ASH 2020 review

I would like to thank the UK Myeloma Forum for the opportunity to attend the ASH conference. For me it was the first time to attend such a significant conference, where all the leading experts in Haematology meet together to present and discuss the new scientific developments. Although this time the conference was held virtually, it was still a great educational experience.

Pre-clinical field

Dr Gulla presented an interesting study, where it was demonstrated that bortezomib induces anti-MM immune responses through immunogenic cell death. By using an ICD-signature, they identified a type I interferon response after use of bortezomib. Activation of the cGAS/STING pathway post BTZ showed correlation between high STING expression and high ICD signature. STING knock out blocked the type I IFN response and impaired T cell activation. Therefore, STING agonists could represent a novel therapeutic approach alone and in combination with BTZ.

Another interesting presentation was from Dr Verkleij, who presented potential mechanisms affecting resistance/lack of response to Talquetamab, which targets the GPRC5D, an orphan G protein-coupled receptor in MM cells. The analysis in BM samples of patients with MM, showed that there was no difference in efficacy depending on stage of disease and high risk cytogenetics. The low expression of GPRC5D and the BM microenviroment, especially the low effector:target ration, high frequency of PD-1+ or HLA-DR+ Tcells or immune-suppressing Tregs could impair efficacy. That could lead to studies aiming to improve response in patients receiving treatments with bispecific antibodies.

In the clinical field

Approved therapies

3 studies (FORTE trial, EMN02/HO95MM, IFM 2009) focused on the significance of autologous stem cell transplant and justified why it remains the backbone of modern myeloma therapies. In regards to standard of care therapies, 2 studies focused on the benefit of triplet vs doublet regimens. Professor Dimopoulos presented the results of APOLLO, a phase 3 study, in which combination of Daratumumab sc +Pomalidomide/Dexamethasone had an acceptable safety profile with low infusion related reactions and resulted in deeper responses compared to Pomalidonime/Dexamethasone and a longer PFS in Lenalidomide refractory patients (9.9 vs 6.5 months).

Dr Martin presented the results of the IKEMA trial, using Isatuximab/Carfilzomib/Dexamethasone vs Carfilzomib/Dexamethasone. Deeper responses and MRD negativity rates were observed with the triplet combination and rates were even higher when mass spectometry was used to eliminate Isatuximab interference.

Novel agents.

Dr Van De Donk presented the results of Iberdomide (CC220) in combination with Daratumumab/Dexamethasone (IberDd) or Bortezomib/Dexamethasone (IberVd) in the CC220-MM-001 phase 1/ 2 study. Iberdomide is an oral, potent novel CRBN E3 ligase modulator (CELMoD). Treatment emergent adverse events were similar in both cohorts, with haematological adverse events more common. ORR rate was 42% for the IberDd cohort and 60.9% for the IberVd cohort.

Antibody drug conjugates (ADC)

Belamaf, an antibody drug conjugate targeting BCMA, showed encouraging results in 2 studies. In DREAMM6, presented by Dr Popat, Belamaf was given in combination with Bortezomib/Dexamethasone. Main AEs were keratopathy, neutropenia and thrombocytopenia. The ORR was 78% and 67% of the patients achieved VGPR or better. Interestingly, all the patients who had only 1 prior line of treatment achieved VGPR or better, suggestive of a potentially use of this combination as early –line of treatment.

Dr Trudel presented the data form the combination of Belamaf with Pomalidomide /Dexamethasone. Most common AEs were keratopathy, neutropenia and thrombocytopenia. ORR was 88% in all cohorts, with a significant efficacy of ≥ 72% VGPR and median PFS of 11.1 months in the triple refractory patients.

Dr Kumar presented the data from a phase 1, FIH study of MEDI2228, which is an antibody drug conjugate that targets the extracellular domain of human BCMA. The patients had RRMM post at least 3 prior lines of treatment. Treatment related AEs occurred in ≥ 15% of the patients. On the MTD of 0.14mg/kg, AEs were photophobia (58.5%), thrombocytopenia (31.7%), rash (31.7%), pleural effusion (24.4%) and GGT increase (24.4%). The pathophysiology of photophobia is not yet known, these patients did not have any signs of keratopathy and it did lead to treatment discontinuation in some cases. MEDI2228 showed clinical efficacy across all dose levels and on the 0.14mg/kg dose the ORR was 66% with a median DoR of 6 months.

Bispecific antibodies

Professor Harrison presented a phase 1 First in Human (FIH) Study of AMG 701, an anti-BCMA Half-life Extended (HLE) BiTE® (Bispecific T-cell engager) Molecule. Most common adverse events were anaemia (42%) and CRS. 9% of the patients had grade 3 CRS with transient increase in liver function tests. In the most evaluable

cohort the ORR was 83%, with 6 of the patients having MRD negativity. Further evaluation of AMG701 is needed.

Dr Garfall presented the updated results of a phase 1 trial with Teclistamab, a BCMAxCD3 bispecific antibody, given either IV or SC in patients with RRMM. Median lines of prior therapies was 6 and 81% of the patients were triple class refractory. The safety profile was acceptable. Impressively, CRS, which occurred in 57% of the patients, was only Grade 1 or 2 with median onset of 2 days. Step up dosing was used to mitigate risk of CRS. Neurotoxicity was low (5%). Teclistamab showed significant efficacy with deep and durable responses with ORR of 73% in the RP2D of 1500 μg/kg sc and a response of more than 70% in the penta drug refractory patients.

Dr Chari presented the data from a phase 1,FIH study of Talquetamab (IV or SC), a first-in-class DuoBody IgG4 PAA antibody that binds to GPRC5D (highly expressed in MM cells) and CD3, causing redirection of T cells to GPRC5D expressing MM cells to promote cell killing. Patients had received a median of 6 prior lines, 82% were triple class refractory, 20% of patients had EMD and 17% had received prior BCMA therapy. The RP2D dose (n=13) was identified at 405 μg/kg sc and in regards to the safety profile at this dose, neutropenia was observed in 47% (inc Grade 3 in 42%) and infections in 16% (no grade 3). CRS(median onset 2 days) was observed in 68% of the patients (no Grade 3) and neurotoxicity was low (5%). Talquetamab showed deep and durable responses in the IV cohort due to longer follow up and an ORR of 69% in the RP2D (> 39%VGPR).

CAR T cell therapies

A number of studies focused on treatments on the relapsed/refractory setting. There were many updates on the anti BCMA CAR T trials, most of which showed promising results. Dr Madduri presented the data from CARTITUDE 1, a phase Ib/II study of Ciltacabtagene Autoleucel, Cilta-Cell is a chimeric T cell receptor antigen with 2 BCMA -targeting single domain antibodies. In terms of adverse events (AEs), most common were haematological AEs and neutropenia occurred in all patient.19,6% developed Grade 3 or 4 infections. The majority of the patients experienced cytokine release syndrome (CRS), mostly Grade 1 and 2, with median onset of 7 days. This could open up the possibility of outpatient administration. Neurotoxicity (presented either as ICANS or other neurotoxicities with unknown mechanism) occurred in 21% of the patients (10% was grade 3). Early and durable responses were observed, with an impressive ORR of 96.9% and sCR 67% and median PFS was not reached after 12.4 months of follow-up.

Dr Alsina presented an update from CRB-402 phase 1 study of anti BCMA CAR T cell therapy bb21217. The bb21217 uses the same CAR molecule as bb2121 but it is cultured with a PI3K inhibitor , bb007 , to enrich T-cell displaying a memory like phenotype, in order to improve durability of response. Adverse events occurred in

20% of the patients. A quarter of the patients developed grade 3/4 infections (1 death). 70% of the patient had low grade CRS but there were 2 deaths due to CRS. Neurotoxicity observed in 16% (one Grade 4 event). The estimated mDOR was 17 months across doses and at the RP2D dose (using new manufacturing process) of 450 x 10^6 CAR T cells, the ORR was 84%.

Dr Mailankody presented the UNIVERSAL study, a first in human study of allogeneic anti BCMA Allo 715 CAR T cell and the Anti CD52 Mab Allo 647. Median time from enrolment to treatment was 5 days. Allo 715 and Allo 647 had an acceptable safety profile. None of the patients experience GVHD or ICANS. CRS(no grade 3) occured in half of the patients. Response rates were dose dependent and an ORR of 60% was achieved in the 320M cell dose of Allo 715 (6 patients) with >40% VGPR.

Above all, I really enjoyed the 3 live Q&A sessions in Multiple Myeloma, for the quality of the presentations but mostly for the discussions between the leading Myeloma experts.

Overall, it was an exciting and extremely beneficial experience for me. I would like to thank the UKMF and Amgen, for the ASH Travel Bursary Award.

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