40 mg, responses lasted up to 24 weeks. Notably, the overall response rate at 40-60mg dosing was 80%. TNB-383B appears well tolerated at the investigated doses. Observed side effects were anaemia, neutropenia, thrombocytopenia, CRS, headache, fever, nausea/vomiting, chills, diarrhoea, headache.

CAR-T therapeutics

CAR-T therapy harnesses the ability of T-cells (patient's immune cells) to destroy cancer cells. This occurs after T-cells are collected from patients and then equipped with a protein molecule called a "chimeric antigen receptor" (CAR). The modified T cells are then infused back into the patient's body and are then able to recognize and destroy myeloma cancer cells. Several CAR-T therapy approaches in the treatment of relapsed/refractory myeloma patients were discussed at ASH this year, many of these are in early stages and involve only a few patients. A novel allogeneic CAR-T product was discussed. Its off-the-

shelf nature circumvents many of the hurdles of CAR-T therapy. In a webinar reviewing the highlights from ASH 2020, and talking particularly about the results from CAR-T clinical trials discussed during the conference, Dr Claudia Stege from VU University Medical Center in Amsterdam commented "We really need to follow up these patients for longer [...] however, the data is still very encouraging".

ALLO-715

The initial results of a first-in-human, ongoing phase 1 trial (NCT04093596) investigating the safety and tolerability of ALLO-715, an allogeneic, genetically modified CAR-T cell product, were presented. ALLO-715 targets the BCMA protein which is expressed on myeloma cells.

Allogeneic means genetically different but from the same species, this implies that the T-cells do not come from the patients themselves as they usually do in other CAR-T therapies.

At the time of the presentation, 35 heavily pre-treated relapsed / refractory myeloma patients who have received 3 or more prior lines of therapy (median prior lines of therapy: 5), including a proteasome inhibitor, immunomodulator, and anti-CD38 mAb had enrolled. Patients received lymphodepletion (a type of therapy given to patients prior to CAR-T cell infusion to prepare their bodies for accepting the manufactured CAR-T cells) followed by ALLO-715 at 4 dose levels (DL; 40, 160, 320, or 480 million CAR-T cells) to determine the most efficacious and safe dose for patients. An overall response rate of 60% was observed in the 10 patients receiving ALLO-715 at dose level 3 (DL3, 320 million CAR-T cells).

Six patients received treatment with low dose of ALLO-647 (an antibody with immune system suppressing capability) FCA as part of the study and 3 of these patients responded. Four patients received high dose ALLO-647 FCA and 3 of these patients had very good partial response or better. Overall, of the 6 patients treated with ALLO-647 FCA all showed a very good partial response or better and 5 were minimal residual disease (MRD) negative. The median time to response was 16 days.

The most common side effects experienced by patients were anaemia, neutropenia, lymphopenia, and thrombocytopenia. All grade infections occurred in 42% of patients. Grade 3 events occurred in 4 patients (13%), 3 of these resolved with treatment. The fourth infection occurred on day 8 after ALLO-715 treatment in a rapidly progressing, refractory myeloma patient, who subsequently died due to an infection related to neutropenia, which was a result of lymphodepletion. No neurotoxicity or graft versus host disease (GvHD, see glossary) occurred by the time of data cut-off. Cytokine release syndrome (CRS) was reported in 45% of patients, all these episodes resolved without additional medical interventions required.

Overall, the data suggests that the side effect profile of ALLO-715 is comparable to that of autologous CAR-T therapies. However, this trial is still in early stages and many questions remain that need further investigation. These include the stringent analysis of the presence of anti-CAR antibodies which may affect the duration of response for patients and may be a factor in relapse after receiving the drug, as well as any other signs of a host immune response to this type of CAR-T treatment. Furthermore, it should be investigated whether the persistence of CAR-T cells varies between this allogeneic product versus traditional autologous (a patient's T-cells are used for manufacturingCAR-T cell products currently under investigation. The trial is ongoing, at the time of writing the researchers are still enrolling patients in the cohorts where higher ALLO-715 (320 and 480 million CAR-T cells) doses are administered.

Quality-of-Life in Patients Treated With Idecabtagene Vicleucel

Idecabtagene Vicleucel is an autologous CAR-T construct being investigated in the Karmma Clinical Trials, for which an update on quality-of-life data was presented during the conference. Patients experienced a significant improvement in most functioning and symptom scores from baseline to month 3-15. When it came to social and emotional functioning and wellbeing, greater than 40% of patients reported a clinically meaningful improvement, ~25% experienced deterioration in these regards and about 35% had no change.

A significant improvement from baseline at month 2-15 was seen in the future perspectives of patients. Patients were asked to report on symptoms of nausea, vomiting, constipation, diarrhoea, difficulty breathing, appetite loss and financial difficulties throughout the study, and these were reported to have remained stable throughout the study.

Ciltacabtagene autoleucel

An update on CARTITUDE 1 (NCT03548207), a phase Ib/II study of Ciltacabtagene autoleucel (cilta-cel or JNJ-4528), BCMA-targeting CAR-T therapy was shared. As of the May 20, 2020 data cut-off, 97 patients had been treated. Promisingly, a high overall response rate of 96.9% was observed, with responses appearing around a month after treatment. Side effects reported in over two thirds of patients were CRS, neutropenia, anaemia, and thrombocytopenia. Cilta-cel-related neurotoxicity was reported in approximately 20% of patients. Fourteen deaths occurred during the study; 9 were due to adverse events, these were CRS, neurotoxicity, respiratory failure, sepsis and septic shock (overwhelming infection causing multisystem organ failure), pneumonia, lung abscess, and acute myelogenous leukaemia.

Antibody-Drug Conjugates

A monoclonal antibody drug conjugate consists of a laboratory engineered antibody carrying a chemotherapy drug, which works by binding to a protein commonly found on the surface of myeloma cells. Once the monoclonal antibody binds to the myeloma cell it is absorbed by the myeloma cell and the chemotherapy drug is released causing the cell to die. Dead cellular components are then released, which activate and trigger the immune system to kill more cancer cells.

MEDI2228

MEDI2228 is an antibody-drug conjugate comprised of an antibody, that binds to BCMA on cancer cells, attached to a chemotherapy agent known as pyrolbenzodiazepine (PBD).

The safety and efficacy of MEDI2228 were tested in a phase 1, first-in-human, open-label, dose-escalation and expansion trial (NCT03489525). Eighty-two patients with advanced, heavily pre-treated multiple myeloma (refractory to three classes of anti-myeloma drugs, including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies).

The maximum tolerated dose was 0.14mg/kg with a response rate of 65.9% at this dose. It took an average 2 months for patients to respond to therapy with that response lasting about 5.9 months. Side effects that occurred in ≥20% of patients in the cohort receiving the 0.14mg/kg dose were photophobia (sensitivity to light), thrombocytopenia, rash, elevated liver enzymes, dry eye, and pleural effusion (excess fluid accumulating in the pleural cavity, the fluid-filled space around the lungs).

It is important to note that the photophobia was an unexpected side effect, which remains poorly understood thus far as no actual changes were seen upon examination of the eyes by an ophthalmologist.

The researchers are investigating the reasons behind the photophobia and ways to prevent it as part of this ongoing clinical trial. These ocular side effects are not the same as in the case of belantamab mafodotin (see below). In the case of belantamab mafodotin where there are obvious changes caused by the drug's effect on cells of the surface of the eye.

Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone

Belantamab mafodotin (belamaf) is another BCMA targeting antibody-drug conjugate, which delivers the chemotherapy agent monomethyl auristatin F (MMAF).

A phase 1, dose finding study presented and is investigating the safety, efficacy and recommended phase 2 dose of belamaf in combination with pomalidomide and dexamethasone (B-Pd). This combination is being tested in relapsed or refractory myeloma patients who received more than 2 prior lines of treatment, including lenalidomide and a proteasome inhibitor and who were refractory to their last treatment line. At the time of data cut-off, 37 patients had enrolled.

The overall response rate reported in this trial was 88% across all cohorts. The median progression-free survival rate has not yet been established.

Most common adverse events detected in this research were keratopathy, which is changes to the cornea of the eye seen in examination by an ophthalmologist and may or may not cause symptoms (75.7%), neutropenia (56.8%), thrombocytopenia (48.6%), decreased visual acuity (45.9%), fatigue (40.5%), fever (35.1%), cataract (35.1%), constipation (32.4%), diarrhoea (29.7%), infusion-related reaction (29.7%). All dose-limiting toxicities were ocular.

Further relevant highlights

Patient's Preference for Making Informed Treatment Decisions Confidently: Results from a Large Multiple Myeloma Patient Survey across 12 Countries in Europe and Israel

Myeloma Patients Europe (MPE), in collaboration with the pharmaceutical company Amgen, carried out a survey in 2019-2020 for myeloma patients across 12 countries in Europe. The purpose of this survey was to better understand myeloma patient information needs and preferences with an emphasis on what type of information patients deem most relevant to make informed treatment decisions. The results of this survey were presented at ASH 2020.

"Patient involvement in treatment decisions or 'shared decision making' has been associated with increased patient satisfaction, increased compliance to advice from health professionals, enhanced treatment adherence and overall improved treatment outcomes.

For this reason, our objective with this survey was to better understand myeloma patient information needs and preferences and, especially, the types of information that are valued by patients to make informed treatment decisions", explains Ananda Plate, CEO of MPE.

Out of the patients who accessed the online survey, 1559 patients met the eligibility criteria and were included in the primary analysis, and 1081 patients completed the full survey. Time since diagnosis was 0-4 years for 53.1% of patients, and ≥16 years for 4.8% of patients. The majority of patients had received 1 line of therapy (40.1%), 20.5% had received 2 lines, 16.0% had received 3 lines and 19.9% had received ≥4 lines of treatment. Last treatment decision was taken <3 months before the survey for 26.1% of patients and >2 years ago for 25.5% of patients.

Of the 1112 patients who responded to the question about confidence in their most recent treatment decision, 54.4% reported being very confident, 37.2% reported being somewhat confident. Regarding the level of involvement in the treatment decision, 56.8%, reported feeling 'very involved' and 28.4% felt 'somewhat involved'.

Confidence in making an informed treatment decision did not seem to be affected by the number of prior lines of therapy, treating physician, treatment site, or carer involvement.

Patients commonly received information about treatment location (84.5%), method of treatment administration (83.0%), treatment frequency (77.7%) and common side effects (72.2%). Information was less commonly received on overall survival benefit (38.4%), how long until myeloma returns (30.9%) and healthcare provider costs (20.0%). Notably however, patients considered information relating to treatment effectiveness as the most important types of information, followed by information on treatment safety and tolerability. Receiving the types of information considered most important by patients was significantly associated with increased patient confidence in making informed treatment choices. This suggests that placing a

bigger emphasis on communicating treatment effectiveness with patients could increase their confidence in making an informed treatment decision.

Consolidation Treatment with VRD Followed By Maintenance Therapy Versus Maintenance Alone in Newly Diagnosed, Transplant-Eligible Myeloma Patients

A phase 3 trial developed by the European Myeloma Network (EMN) presented data that investigated the effectiveness of stem cell transplants and consolidation treatment in newly diagnosed myeloma patients. This trial is an independent clinical trial (not guided by pharmaceutical industry). The aim of consolidation treatment is to get rid of myeloma cells that might still be in the body and to stop them from coming back. Dr Pieter Sonneveld, president of the European Myeloma Network (EMN) commented: "The aim of this trial was to look at the role of high dose therapy compared with standard chemotherapy in newly diagnosed patients that were transplant eligible" he also added that: "The other part of the study concerned the role of consolidation therapy after the transplant."

In this trial, 1503 patients were first treated with bortezomib, cyclophosphamide, and dexamethasone for 3-4 cycles (induction treatment). Patients were then randomized to treatment with either bortezomib, melphalan, and prednisone for 4 cycles, or high dose melphalan (a chemotherapy drug) with autologous stem cell transplant. Patients were then randomized again to receive either consolidation treatment with bortezomib, lenalidomide, and dexamethasone for 2 cycles or no consolidation treatment. For this round of randomisation, 878 patients were eligible.

All patients then received maintenance treatment with lenalidomide until their disease worsened. The results of this study showed that patients who received consolidation for 2 cycles with bortezomib, lenalidomide, and dexamethasone were more likely to achieve complete response (59% of patients showing a sCR or CR in this group, and only 46% of patients having responses of this depth in the lenalidomide only group). Moreover, patients treated with bortezomib, lenalidomide, and dexamethasone lived for a longer period without their myeloma getting worse (progression free survival). Most common adverse events caused by VRD treatment were mainly neutropenia and thrombocytopenia, with 23% of patients experiencing grade 3 adverse events and 5% of patients experiencing grade 4 adverse events.

Selinexor in Combination with Pomalidomide and Dexamethasone (SPd)

Selinexor is a selective inhibitor of nuclear export (SINE), which blocks the XPO1 protein. By blocking the XPO1 protein there is a preservation of tumour suppressor proteins in the nucleus of cells causing activation of the tumour suppressors, which in turn causes death of myeloma cells.

Selinexor and Backbone Treatments of Multiple Myeloma Patients (STOMP) is an ongoing dose finding trial of selinexor in combination with pomalidomide and dexamethasone (SPd).

As of 14th of November 2020, 65 myeloma patients who received ≥2 prior therapies (median prior lines of therapies: 3) including lenalidomide and a proteasome inhibitor have been enrolled.

Sixty patients were evaluable for a response to SPd. Out of these patients, among the 46 who have not been exposed to pomalidomide before, the overall response rate was 54.3%, in the 14 patients who were pomalidomide refractory, it was 35.7%. In the 20 patients who received the recommended phase 2 dose of 60mg Selinexor administered once weekly with 4mg of pomalidomide, the overall response rate was 60%.

Treatment related adverse events included: neutropenia (60.3%); anaemia (54%); thrombocytopenia (54%); nausea (60.3%); fatigue (50.8%); decreased appetite (44.4%); weight loss (24%); diarrhoea (28-6%); vomiting (20.6%).

Iberdomide (IBER; CC-220) in Combination with Dexamethasone and Daratumumab or Bortezomib

Iberdomide is an oral cereblon E3 ligase modulator (CELMoD) agent. CELMoD agents are a new class of drugs being investigated to treat myeloma. They work by making changes to the protein cereblon (CRBN) which results in the breakdown of Ikaros and Aiolos (transcription factors required for the growth of myeloma cells), therefore leading to the death of myeloma cancer cells. Iberdomide also stimulates immune T cells and natural killer (NK) cells to kill myeloma cancer cells. A phase 1/2 dose finding study of Iberdomide in combination with other therapeutics (NCT02773030) was presented during ASH 2020. This update focused on the cohorts who received Iberdomide in combination with dexamethasone and daratumumab or dexamethasone and bortezomib. At the time of the presentation, 27 myeloma patients who have received >2 prior lines of therapy were treated with iberdomide with dexamethasone and daratumumab (IberDd cohort, median previous therapies was 4); 23 patients who have received >1 prior lines of therapy were treated with iberdomide with dexamethasone and bortezomib (IberVd cohort, median previous therapies was 6), all patients were refractory to their previous treatment regimen.

Most frequent haematological adverse events in the IberDd cohort were neutropenia (70.4%), thrombocytopenia (40.7%), and anaemia (37%). In the IberVd cohort, the most frequent haematological adverse events were neutropenia (34.8%), thrombocytopenia (34.8%), and anaemia (21.7%). Most common non-haematological adverse events reported in both cohorts included fatigue, diarrhoea, peripheral neuropathy, decreased appetite, rash.

The overall response rate in the IberDd cohort was 42.3% across all dosing groups, the median time to response was 4.1 weeks. In the IberVd cohort, the overall response rate was 60.9% with a median time to response of 3.6 weeks. A recommended phase 2 dose of 1.6 mg 21/28 days for Iberdomide with dexamethasone alone has previously been established. Enrolment of patients and the evaluation of cohorts receiving 1.6 mg of Iberdomide in combination with dexamethasone and daratumumab or bortezomib for 21/28 days is ongoing at the time of writing.

Survival Analysis of Newly Diagnosed Transplant-Eligible Multiple Myeloma Patients in the Randomized Forte Trial

Given there have been a significant number of advancements in immunotherapy drugs for treatment of multiple myeloma, there are various ongoing studies which investigate the utility of autologous stem cell transplant vs immunotherapy alone. In the FORTE trial, 474 patients were divided into three randomised cohorts. One cohort received 4 cycles of carfilzomib (Kyprolis), cyclophosphamide and dexamethasone (KCd), then an autologous stem cell transplant (ASCT), followed by 4 more cycles of KCd. The second cohort received 4 cycles of carfilzomib (Kyprolis), lenalidomide (Revlimid), dexamethasone (KRd), then an ASCT, followed by 4 cycles of KRd. The third cohort received 12 cycles of carfilzomib (Kyprolis), lenalidomide (Revlimid), dexamethasone and no ASCT. Next, patients were randomised to maintenance therapy with either Revlimid or Kyprolis and Revlimid.

Notably, patients in the KRd + ASCT cohort had the highest overall response rate (89%) and the longest progression free survival: 78% of patients were progression free 3 years after treatment.

Apollo: Subcutaneous Daratumumab with Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone

The Apollo trial is a phase 3 trial studying the effects of treatment using pomalidomide and dexamethasone with or without daratumumab. Here it was found the addition of daratumumab improved risk of disease progression by 37%. The addition of this drug showed an ORR of 69% vs 46% without daratumumab.

Click here for more safety and disease response information.

AL AMYLOIDOSIS UPDATES

After many years without treatment pathways and drug combinations specifically approved for AL Amyloidosis, several promising phase 2 and phase 3 trials have been published recently.

Several of these trials were discussed at ASH2020 and are summarised below.

First Glimpse on Real-World Efficacy Outcomes for 2000 Patients with Systemic Light Chain Amyloidosis in Europe: A Retrospective Observational Multicentre Study By the European Myeloma Network

Results of a retrospective observational multicentre study investigating AL amyloidosis management and treatment efficacy across Europe have been discussed. To date, 2,787 patients have been enrolled in this study with the aim being to enrol 4,000 patients. A notable insight from this research project is the key importance of early diagnosis, which remains an unmet need in AL amyloidosis. Dr Paolo Milani, Amyloidosis Research and Treatment Center, University Hospital San Matteo, Pavia, Italy said: "There is still the need for a better knowledge about the disease, as unfortunately, most of the patients [...] are diagnosed late, when the organ damage is really advanced." When commenting on this study in an interview with MPE Dr Giampaolo Merlini, Research Director at the University of Pavia, pointed out that it is important to "improve diagnostic probability" and aim for earlier diagnosis, in order to "reduce the number of patients who present with very advanced cardiac involvement" as this leads to very poor prognosis.

The study also analysed first and second-line treatment schemes. Until 2010, chemotherapy-based regimens were a first line of choice for treatment of AL amyloidosis, but since then, bortezomib-based regimes have become the preferred options. Bortezomib-based regimens lead to significantly better outcomes, however, haematologic complete response rates remain unsatisfactory, and there is a clear need for more effective treatment options in AL amyloidosis. Dr. Pieter Sonneveld highlighted that: "We could see that bortezomib-based regimens are now most widely used for this disease and this is good; [...] patients that can tolerate autologous transplants have complete responses up to 40%. Patients without autologous transplant have a much lower response rate so there is still work to do there."

Bortezomib, Cyclophosphamide, and Dexamethasone with or without Daratumumab: Results from Andromeda

ANDROMEDA is a phase 3 study (NCT03201965) that aims to assess the efficacy and safety of daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone (VCd). Daratumumab is a monoclonal antibody that binds to CD38, a protein present on the surface of plasma cells that produce AL amyloid deposits, and therefore mark these cells for destruction by the patient's immune system.

In this randomised study, 388 patients received either VCd in combination with daratumumab (n=195) or VCd alone (n=193). 65% of patients had ≥2 organs affected by AL amyloidosis. The median treatment duration was 5.3 months for VCd alone and 9.6 months for VCd with daratumumab. Combining daratumumab with bortezomib, cyclophosphamide, and dexamethasone (VCd) led to significantly better outcomes in patients with AL amyloidosis than VCd alone.

It should be noted, however, that the definition of haematologic complete response in AL amyloidosis is evolving, and generally is accepted to mean a reduction in light chains, in the plasma cells in bone marrow and in monoclonal protein levels in the blood, this being the goal of any treatment.

By all criteria generally included within the definition of haematologic complete response in AL amyloidosis as explained above, this study shows that the addition of daratumumab to VCd treatment leads to an over 2-fold increase in the percentage of patients showing a deep haematological response. Additionally, major organ deterioration progression-free survival was seen to be significantly longer in this patient cohort.

When asked about this study in an interview, Dr Giampaolo Merlini, the Research Director of the University of Pavia, commented: "This combination

represents a new standard of care for AL Amyloidosis patients."

Cael-101

Finally, a phase 2 open-label, dose selection study (NCT04304144) investigating the safety of CAEL-101 was discussed. CAEL-101 is a monoclonal antibody that binds to AL amyloid deposits; hence it may trigger the immune system-mediated removal of these deposits. This mechanism of treatment represents a very important and yet unmet therapeutic goal in AL amyloidosis treatment, as it could lead to the restoration of organ function. When commenting on CAEL-101, Dr Giampaolo Merlini remarked: "This trial is very important because it will tell us if this approach can really rescue organ dysfunction even in patients with very advanced organ damage".

As part of the study, CAEL-101 was administered to patients in escalating doses at 500 mg/m2, 750 mg/m2 and 1000 mg/m2. No dose limiting toxicities were observed during this study.

Organ responses were observed early on during treatment, these are expected to increase over time, and will be characterised in the upcoming phase 3 trial where the highest, 1000 mg/m2 dose will be administered to patients.

GLOSSARY

- Adverse event (AE): any unfavourable event and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure that may or may not be considered related to the 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
- Allogenic: tissue or cells which are genetically different and/or 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 which help our body fight infection; these are made up of large/ heavy chain proteins and small/ kappa and lambda light chain proteins
- Autologous stem cell transplant: patient receives stem cells from themselves
- 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
- Complete Response (CR): when less than 5% of plasma cells can be found in bone marrow and no paraproteins are detectable in blood or urine
- Consolidation therapy (intensification therapy and postremission therapy): Treatment given once cancer can't be detected following the initial therapy. It serves to kill cancer cells that may be left in the body. Intensification therapy may include radiation therapy, a stem cell transplant, or treatment with chemotherapy agents
- Cytokines: proteins released by cells throughout the body to stimulate cell growth, kill target cells / microbes; part of the immune response
- Cytokine release syndrome (CRS): a side effect characterized as a systemic inflammatory response causing flu-like symptoms such as fever, body aches and fatigue, which can, in severe cases, be life-threatening
- Dose-limiting toxicity (DLT): Side effects of a therapy that are serious enough

to prevent a further increase in the dose of the given treatment

- Graft-versus-host-disease: a condition that can occur after bone marrow, stem cell or other immune cell containing transplants where the graft (cells from the donor) recognize the host (recipient of the transplant) as foreign and attack the recipient's body
- Inclusion criteria: characteristics subjects must have if they are to be included in a clinical trial
- Lymphodepletion: therapy given prior to stem cell transplant which is usually high dose chemotherapy to kill remaining cancer cells and gets rid of blood-producing cells that are left in the bone marrow
- Mean: average of data / numbers
- Median: middle value in a list of data / numbers
- Minimal Residual Disease: use of specialized testing such as Next Generation Sequencing or Next Generation Flow Cytometry to count the number of abnormal myeloma cells left in a patient after treatment
- Minimal response: less than 50% decrease in paraproteins
- Non-secretory myeloma: rare type of myeloma that occurs in about 3% of patients; occurs when very little (oligosecretory) or no (non-secretory) abnormal paraproteins are produced. It is very challenging to diagnose these patients
- Overall response rate /objective response rate (ORR): % of patients with partial or complete response
- Overall survival (OS): median number of individuals in a group who are alive after a duration of time
- Partial response (PR): greater than 50% reduction in paraproteins in the blood
- Penta-drug refractory: patients who have been treated with a combination of 4 drugs such as an immunomodulatory drug, proteasome inhibitor, monoclonal antibody and dexamethasone and are no longer responding to therapy
- Plasma cell: type of cell found in bone marrow which produces antibodies
- Plasmacytoma: a condition where cancerous myeloma plasma cells are found outside of the bone marrow in the form of a tumour
- Progressive disease (PD): increase by 25% of urine or serum paraproteins
- Proteasomes: protein complex in the body which degrades and gets rid of damaged proteins

- Randomisation: the process of assigning study participants into treatment vs placebo arm (dummy treatment) of study at random (done using computer programs, random numbers, etc)
- Recommended phase 2 dose (RP2D): The dose chosen for administration in a phase 2 trial, based on the results of the phase 1 portion of the trial
- Refractory: when the number of myeloma cells 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/ symptoms are present but at lower levels) or full (cancer cells/ symptoms are undetectable)
- Stable disease: no worsening or improvement of disease after treatment; also, disease that has previously responded to therapy and paraprotein levels have not increased
- Step up dosing: a method used in clinical trials where patients are initially given a drug at low doses with the dose then gradually increased in a step wise fashion
- Stringent Complete response (sCR): no detectable presence of paraproteins in blood or urine; absence of abnormal myeloma plasma cells in the bone marrow
- Transcription factors: protein that control the rate of transcription of genetic information from DNA to mRNA
- Triple class refractory: patients who have been treated with a combination of 3 drugs, such as an immunomodulatory drug, proteasome inhibitor and a monoclonal antibody and are no longer responding to therapy
- Very good partial response (VGPR): a response type which shows a greater than 90% decrease in paraproteins in blood and a paraprotein level in urine of <100 mg/24 h

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