Conference report – 22nd Annual Meeting of the IMS (Toronto 2025)

I am very grateful to the UK Myeloma Society & the generosity of Pfizer for the travel bursary which allowed me to attend the International Myeloma Society conference in Toronto. Almost as soon as I left Toronto airport, the bus passed a giant billboard advertising BLENREP (Belantamab) on the side of the motorway, and so the tone was set!

The conference was held in the vast Metro Toronto Conference Centre, nestled just underneath the iconic spike of the CN tower, which looks out over the expanse of Lake Ontario. Signs for the IMS quite literally hung from the lampposts around the city, and the conference had an attendance of over 3,000 delegates from all over the world. As you can imagine, it took an impressively cavernous hall to seat that many people, and the exhibition space was equally as huge, with interactive stalls from all the big drug companies.

The keynote speech was given by Professor Tak Mak, a Toronto based scientist whose group had recently been focussing on the role of gamma/delta T-cells, an MHC class 1 independent subset of T-cells which are of particular interest as an off-the-shelf therapy option (in contrast to CAR-T, which uses classical MHC restricted alpha/beta T-cells). His group were able to demonstrate that the presence of tumour reactive gamma/delta T-cells predicted superior response to antibody-drug conjugates (ie. Belantamab). By looking at the RNA sequencing of B and T-cells during Belantamab treatment, they showed that responders had granzyme B positive gamma/delta T-cells, which were absent in non-responders. These granzyme B positive gamma/delta and CD8+ T-cells also did not demonstrate any of the usual markers indicative of T-cell exhaustion, exhaustion being the process which is thought to underlie at least some of the loss of efficacy in bispecific and CAR-T therapies. This class of cells and our ability to understand their role clearly could hold significant for future therapeutic avenues.

The first core topic of the conference was precursor disease. In terms of risk stratification, Mehmet Samur presented data showing that there is a relatively stable clonal structure when comparing patients at a Smouldering Multiple Myeloma stage with when they go on and progress to frank Multiple Myeloma – in other words, targeting the clone at an early stage probably targets more or less the same clone as at an MM stage. However it also identified that there are a series of key genomic changes within those clones that then act as drivers for conversion from SMM to MM (GSS, NRAS, gain 1q, Chr 8CNAs and focal loss), which, when combined with conventional 20/2/20 criteria, give a more accurate composite predictor of who the high risk SMM patients might be when compared with using genomic risk or 20/2/20 alone.

Sigurdur Kristinsson gave a presentation about the use of iStopMM, a new calculator for risk stratifying MGUS patients based on data from an Icelandic cohort, that predicts the

likelihood of having X% plasma cells in the bone marrow based on the parameters entered. This free online tool can be used to help frame discussions with patients eg. around timing of initial bone marrow, and is already available for use.

The second core topic was on risk adapted management. A lot of it centred around the concept of 'functional high risk' patients – these are patients who are not high risk by current scoring systems but nonetheless go on to progress significantly faster than expected, relapsing within 12-18 months of first line treatment. Depending on the study being looked at, 30-50% of such patients do not have high risk cytogenetics at presentation (in other words they are a substantial group), and Faith Davies discussed whether there might be a role for molecular mutation detection for these patients. Martin Kaiser's group have produced a paper showing that applying the new IMWG/IMS criteria (from June 2025) plus a gene expression profile looking for high risk genes was able to correctly identify almost all of a group of 25 patients who were ultimately found to be functionally high risk.

Aging was also discussed – a Dutch group has profiled the T cell repertoire of younger and older patients – older patients tend to have a more senescent, activated T cell profile - and showed that having signs of immune senescence correlated with worse outcomes to front line treatments compared with having a relatively young 'immune clock'. This was followed by a discussion about treating frail patients, and the need to incorporate this as a dynamic assessment tool at different points throughout treatment – the majority of the audience reported using the IMWG frailty index.
The role of MRD was also mentioned – for example patients who are high risk and fail to achieve MRD negativity have a worse prognosis, and this may have a role in helping make treatment decisions eg. for standard risk patients who wish to take a treatment break - although it was acknowledged that many of us around the world (including in the UK) do not have ready access to MRD, and that lack of access to MRD testing outside of academic study settings is currently the biggest barrier to actual use of MRD in clinical practice.

Core session 3 was on immunotherapy, and dwelt largely on the topic of T cell exhaustion; chronic stimulation of T cells can cause a state of exhaustion in which proliferative capacity and cytotoxic ability are both impaired, with up-regulation of exhaustion markers such as PD1, TOX and T1M. This results in poor anti-tumour activity and increased susceptibility to infections. Data was presented which showed that patients with a lower % of exhausted phenotype CD8+ T cells had a higher progression-free survival rate. All of this is particularly relevant given the increased role of bispecific antibody based treatments for myeloma.

One potential way of limiting T cell exhaustion may be through the use of CelMods such

as Mezigdomide, Iberdomide, Lenalinomide and Pomalidomide, which bind to cereblon with high affinity (100%, 50%, 25% and 20% respectively) and cause protein degradation of transcription factors such as Ikaros and Aiolos. Exhausted T cells have been showed to have high activity of Ikaros, which shuts down binding sites which are needed for T cell activation, and so contributes to the exhausted phenotype. Degradation of Ikaros via a CelMod therefore may have a role in preventing the exhausted phenotype.
IL-2 secretion has also been shown to be higher in T cells that have been treated with the CelMods Mezigdomide/Iberdomide, which seems to improve T cell stimulation and traffic into tumour.
The use of CelMods to reduce exhaustion was proposed to have multiple potential applications, not only alongside the use of bispecific antibody treatments but also eg. in apheresis pre-CAR-T to improve the quality of T cells harvested. In terms of clinical evidence, one study of Iberdomide maintenance post-ASCT showed higher rates of MRD negativity conversion and responses compared with Lenalidomide maintenance post-ASCT (corresponding with known greater efficacy of Iberdomide vs Lenalidomide on Cereblon).
The intensity of bispecific antibody treatment and its relationship with exhaustion was also discussed, the argument being that intermittent exposure may well be theoretically superior to more intense/continuous exposure, on the basis that less constant stimulation of T cells minimises the development of T cell exhaustion. In turn less frequent dosing therefore ought to (perhaps counter-intuitively) improve T cell efficacy.

Paola Neri presented some interesting data on BCMA resistance – they have found that mutations in different parts of the extracellular domain of BCMA may mean that one BCMA targeted bispecific can be more effective than another. These mutations appear to be acquired and selected for during immunotherapy rather than pre-existing, which means there is a theoretical argument for switching to a different BCMA targeted therapy at the point these mutations start to arise (although we of course do not have access to this testing). Similar to BCMA, there is evidence showing a high incidence of GPRC5D mutations post-exposure to Talquetamab, including through epigenetic silencing. Antigen escape appears to be the major cause of acquired resistance to T cell therapy.
The clinical implications of these findings might be baseline screening for BCMA/GPRC5D mutations using genomic based methods and then surveillance for new mutations. It may also support more limited duration of T cell engager therapy, and that dual targeting or sequencing approaches may be helpful. Additionally there may be a role for developing T cell engagers with high avidity which can bind to multiple target epitopes.

Highlights from the Late Breaking Abstract session included a presentation from Adam Cohen who presented the preliminary safety and efficacy data from the Phase 2 Study of Cevostamab consolidation following BCMA CAR T Cell Therapy. This included 27

patients (5 with EMD) and showed that pre-Cevostamab 63% of patients were in a CR, with 93% subsequently in CR at one year, with no DLTs.

Core session 4 covered treatment of relapse within 1-3 lines of therapy, and in particular whether CAR-T and bispecific options ought to be brought forward. Amrita Krishnan spoke about the use of immunotherapy versus conventional therapy at first relapse and made the point that although we are familiar with conventional chemotherapy and its predictable largely reversible side effect, we have to remember that some patients have very aggressive disease and that treatment for such patients may need to be more of a 'sprint' than a marathon with 'best' treatment given earlier on - CAR-T in particular showing significant advantages in terms of PFS in the data from Cartitude4, followed by bispecific antibodies. Data from trials where patients have had CAR-T followed by bispecific antibodies and vice versa seem to show that the optimal order is CAR-T first, as outcomes from CAR-T post-BsAbs are worse. In terms of when to treat, PFS appears to be better when patients are treated at biochemical relapse than at symptomatic relapse.
Cyrille Touzeau spoke about whether lines of therapy should still be used to define treatment pathways in multiple myeloma and made the point that these mainly relate to regulatory approvals rather than being an actual proxy for refractoriness. For example even though patients may have had similar or more numbers of lines of treatment when we look at trial entry, they may still not necessarily even have been triple class exposed – in the KARMMA trial for Idecel patients had a median of 6 prior lines of therapy with 84% documented as triple class refractory, whereas in KARMMA 3 the median lines of therapy was far fewer at 3, but 65% were already triple class refractory. She argued that we should prioritise refractoriness to available therapies rather than pure number of lines of therapy.

There were of course many, many other very interesting talks, but those were the main highlights I jotted down from each of the major sessions. At some point during proceedings, on the Wednesday lunchtime, I also had the opportunity to present my poster on CMV reactivations in myeloma patients who had been treated with BCMA-targeted bispecific antibodies. The social highlight of the conference was of course the President's dinner which was held on the final night at a venue called Casa Loma. Anybody who has previously been to Toronto may recognise this from the tourist map… but for anybody who has never been suffice to say it is the Disney-esque mansion of a 1900s Canadian millionaire, built in the style of a gothic castle, and proved a very impressive venue for the final dinner! Complete with a jazz swing band and limitless sushi bar, we all had a brilliant final evening celebrating the achievements of the great and good in myeloma.

In short I had a really fantastic time, learnt a great deal from attending the conference, and have come back to the UK feeling very inspired and positive - there is excellent work

going on, continuing to advance our understanding of myeloma, and in doing so helping extend and improve the lives of our patients.

Thanks again to the UKMS for giving me the opportunity to attend!

Alice