MultipleMyelomaHub

62nd ASH Annual Meeting and Exposition

Breakthrough abstracts in multiple myeloma (MM)

December 5–8, 2020

The Multiple Myeloma Hub Steering Committee members shared their insights on the most innovative data presented at ASH 2020 about multiple myeloma (MM).

Review with us the most exciting news about monitoring MM with less-invasive techniques and promising alternative targets to treat refractory disease. Discover underlying resistance mechanisms that could help to early identify relapse or fundament new drug combinations. Find here the initial results with novel targeted agents and the latest about BCMA-directed immunotherapies (bispecific antibodies and CAR T-cells) in clinical development.

Click the articles to view

Brought to you by SES Scientific Education Support

From bench to bedside: monitoring plasma cells

#57 Longitudinal Immunogenomic Profiling of Tumor and Immune Cells for Minimally-Invasive Monitoring of Smoldering Multiple Myeloma (SMM): The Immunocell Study

"The study explores the role of circulating tumor cells (CTCs) to predict the risk of transformation in patients with SMM. May be practice changing if it can demonstrate that CTCs can replace bone marrow plasma cells in the 2/20/20 model. In such case, the model could be measured much more frequently due to the minimally invasive nature of CTC screening."

Bruno Paiva

Can circulating tumor cell assessment by flow replace bone marrow aspirates to monitor SMM?

#720 Poor Prognosis of Multiple Myeloma Predicted By High Levels of Circulating Plasma Cells Is Independent from Other High-Risk Features but Is Modulated By the Achievement of Minimal Residual Disease Negativity

"The study demonstrates the important role of high levels of circulating plasma cells to identify high-risk MM patients treated with optimal, intensive treatment. It's complementary to cytogenetics and is a poor prognostic factor that is only abrogated by MRD negativity after treatment."

Bruno Paiva

Can we use circulating tumor cells to identify high-risk patients?

#665 Bortezomib Induces Anti-Multiple Myeloma Immune Response Mediated By Cgas/Sting Pathway Activation, Type I Interferon Secretion, and Immunogenic Cell Death: Clinical Application

"This study delineates a novel mechanism whereby bortezomib triggers anti-MM immune responses, and shows that STING agonists can enhance this response. Could be important data due to the increasing role of various immunotherapies in MM, and may be useful to identify synergistic combinations with proteasome inhibitors."

Bruno Paiva

#721 Biallelic Loss of BCMA Triggers Resistance to Anti-BCMA CAR T Cell Therapy in Multiple Myeloma

"It raises awareness to the ability of MM cells to survive without BCMA expression, and to the potential biallelic loss of the BCMA locus as a potential resistance mechanism to BCMA-targeting therapy. Could be important for future screening of mutations and precision immunotherapy in cases of biallelic BCMA deletion."

Bruno Paiva

Triplet combinations in earlier stages of development for patients exposed or refractory to lenalidomide

#417 ANCHOR (OP-104): Melflufen Plus Dexamethasone (dex) and Daratumumab (dara) or Bortezomib (BTZ) in Relapsed/Refractory Multiple Myeloma (RRMM) Refractory to an IMiD and/or a Proteasome Inhibitor (PI) - Updated Efficacy and Safety

"The combination of melflufen plus Dara was effective in RRMM patients after at least two prior lines of therapy with a median PFS of 1 year. Thrombocytopenia is the most relevant adverse event, but manageable."

María-Victoria Mateos

"Melflufen will be one of the next drugs approved for the treatment of RRMM. Its activity has already been shown in combination with Dex. In the respective abstract, melflufen has now been combined with Dara-Dex and with Btz-Dex for treatment of patients with RRMM who were refractory to an IMiD and/or proteasome inhibitor; a patient group that is difficult to treat. The ORR with melflufen-Dara-Dex was 70% and the treatment was well tolerated. Progression-free survival was 11.5 months and the toxicities observed were those associated with melflufen, which primarily affect the hematopoietic system resulting in anemia, neutropenia, and thrombocytopenia. When melflufen was combined with Btz-Dex, similar results were noted, with overall response rates of 60%, and the PFS data are not mature yet."

Heinz Ludwig

"Melflufen+Dex combined with either Btz or Dara achieved a respectable overall response rate, though we have to watch for cytopenias. It's important to do the work of these combo trials; as BCMA-directed therapy will move to earlier lines, we will have to go back to our old combination tricks to salvage patients."

Nina Shah

ANCHOR: Melflufen triplet regimens for relapsed/refractory multiple myeloma

Should we use melflufen to treat relapsed patients with poor prognosis?

Triplet combinations in earlier stages of development for patients exposed or refractory to lenalidomide

#724 First Results of Iberdomide (IBER; CC-220) in Combination with Dexamethasone (DEX) and Daratumumab (DARA) or Bortezomib (BORT) in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

"Iberdomide (Iber) is an oral, potent novel cereblon E3 ligase modulator (CELMoD) agent with marked synergistic tumoricidal and immune-stimulatory effects in combination with Bort or Dara in preclinical models. CC-220-MM-001 is a phase I/II study evaluating dose escalations of Iber with different treatment combinations in independent cohorts, in patients with RRMM. Here, the researchers present results from the Iber+Dara+Dex (IberDd) and Iber+Bort+Dex (IberVd) cohorts and demonstrate a response rate of 35% and 50%, respectively, in heavily treated patients. Importantly, the combinations were well tolerated, and this sets the platform for randomized studies."

Miles Prince

"Although these are preliminary results from ongoing studies, with no optimal doses defined yet, Iber shows how it is able to rescue patients exposed and refractory to previous IMiDs with a synergistic effect when combined with proteasome inhibitors or monoclonal antibodies."

María-Victoria Mateos

"Iber is a novel IMiD (called CELMoD) that is active in Len- and Pom-refractory myeloma cell lines. Iber in combination with Dara or Bort, showed a favorable safety profile in heavily pretreated patients with a promising clinical activity, even in heavily pretreated patients."

Hermann Einsele

"Novel combination of the new CELMoD: Iber with Dex and Dara or Bort, reported an ORR of 35–50%. This data is useful to show us how to combine this new drug with available therapies. Clinical utility will be based on how early we want to incorporate it."

Nina Shah

"The potential of the available IMiDs, namely Len, Pom, and thalidomide, has been fully exploited. Hence, the introduction of new, even more potent drugs with similar target proteins (Ikaros, Aiolos) called 'CELMoDs', is highly appreciated. These drugs are larger molecules than IMiDs and active modulators of the cereblon E3 ligase complex. Iber is a representative of this new drug class and has been previously evaluated in combination with Dex in heavily pretreated patients, yielding response rates slightly above 30%. In the present study, Iber-Dex has either been combined with Dara or Bort. The former combination yielded an overall response rate of 35% and the latter yielded an overall response of 50% in these highly refractory patients, which is quite remarkable."

Heinz Ludwig

"The results of this trial demonstrate that the new CELMoDs can be safely combined with other standard-of-care agents, like Dara and Bort, in patients with RR disease. They certainly open new options for patients who are increasingly refractory to the current IMiDs, as Len and Pom, at the time of later relapses. It also provides data supporting that these new drugs with similar mechanism of actions, and more potent than the current IMiDs, can potentially replace them in the earlier lines of therapy."

Shaji Kumar

#177 CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma

"Cilta-cel is a very effective BCMA CAR T-cell with an impressive 96% of overall response rate and 67% of sCR/CR rate. Durability of the response is pending but cilta-cel covers the unmet medical need for three-drug class refractory patients."

María-Victoria Mateos

"CARTITUDE-1 trial: a BCMA-directed CAR T-cell product (cilta-cel) was administered to heavily pretreated patients (median six lines of prior therapy) and induced a response rate of nearly 100% and stringent CR in 67% of patients. The PFS survival is clearly beyond 1 year. The CRS and ICANS rates were very much in line with other BCMA CAR T-cell products. A late occurring neurotoxicity in some patients can be prevented by modifications of the protocol."

Hermann Einsele

"We waited to see all the patients, and it was worth it!"

Nina Shah

"This important study aims to confirm the very positive LEGEND-2 study performed in China. These preliminary results seem to demonstrate comparable results. The response rates were indeed impressive."

Miles Prince

"This years' meeting was a festival for cellular therapies in multiple myeloma. CARTITUDE is one of the highlights of the several CAR T-cell and NK cell studies presented. It had initially been developed by a Chinese group and has already been presented at earlier meetings as the 'LEGEND' study, which now has been taken over by Janssen. The results are highly impressive with an overall response rate of 96.9% in 97 patients with a median of six prior lines of therapy. CAR T-cell treatment resulted in very rapid responses, and the main task now is to maintain the achieved responses, as they usually are not sustained for long. However, this was different in the CARTITUDE study, with excellent PFS and OS rates at 6 months, of 87.4% and 93.8%, respectively."

Heinz Ludwig

"The data from this trial, which is more mature than was previously presented, demonstrates response in nearly all patients who have been treated. A significant proportion of patients were also able to achieve minimal residual disease negativity. The responses appear to be durable with a median PFS that is exceeding 1 year. The toxicity observed has been in line with other CAR T-cells, except for some additional neurological symptoms. A long-term follow-up will be required to get a better assessment of any unique toxicity associated with this product."

Shaji Kumar

CARTITUDE-1 results indicate deep and durable responses with cilta-cel for RRMM

Anti-BCMA CAR T-cell therapies reporting longer follow-up

#131 Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy, in Patients with Relapsed and Refractory Multiple Myeloma: Updated Results from Phase 1 CRB-401 Study

“The long-term follow-up of ide-cel in relapsed/refractory myeloma patients has shown how, in spite of a median PFS of approximately 9 months, the benefit in OS was of nearly 3 years, indicating that BCMA CAR T-cells can modify the biology of the disease and allow the patients to receive subsequent lines of therapy.”

María-Victoria Mateos

“One of the first studies with an anti-BCMA CAR T-cell for MM. Despite many other CAR-T therapies are being developed with the same target, and the results of bb2121 in terms of response and PFS are not the best, the availability of a prolonged follow-up time, close to 4 years now, is important to give reliability to the product and to define long-term outcomes. The median OS of patients who received a median of six lines of therapy is now 34 months.”

Elena Zamagni

#129 Universal: An Allogeneic First-in-Human Study of the Anti-Bcma ALLO-715 and the Anti-CD52 ALLO-647 in Relapsed/Refractory Multiple Myeloma

"Allo-CARTs represent the solution for at least two of the most relevant challenges with autologous CAR Ts: manufacturing process, bridging therapy, and the quality of the product. Preliminary data are encouraging, especially from the safety point of view, and are the right way to move forward with CAR Ts in MM."

María-Victoria Mateos

"The revolution in cellular therapies is ongoing and this is exemplified by abstract #129, which evaluated the efficacy of specifically engineered allogeneic T cells. The two major problems, namely graft-*versus*-host disease and immune rejection, need to be prevented. The authors silenced the genes for TCR alpha and CD52 to enhance the tolerability of the product and to obviate potential graft-*versus*-host disease. Using these modified CAR T-cells in 19 heavily pretreated patients, resulted in an ORR rate of 33.3% with a clear cellular dose-response relationship with higher cell doses, leading to higher success rates. Cytokine storm was noted in 4 of 15 patients, indicating that further attempts are necessary to modify this cellular drug accordingly to further improve tolerance."

Heinz Ludwig

"One of the disadvantages of autologous CAR T-cells for treatment of MM is the time taken for manufacturing, which can be a disadvantage for patients with advanced relapsed/refractory disease. The possibility to use allogeneic CAR T-cells from a donor allows the use of this therapeutic strategy as an 'off-the-shelf' treatment, that can be rapidly deployed in a relapsing patient. The data from this clinical trial demonstrates efficacy for this approach without any significant graft-*versus*-host disease, which was the main concern."

Shaji Kumar

"ALLO-715 achieved a significant overall response rate at the higher dose, within 5 days. We need a longer follow-up to see how the duration of response will compare with autologous CAR T-cells. It will also be interesting to study the host-*versus*-graft."

Nina Shah

Novel anti-BCMA CAR T-cell strategies: 'off-the-shelf' alternatives and optimizing the manufacturing process

#134 Phase 1/2 Study of the Safety and Response of P-BCMA-101 CAR-T Cells in Patients with Relapsed/Refractory (r/r) Multiple Myeloma (MM) (PRIME) with Novel Therapeutic Strategies

"The use of transposons instead of lentivirus in the manufacturing process of autologous CAR-Ts contributes to optimizing the quality of the product, enriching it with more naïve, stem cell memory and central memory phenotypes for T cells to improve their persistence with potential benefit in the durability of the response."

María-Victoria Mateos

"This abstract also illustrates the enormous progress that had been achieved by modifying the cellular treatments. The authors used transposons instead of lentivirus to preferentially transpose stem cell memory T cells in order to overcome the issue of short half-life of infused CAR T-cells. By following this principle, they succeeded to maintain long-lasting presence of therapeutic T cells, which were detectable up to 1.5 years after the infusion. These modified T cells showed remarkable good tolerance with no cytokine release symptoms and were found to be highly efficacious."

Heinz Ludwig

"This product is unique in the sense that it is based on a transposon technology for expression of the chimeric antigen receptor in the autologous T cells. This overcomes some of the theoretical risk of transfection with a lentiviral vector. The results from this study show some evidence of activity especially at the higher dose levels, and the trial design is exploring a variety of different pre-infusion and post-infusion approaches to enhance efficacy while decreasing the toxicity."

Shaji Kumar

#133 Results from Lummicar-2: A Phase 1b/2 Study of Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT053) in Patients with Relapsed and/or Refractory Multiple Myeloma

"Several CAR T-cells have been developed targeting BCMA in multiple myeloma with significant efficacy. CT053 is a BCMA targeting CART that allows for a short manufacturing process that limits the interval between apheresis and infusion. The data from the trial clearly show activity at all those levels examined and the product has been very well tolerated with very manageable toxicity."

Shaji Kumar

"I-LUMMI-nating! LUMMICAR CT053 CAR-T achieved a 94% overall response rate, mostly MRD-negative."

Nina Shah

How is CT053 different from other BCMA-directed CAR T-cell therapies?

#290 A Phase 1, First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D (GPRC5D) × CD3 Bispecific Antibody, in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM)

"Talquetamab targeting GPRC5D puts in context that there are more things beyond BCMA-targeted therapy. Moreover, talquetamab can rescue patients previously treated with BCMA-targeted therapy. Good preliminary efficacy with acceptable safety profile and subcutaneous (SC) administration, which is convenient for patients."

María-Victoria Mateos

"New target, SC administration, tested in some patients with prior BCMA exposure. This could be another possibility when BCMA-targeted therapy fails, a new MM frontier."

Nina Shah

"This phase I/II study showed early results of efficacy and tolerability of a new generation of bispecific antibody therapy directed against the GPRC5D protein. The high efficacy in a very advanced population of RRMM is encouraging and enlarging the possibility of treating patients in advanced phases of the disease, who developed resistance to all the main drug classes. The importance of this study for the future resides in the growing presence of patients who received anti-BCMA agents; therefore, the availability of different targets is essential."

Elena Zamagni

"This abstract is a further example of the manifold approaches to create highly active T-cell-engaging therapies. Talquetamab binds to T cells via CD3 and to myeloma cells via GPRC5D, a protein that is highly expressed on myeloma cells but not on other cell types. The authors aimed to establish the optimal dose for phase II studies and already treated 137 patients, most of them heavily exposed to several treatment lines. Responses were observed in 87% of patients, which is very encouraging given the heavy pretreatment of the patients. Talquetamab may become a very important treatment and challenges the role of CAR T-cells. It can be easily and repeatedly administered, can be stored on the shelf, and will be used for up-front treatment as well. Before this may become a reality, proof of its long-term efficacy and tolerance is required."

Heinz Ludwig

"One of the disadvantages of the current immunotherapy platforms including CART and bispecifics has been the use of BCMA as the target. It is unclear at this time, if a different BCMA-targeting agent will be effective in a patient in whom another similar therapy has previously stop working. From this standpoint, targeting additional antigens that are relatively specific to plasma cells will have a significant value. This bispecific, appears to be quite effective with over 70% of the patients at the highest doses, despite being heavily pretreated with a median of six prior lines of therapy. This also includes some deep responses achieving MRD-negativity. The SC administration is an added advantage. The toxicity appears to be in line with what has been observed with similar molecules, except for cutaneous toxicity consistent with the expression of the target in normal tissue."

Shaji Kumar

Talquetamab for relapsed/refractory multiple myeloma: Results from a phase I study

#292 Initial Clinical Activity and Safety of BFCR4350A, a FcRH5/CD3 T-Cell-Engaging Bispecific Antibody, in Relapsed/Refractory Multiple Myeloma

"Cevostamab represents another new drug targeting a novel target for myeloma, FcRH5, with promising efficacy and safety data reported so far. A longer follow-up is required to see the durability of the response. The good news is that patients previously exposed to BCMA-targeted therapy can be rescued by FcRH5-targeted therapy."

María-Victoria Mateos

"A further example of progress in antibody engineering is shown in abstract #292. The authors report on a BiTE targeting both CD3 on T cells, and the FcRH5 receptor on myeloma cells, thereby guiding T cells to their target on myeloma cells. In a phase I/II study, this BiTE showed an ORR of 51.7% in heavily pretreated patients, also in those with high-risk cytogenetics. Importantly, the treatment was well tolerated, and responses were deep and durable, and therefore, are of significant clinical relevance."

Heinz Ludwig

"This bispecific molecule targets a different antigen on the myeloma cell, other than BCMA, providing an opportunity for activity in patients who may have previously failed a BCMA-targeting agent. The responses have been quite encouraging with this bispecific, including some deep responses. The toxicity has been very manageable."

Shaji Kumar

"Cevostamab – a bispecific T-cell engager targeting FcRH5 for MM. With infusions every 3 weeks, and 21% of patients with prior BCMA-targeted therapy, the study reported 53–61% of response rates at the higher doses evaluated. Very exciting data beyond BCMA."

Nina Shah

#293 Initial Results of a Phase I Study of TNB-383B, a BCMA x CD3 Bispecific T-Cell Redirecting Antibody, in Relapsed/Refractory Multiple Myeloma

"Both abstracts #292 and #293, demonstrate a new construct of BiTEs. These are 'off-the-shelf' therapeutics that did not require bridging chemotherapy and were tested in a very heavily pretreated patient population. Both agents showed a preliminary overall response rate of ~52%. These are promising results, including deep and durable responses with rather unimpressive toxicity. I was more impressed with these data than the CAR T-cell reports at ASH 2020."

Morie Gertz

"This bispecific molecule assay has a different structure that allows it to bind more efficiently with the cell-bound BCMA compared with the soluble BCMA. It is also designed to limit the cytokine secretion by T cells, which can theoretically lead to a reduction in risk of cytokine release syndrome. Among the patients who have been treated with this product in the dose escalation study, a high response rate has been observed, particularly at the higher dose levels. The overall rate of cytokine release syndrome appears to be lower compared with some of the other bispecifics, and has been mostly low grade."

Shaji Kumar

#180 Updated Phase 1 Results of Teclistamab, a B-Cell Maturation Antigen (BCMA) x CD3 Bispecific Antibody, in Relapsed and/or Refractory Multiple Myeloma (RRMM)

"Bispecifics represent a novel immunotherapy approach that uses autologous T cells to generate an antitumor immune response. Using a target like BCMA that has been well validated for immunotherapy approaches, this drug has shown high-rates of activity in a heavily pretreated patient population and achieved deep responses, such as minimal residual disease negativity. The toxicity appears to be easily managed, and most of the cytokine release syndrome seen with this drug appears to be of Grade 1–2. As with other bispecifics, there is a significant proportion of patients with infections and this needs to be better delineated with a longer follow-up."

Shaji Kumar

"Impressive response rate and safety profile of teclistamab, with subcutaneous administration. Looking forward to the long-term data."

Nina Shah

Is the bsAb teclistamab safe and effective in patients with relapsed/refractory MM?

#291 REGN5458, a BCMA x CD3 Bispecific Monoclonal Antibody, Induces Deep and Durable Responses in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

"This is another bispecific that is targeting the BCMA. The early data from this bispecific appears to be quite promising with very manageable toxicity. The responses in a small number of patients treated at the higher dose levels, appear to be deep and durable. Ongoing studies will give a better sense of the efficacy of this agent."

Shaji Kumar

#179 Phase 1, First-in-Human Study of MEDI2228, a BCMA-Targeted ADC in Patients with Relapsed/Refractory Multiple Myeloma

"This BCMA-targeting antibody–drug conjugate (ADC) was evaluated in a dose escalation study that included patients who had been exposed to most of the standard of care therapies. Nearly 2/3 of patients responded to treatment, especially at the recommended phase II dose. The treatment was associated with eye toxicity, which appears to be distinct from what has been observed with the other BCMA-targeting ADC, belantamab mafodotin. The other observed toxicities included hematological toxicity, rash, and serositis."

Shaji Kumar

Phase I results of MEDI2228, an anti-BCMA antibody–drug conjugate, in patients with RRMM

MultipleMyelomaHub

multiplemyelomahub.com

@MM_Hub #mmsm