Review of the 20th International Myeloma Society Annual Meeting
Athens 27th-30th September 2023

Dr Daniel Hughes, Myeloma clinical research fellow, UCL Cancer Institute

I am most grateful to the UK Myeloma Society and Amgen for awarding me a travel bursary to attend the International Myeloma Society Annual Meeting for the first time. This was an excellent experience which allowed for learning from and networking with colleagues and experts in myeloma from around the world. I gained new insights from clinical and scientific presentations and further encouragement for ongoing academic work in the field.

During the meeting, I was given the opportunity to present my poster – characterising risk and biology of smouldering myeloma for early detection of symptomatic myeloma: data from the UK COSMOS study. The COSMOS study has been running in the UK since 2021 enrolling patients with previous history, newly diagnosed or suspected smouldering myeloma (SMM). I was pleased to present updated baseline characteristics and baseline clinical and immune correlations as well as to briefly introduce ongoing and planned outputs from the study.

Myeloma precursors

At the meeting the MSKCC group presented a poster evaluating the effect of dynamic change in paraprotein and serum free light chains during follow-up of smouldering myeloma (SMM) and the associated risk of progression. As expected, increasing baseline paraprotein and serum free light chains associated with increased risk of progression. Change in the free light chain ratio from baseline to one year was also associated with increased risk of progression with those in the highest quintile of rise (>55% increase) showing a hazard ratio of 2 (95%CI 1.1-3.8) compared with those in the lowest quintile. For those in the second highest quintile (17-55% increase) hazard ratio was 1.8 (95%CI 0.9-3.3). Rise in paraprotein (>30g/L increase) associated with HR 2.9 (95%CI 1.6-5.4) compared with the lowest quintile. Similar data was presented by Dr Werly from the Heidelberg group with evolving paraprotein (>20g/L and >10% rise in 12m) or free light chains (>25% and >50mg/L rise) were associated with HR for progression of 5 and 3.7 respectively, using either/or the hazard ratio increased further to 6.4. Incorporation of this combined definition of evolving disease to the 20-2-20 model increased C-statistic from 0.75 to 0.78 (although non-significant) and for the IMWG model increased C-statistic from 0.75 to 0.81 (p=0.014). Further validation is required but demonstrates the importance of dynamic change in light chains in predicting progression in SMM.

Also examining precursor conditions Dr Lightbody from the Ghobrial group at DFCI presented a poster on their single cell RNA and V(D)J sequencing of bone marrow and circulating tumour cells (CTCs) in predominantly smouldering patients. Circulating malignant plasma cells showed exact matched VDJ sequences to bone marrow malignant plasma cells and their clonality could be used to determined malignant nature. CTCs as a percentage of total plasma cells increased with increasing disease stage (from MGUS through low-risk SMM to high-risk SMM and on to MM) and showed moderate but imperfect correlation with clinical bone marrow infiltration. CTCs as a percentage of total plasma cells also increased in some cytogenetic groups (increased in t(4;14) and t(14;16) as well as in amp(1q) and del(13q)), and with increased cell cycling in the bone marrow. Overall, CTCs were less likely to be cycling that bone marrow plasma cells but the proportion of cycling CTCs increased with disease stage (MGUS-SMM-MM) Taken together these suggest that bone marrow infiltration is not the only factor influencing CTCs and that additional features may aid in prognosis in SMM.

Dr Dhodapkar, from Emory University, gave a talk on the early events in myeloma pathogenesis including the role of chronic B-cell activation and immune dysfunction. Highlighting the role of chronic B-cell activation and risk of monoclonal gammopathies in Gaucher disease his lab has examined the role of chronic stimulation from the gut microbiome showing that clonal immunoglobulin can be found that binds gut microbes. In pilot studies of gut selective antibiotics, the number of these bacteria can be reduced and this associates with a significant reduction in inflammatory cytokines, especially interferon. They are currently working on validation in mouse models. In an oral abstract Laura Cogrossi, from San Raffaele Scientific Instiute in Italy, presented work using *P.melaninognica* probiotic therapy in combination with anti-PD1L1 therapy in mouse models of MM and SMM based on previous work showing that this gut commensal was associated with lower Th17 expansion and reduced myeloma progression. They showed increased efficacy of anti-PDL1 therapy in limiting Th17 expansion

and delayed progression from SMM to MM in the Vk*MYC mice suggesting potential for therapy directed at the microbiome in delaying progression in smouldering myeloma.

Dr Medina-Herrera, from the GEM-PETHEMA group, presented genomic profiling data of high-risk smouldering myeloma (HRSMM) patients treated with a curative strategy on the GEM-CESAR trial (6xKRd induction, ASCT, 2xKRd consolidation, Rd maintenance for two years). As previously reported the genomic profile (single nucleotide variants and translocations) was similar between HRSMM and that seen in NDMM patients. They identified a population of ultra-high risk (UHR) patients (meeting IMWG 2014 SLiM criteria) with free light chain ratio >100 that were enriched in *TRAF3* mutations and had superior outcomes (5y biologic PFS 100% versus 40% in UHR patients with wild-type *TRAF3*). The association between *TRAF3* mutations and FLC ratio >100 was seen also in the CoMMpass dataset of NDMM patients as was association with improved PFS. Looking at known SMM genetic factors associated with progression they found no association between t(4;14), *NRAS/KRAS* mutations, DNA repair pathway mutations and biological PFS on treatment but found that t(4;14) with *FGFR3* mutations, and *NRAS* mutations did associated with biological PFS on treatment however, accepting small numbers in this group compared to prior studies. Further work sequencing progressors on treatment may provide critical information on potential clonal evolution seen with therapeutic pressure in smouldering myeloma which may impact on treatment on progression.

Newly diagnosed myeloma

Interim results on sustained MRD negativity from the phase II GMMG-CONCEPT trial were presented by Dr Leydpolt. Patient with high-risk MM (ISS II or III plus any of: del(17p), t(4;14), t(14;16), or amp(1q)) were treated with Isa-KRd induction. 82% of transplant eligible (TE) patients and 69% on non-transplant eligible (NTE) patients achieved MRD negativity at any timepoint with 63% of TE and 46% of NTE patients sustaining this for ≥1 year. Three markers were associated with impaired survival – elevated LDH<, ≥2 high-risk cytogenetic abnormalities, and del(17p). Achievement of MRD negativity at any timepoint conferred prognostic benefit with a hazard ratio of 0.118. These data show deep responses with Isa-KRd in high-risk patients regardless of transplant status and the promise of alternative anti-CD38 agents in quadruplet induction regimens.

Dr Maclachlan, from MSKCC, presented on the genomic characterisation of response or resistance to upfront daratumumab-based quadruplet therapies. Genomic features of patients undergoing DKRd induction in the Manhattan trial showed novel genetic features associated with response including deletion of *RPL5, IKZF3,* and APOBEC mutational signature. 262 patients treated with either carfilzomib or bortezomib with lenalidomide as the IMiD with a median follow-up of 1.4 years. Patient samples underwent various genomic investigations including targeted sequencing in 84 patients and WGS in 57 patients. ISS poorly discriminatory for PFS but genomic features remain prognostic with quadruplet induction (i.e. *MMSET, MAF, MAFB, MYC* translocations, gain(1q)) for PFS. Similar deletions as those in the Manhattan study were seen to have inferior prognosis as was increased APOBEC activity and a trend for the same with chromothripsis. A combination of genetic features appears important to discriminate patients with poor prognosis (PFS <18m) with induction quadruplets (not discriminated with ISS, R-ISS, nor R2-ISS).

Jian Cui, from Tianjin Institute of medical sciences, presented data from single-cell RNA sequencing of MRD persisting clones to identify resistance pathways and genomic evolution with treatment. They observed three patterns of transcriptional evolution post-treatment with transcriptional elimination in those attaining MRD negativity while those with residual MRD showed either transcriptional stability (with the same major clone remaining dominant) or transcriptional switching (with a dominant clone becoming minor and a previously minor clone becoming more dominant). In resistant clones which persistent with treatment pathaway analysis revealed upregulation of the unfolded protein response, hypoxia and cell-cycle pathways. In selected clones that gained a growth advantage under therapeutic pressure pathways upregulated included NF-κB signalling and anti-apoptotic pathways.

Dr Malandrakis, from University of Athens, presented data on stopping lenalidomide in patients with sustained bone marrow and imaging MRD negative patients. Dr Pawlyn has previously presented data (ASH, 2022) from the Myeloma XI trial showing potential loss of benefit from lenalidomide maintenance after three years in those attaining MRD negativity. In this study those patients who were MDR negative for at least 18 months and in stringent complete response who had received at least 36 months of maintenance lenalidomide post-transplant were enrolled to stop treatment. 42 patients stopped treatment at a median 53m from start of maintenance, most were ISS I and only 29% had high-risk cytogenetic abnormalities. Of these 5 patients converted to MRD

positive and restarted lenalidomide, of these one progressed and one died for reasons unrelated to lenalidomide. They conclude that sustained MRD negativity seems a reasonable marker to guide decisions on stopping lenalidomide in these patients and close surveillance can detect relapse in MRD although longer-term and randomised studies are required. Of note, 101 patients in total achieved MRD negativity at some point and of these 14 converted to MRD positivity of which 9 progressed suggesting intensification of treatment may be required for patients that have MRD resurgence on lenalidomide maintenance.

Relapsed-refractory myeloma

Philppe Moreau presented the final overall survival results from the IKEMA trial of Isa-Kd versus Kd in RRMM (1-3 prior lines (median 2), no prior carfilzomib and not refractory to anti-CD38 antibody therapy). The final PFS analysis as reported previously showed median PFS of 35.7 months in the Isa-Kd arm versus 19.2 months in the Kd arm (HR 0.58, 95%CI 0.42-0.79). After median follow-up of 56.61 months median OS 50.6 months in the Kd arm versus not reached in the Isa-Kd arm, with extrapolation estimated median PFS in the Isa-Kd arm is 63m (95%CI 59-69m). This trend for improved OS held across groups in the isatuximab arm. Looking at subsequent therapy fewer patients in the Isa-Kd arm received further anti-CD38 therapy and more received anti-BCMA therapy with belantomab. There were no new safety concerns from previous final PFS analysis. Overall, Isa-Kd is a good option for RRMM patients.

Maria-Victoria Mateos presented the primary analysis from the phase III CANOVA trial of venetoclax-dexamethasone (VenD) versus pomalidomide-dexamethasone (PomD) in patients with relapsed/refractory (≥2 prior lines including prior PI and refractory to lenalidomide) t(11;14) myeloma. Venetoclax was given at a dose of 800mg daily (d1-28) with pomalidomide at a dose of 4mg daily (d1-21) of a 28d cycle in combination with dexamethasone 40mg weekly in both arms. Patients were well-matched for baseline characteristics although patients randomised to VenD were slightly more treated (median 3 v 2 lines of prior therapy), in both groups around one-third were triple refractory). Overall response rate was 62% (39% ≥VGPR) for VenD compared with 35% (14% ≥VGPR) for PomD with MRD negativity at 10^{-5} in 8% and 0% respectively. At a median follow-up of 24.9m for VenD and 25.6m for PomD median PFS was 9.9 months for VenD and 5.8 months for PomD (HR 0.823, 95%CI 0.596-1.136). Notably more patients in the PomD arm discontinued treatment for reasons other than progressive disease and commenced subsequent therapy prior to meeting IMWG progressive disease (PD) criteria. In a post-hoc sensitivity analysis with censoring patients at time of subsequent therapy if not meeting IMWG PD criteria median PFS was 9.4m in the VenD arm and 4.0 months in the PomD arm (HR 0.651, 95%CI 0.487-0.870). Similar benefit in time to next treatment was seen with VenD. Interim overall survival analysis showed median OS of 32.4m in the VenD arm versus 24.5m in the PomD arm (HR 0.697, 95%CI 0.471-1.02) with further analysis following more events planned. Overall, rates of adverse events were similar with slightly greater numbers of G3/4 events with PomD (83 v 67%). Laboratory tumour lysis syndrome (TLS) was seen in 4 patients in the VenD arm and 2 patients in the PomD arm with no clinical TLS observed. Death due to infection on treatment was seen in 7 patients on VenD and no patients on PomD with no apparent trends in timing of infection nor in pathogen type. Venetoclax appears effective in t(11;14) myeloma but has an important side effect profile and further data on overall survival is needed.

Immunotherapy

There were, of course, numerous abstracts in the field of immunotherapy including many on real world data and on factors impacting on success. Cilta-cel is licenced for patients with RRMM after four prior lines. Earlier treatment is being trailed and Dr Manier, from Universitaire de Lille presented data in a prespecified population of the CARTITUDE-4 trial (Cilta-cel versus physicians' choice of standard of care, in len-refractory patients with 1-3 prior lines of therapy and ECOG ≤1). At a median follow-up of 15.9 months 208 patients were randomised to cilta-cel and 211 to standard-of-care (SOC) with balance in baseline characteristics. Cilta-cel significantly improved PFS versus SOC in all subgroups and regardless of comparator treatment (PVd or DPd) increasing interest in early therapy with CAR T-cell therapies.

Dr Harrison, from the Peter MacCallum Cancer Centre in Melbourne, presented results from an early phase trial of forimtamig a GPRC5D-directed bispecific T-cell engager in patients who had received ≥1 prior line of therapy and were refractory to a PI and an IMiD. Initial results of forimtamig presented at ASH 2022 showed deep and durable responses. In this analysis in high-risk patients (age ≥65years, >4 prior lines, triple-class or penta-class refractory, prior BCMA-directed therapy, high-risk cytogenetics, ISS III, extramedullary disease). Overall response rate was 67% with similar responses across groups. Further dose-finding studies are planned and there is clear ongoing interest in novel immunotherapies and combination treatments of immunotherapy.

In summary, this was an excellent programme of presentations and abstracts with great opportunities to meet colleagues involved in myeloma research. Once more I would like to sincerely thank the UK Myeloma Society and Amgen for this valued opportunity to attend this meeting.