UK Myeloma Forum: EHA 2020 Virtual Congress Highlights

By, Dr Rakesh Popat, University College London Hospitals NHS Foundation Trust, London, UK

Relapsed Multiple Myeloma: Isatuximab

(LB2603) ISATUXIMAB PLUS CARFILZOMIB AND DEXAMETHASONE VS CARFILZOMIB AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (IKEMA): INTERIM ANALYSIS OF A PHASE 3, RANDOMIZED, OPEN-LABEL STUDY

Isatuximab (Isa) is a monoclonal antibody (Mab) targeting CD38 which is licensed in combination with pomalidomide and dexamethasone for patients with relapsed myeloma. This late breaking abstract investigates the proteasome inhibitor, carfilzomib (K) as a partner for the Mab. This study enrolled patients with 1-3 prior lines that were carfilzomib naïve and not refractory to a CD38 Mab and randomised to Kd or Isa-Kd. The primary endpoint of an improvement in PFS was met with a HR of 0.531 (p=0.0007), Kd PFS 19.15m vs Isa-Pd not reached. The overall response rate was quite similar however the VGPR and CR rates were higher for Isa-Kd. In addition, the MRD negativity rates by NGS were higher for Isa-Pd. The overall survival data is still immature to report. Generally, the adverse event profile was comparable, although there appeared to be a higher number of respiratory infections and neutropenia for Isa-Kd. Overall this was a positive study and Isa-Kd represents a new treatment option for patients with relapsed myeloma.

Opinion: This trial shows a clear benefit of Isa-Kd over Kd. As data continues to emerge with CD38 Mabs, there seems to be a consistent signal of increased risk of respiratory tract infections. This may in part be related to hypogammaglobulinemia. A similar study to this is the CANDOR trial using

daratumumab which demonstrated a PFS benefit of Dara-Kd over Kd. However, the PFS for both the D-Kd and Kd arms are different to this study which limits comparability.

Relapsed Multiple Myeloma: CelMods

(S208) FIRST-IN-HUMAN PHASE 1 STUDY OF THE NOVEL CELMOD AGENT CC-92480 COMBINED WITH DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

We're all familiar with the IMiDs (thalidomide, lenalidomide and pomalidomide) for patients with myeloma. Last year we also saw early data for the newer IMiD, Iberdomide (CC-220). CC-9240 is a novel CelMod (cereblon E3 ligase modulator) that has been designed to have high potency for cereblon and leads to rapid degradation of the downstream molecules Ikaros and Aiolos. *In-vitro* it has activity in myeloma cell lines resistant to lenalidomide and pomalidomide and those with low levels of cereblon.

This phase 1 clinical trial investigated CC-92480 for patients with myeloma that were resistant, intolerant or not suitable for currently available therapies and had disease progression on or within 60 days of the last therapy. The primary objective was to investigate the safety and determine the recommended phase 2 dose. The study investigated various different schedules of administration of CC-92480 plus dexamethasone, looking at continuous and intensive schedules at increasing doses. 76 patients were enrolled, 36.8% had EMD, and they had a median of 6 prior lines (range 2-13). Of note 89.5% were IMiD refractory and 50% were triple class refractory. Main reported adverse events were haematological, predominantly neutropenia as well as anaemia and thrombocytopenia. 71% had infections. The overall response rate at the MTD for the 10/14 day schedule was 40% and for the 21/28 day schedule was 54.5%. Responses were observed in double IMiD refractory patients as well as those with EMD. The schedule being taken forward in the 21/28 day schedule based on PK/PD data. Combination studies are ongoing.

Opinion: This is the 1st presentation of the new CelMod CC-92480 for relapsed myeloma. It appears to be a well tolerated oral regimen, with neutropenia managed with GCSF support. Importantly it has activity in patients previously refractory to lenalidomide and pomalidomide. Studies are ongoing, including combinations; however with this efficacy and tolerability, CC-92480 looks set to be a part of the future treatment paradigm for myeloma.

BCMA targeted therapies

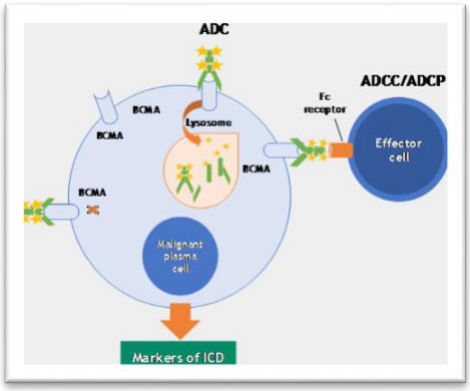
Over the last few years we have seen a large number of agents under investigation that target B cell maturation antigen (BCMA). The main modalities being used are 1) antibody drug conjugates, 2) bi-specific T cells, 3) CAR-T cells. At EHA there were updates and new data for all of these different approaches and are summarised below:

1. Antibody drug conjugates:

(EP1031) DREAMM-6: SAFETY AND TOLERABILITY OF BELANTAMAB MAFODOTIN IN COMBINATION WITH BORTEZOMIB/DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

Belantamab mafadotin (belamaf) is a BCMA targeted ADC that demonstrated monotherapy activity in the previous DREAMM-2 trial for patients that were refractory to a PI, IMiD and refractory/ intolerant to a CD38 antibody. This study was investigating belamaf in combination with lenalidomide and

dexamethasone (Part A) and bortezomib and dexamethasone (Part B) at various doses and schedules for patients that had at least 1 prior line, irrespective of refractory status to PI or IMiDs. The primary objective was the safety, tolerability and the determination of the recommended doses for combinations. This presentation was focussed on the belamaf 2.5mg/kg single dose (every 21 days) with bortezomib days 1,4,8,11 plus dexamethasone. 18 patients had a median of 3 prior lines (range 1-11) and had a median of 18.2 weeks (range 6-46.4) of treatment. Infusion reactions were infrequent (pre-medications were not required), and thrombocytopenia in 12 patients (mainly G3-4). All 18 patients reported corneal events (G2-3 mainly) which was managed by dose interruptions and modifications. The overall response rate was 78% with 50% achieving VGPR. The study is ongoing exploring other doses and schedules of belamaf.



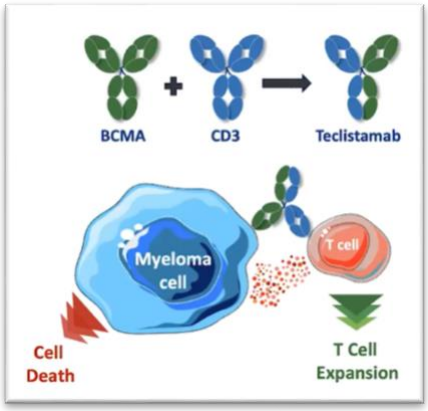
Opinion: Belamaf appeared to be tolerated at the 2.5mg/kg dose with bortezomib and dexamethasone with similar adverse events to that previously reported (mainly keratopathy and thrombocytopenia). The response rate was encouraging for a heavily pre-treated population and overall this paves the way forward for further combinations to be developed with this ADC. Further data are to be presented later in the year.

2. Bispecific T cell engagers:

Bi-specific T cell engagers (TCE) represent an "off-the-shelf" therapy that redirects T cells to their target. In the case of myeloma, most of the TCE's under investigation target BCMA and CD3. The first TCE for myeloma was AMG-420 and required long periods of hospitalisation due to the continuous infusion; however this was discontinued in favour of the longer acting AMG-701. We are currently awaiting data this. Since then a further 2 TCE that can be dosed weekly were reported at EHA: an update of the phase 1 trial of CC-93269 and the first report of teclistamab.

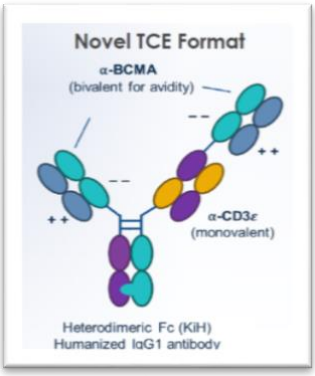
(S206) A PHASE 1 STUDY OF TECLISTAMAB, A HUMANIZED B-CELL MATURATION ANTIGEN (BCMA) X CD3 BISPECIFIC ANTIBODY, FOR THE TREATMENT OF RELAPSED AND/OR REFRACTORY MULTIPLE MYELOMA (RRMM)

Teclistamab is a humanised IgG-4 bispecific "Duobody" that binds to BCMA and CD3. This was a phase 1 study that aimed to identify the recommended phase 2 dose as well as the safety, tolerability and efficacy of the molecule. Patients that were relapsed and refractory or intolerant to established myeloma therapies were enrolled. Teclistimab was intitially dosed weekly with step-up dosing (1st week comprised of 1-3 doses). Part 1 of the study investigated increasing doses before the recommended dose was taken forward to cohort expansion in part 2. 78 patients from Part 1 were reported who had a median of 6 (range 2-14) prior lines of which 80% were triple class refractory, 41% penta-refractory and 86% were refractory to the last line of therapy. Cytokine release syndrome (CRS) was reported in 56% (0 ≥G3, and neurotoxic events on 6 patients (grade 1-2 (n=4); grade 3-4 (n=2: G4 delirium, G3 mental status change)). CRS appeared to be generally confined to the 1st step-up and full



doses and managed with tocilizumab in 26%. The response rate was 30% at 38.4-180mcg/kg doses, and 67% at 270mg/kg. Response data at 720mcg/kg was not ready for reporting. The data remains immature, but some of the responses appear durable and MRD negativity begin achieved with some patients. The study is ongoing.

(S205) INTERIM RESULTS FROM THE FIRST PHASE 1 CLINICAL STUDY OF THE B-CELL MATURATION ANTIGEN (BCMA) 2+1 T CELL ENGAGER (TCE) CC-93269 IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)



The preliminary results of CC-93269 were reported at ASH 2019, and this was an update of the phase 1 clinical trial for patients with relapsed myeloma that had ≥3 prior lines. CC-93269 is a asymmetric 2 arm humanised IgG1 TCE that binds bivalently to BCMA and monovalently to CD3 in a 2+1 format. 30 patients who had a median of 5 (range 3-13) prior lines and were refractory to their last line were treated in dose escalation from 0.15to 10mg. CRS was reported in 77% of patients and was predominantly associated with the 1st or 2nd dose. CRS prophylaxis included the use of dexamethasone and 43% received tocilizumab as treatment. Overall across the doses, the response rate was 43%; however for the 9 patients treated with 10mg, 8 (89%) responded. MRD negative cases were observed and whilst the data remains immature, some durable responses were observed.

TCE abstracts opinion: This is a very exciting class of agents under development for myeloma and other cancers. There are a number of different TCE structures and platforms under investigation; however, it is yet unclear if these have any clinical advantage in terms of efficacy or tolerability. The major attraction with this class is the ability to treat patients without the need for leukapheresis and manufacturing that is required for CAR-T cells. In addition, CRS and neurotoxicity appears to be tolerable and manageable with dexamethasone prophylaxis and step-up dosing. The long-term durability of response will be very important.

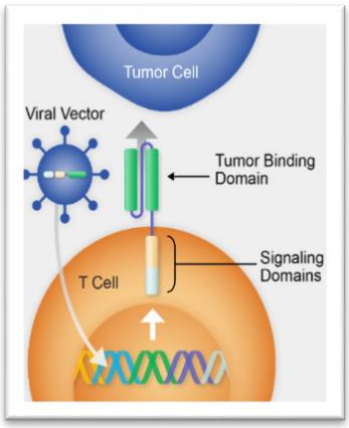
3. CAR-T cells

A number of CAR-T cells are currently under evaluation for myeloma. The 2 most advanced programs had updates reported at EHA. Both have breakthrough designation from the FDA due to impressive phase 1 results. Again, many of the CAR-T cells have been designed to target BCMA, although a number of new targets are now under evaluation (watch this space!).

(S209) IDECABTAGENE VICLEUCEL (IDE-CEL; BB2121), A BCMA-TARGETED CAR T CELL THERAPY, IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA: INITIAL KARMMA RESULTS

This is the results of the phase 2 trial of Ide-cel, a BCMA autologous CAR-T cell. The phase 1 study (CRB-401) reported an overall response rate of 85% and a median PFF of 11.8 months. This trial was for relapsed patients that had ≥3 prior lines and had been exposed to an IMiD, proteasome inhibitor and a CD38 antibody. The primary endpoint was the overall response rate. 128 patients were treated at a median age of 61 (33-78), of which 39% had EMD. They had a median of 6 (3-16) prior lines and 84% were triple refractory, 26% penta-refectory and all were refractory to their last line. Most patients required bridging therapy. The overall response rate was 73%, and 82% for the 54 patients

treated at the highest cell dose ($450x10^6$). MRD negative CR was reported in 26% overall, 28% at the highest cell dose. Of note responses were observed in patients with EMD and high risk cytogenetics.

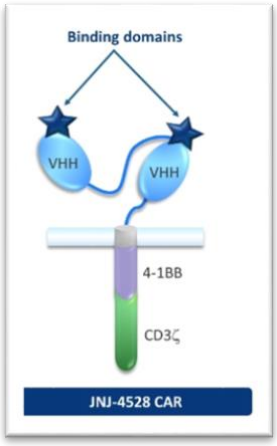


Greater CAR-T expansion was associated with a longer PFS. The median duration of response was 10.7m overall and 11.3m at the $450x10^6$ cell dose. Those achieving CR had a duration of response of 19m. Overall, the median PFS was 8.8m, and 12m at $450x10^6$ cells. Again, those achieving CR had the longest PFS (20m). CRS was observed in 84%, with few ≥ grade 3 events. Tocilizumab was used in 52% of patients. Neurotoxicity was reported in 18% of patients with ≤6% grade 3 events.

Also, Da-Via et al. abstract EP883 demonstrated that biallelic deletion of chromosome 16p encompassing the BCMA locus may be an intrinsic resistance mechanism to BCMA-directed CAR T in multiple myeloma.

(EP926) TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA WITH JNJ-4528, A B-CELL MATURATION ANTIGEN (BCMA)-DIRECTED CHIMERIC ANTIGEN RECEPTOR (CAR)-T CELL THERAPY: UPDATE OF PHASE 1B RESULTS FROM CARTITUDE-1

This was an update of the phase 1 results reported at ASH 2019. JNJ-4528 has 2 BCMA-targeting domains and a 4-1B co-stimulatory domain and was investigated for patients that had ≥3 prior lines including PI, IMiD and anti-CD38/ or were double refractory. The median age was 60 (50-75) and had a median of 5 (3-18) prior lines. 86% were triple refractory and almost all (97%) were refractory to their last line. CRS was observed in almost all patients (93%, 7% had ≥grade 3 events) at a median of 7 days from infusion. 79% of patients were given tocilizumab. Neurotoxicity (ICANS) was seen in 10% with only 1 grade 3 event. The overall response rate was high at 100%, with 97% achieving ≥VGPR. Of those that were in CR and had a MRD result, 81% were negative at 10^{-5}. The 9 month PFS rate was 86% which gives an idea of the durability of response.



CAR-T cell abstracts opinion: The response rates and depth of response including MRD negativity continues to be very high with CAR-T cell therapy. This is particularly impressive in such heavily pre-treated refractory populations. The expected toxicities of CRS and ICANS appear to be reasonably managed as experience grows in specialist centres with the use of tocilizumab and other agents. The major challenge remains the durability of response, with the phase 2 KarMMa trial reporting a median PFS of 12 months at the highest cell dose with no plateau. The Cartitude trial data is still too immature to make any meaningful comparisons. Nevertheless, CAR-T cells still have significant potential and are likely to produce more durable responses in less heavily pre-treated patients. A number of clinical trials are ongoing at earlier relapses and these results are eagerly awaited.