Aims: Using our large dataset from uniformly treated newly diagnosed patients as well as relapsed patient samples, we investigated the somatic alterations in the non coding genome to identify critical hotspots. 

Methods: We performed a deep (average coverage > 80X) whole genome sequencing (WGS) on 376 MM samples (240 newly diagnosed, 52 first relapse and 84 mrMM) as well as RNAseq to comprehensively analyze recurrent somatic alterations in non-coding regions. Results: We detected median 9,649 (Range 3,194–126,935) mutations and indels per sample with overall more than 4 M total somatic mutations. Introns (> 2.5 mutations/PER Mb) and intergenic regions (> 3 mutations/PER Mb) had significantly higher number of mutations per megabase compared to Exons (~2 mutations/PER Mb) (p < 1e-5). Mutations in coding regions in our data was similar to published whole exome sequencing studies with increase in several driver mutations at relapse. We observed 57 (range 7 - 376) structural variants (SVs) per sample with > 98% involving non-coding regions. We identified 48 SV hotspots that are targeting tumor suppressor genes or key regulatory elements such as TCF5 and TNFSF10 and these SVs were also associated with significantly altered expression of the target genes. We have detected two mutations in 1,500 single nucleotide variants targeting MAP3K14 and NFKB1 and driving the expressions of these genes. Our data showed that >80% of translocation breakpoints are in the close proximity of super enhancers and therefore Ig is not the only mechanism over express available genetic content. We detected 103 somatic CNAs in the non-coding genome of some of which are targeting 5’UTR and introns of BCL7A, BCL6, CD93, CCND1, PAX5. Some of these hotspots were correlated with disease outcome. We also observed that overall mutational load is also associated with disease outcome. We detected chromothripsis in ~25% of newly diagnosed samples; and katagous hotspots on chromosome 3q27-3q28 (24%), 11q13 (5.8%) and 12q24 (5.3%).

Summary/Conclusion: In conclusion, this deep large whole genome sequencing data from newly-diagnosed MM patients identifies a vast majority of non-coding mutations with potentially significant functional and biological role in MM. Our integrative approach using both WGS and RNA-seq data from the patients now provides us important tools to further characterize the impact of these mutations and develop opportunities for targeted therapeutics.

S120 CHRONOLOGY OF COPY NUMBER ALTERATIONS FROM PRECURSORS TO MULTIPLE MYELOMA: WHAT COMES FIRST?

A. Aktas Samur1, S. Minvielle2, M. Fulciniti3, R. Szalat3, M. Shammas4, F. Magrangeas5, P. Moreau6, M. Atta1, K. Anderson7, G. Parmigiani2, H. Ayala8, N. Mariani9, M. Actions targeting MAP3K14 and NFKB1 and driving the expressions of these genes. Our data showed that >80% of translocation breakpoints are in the close proximity of super enhancers and therefore Ig is not the only mechanism over express available genetic content. We detected 103 somatic CNAs in the non-coding genome of some of which are targeting 5’UTR and introns of BCL7A, BCL6, CD93, CCND1, PAX5. Some of these hotspots were correlated with disease outcome. We also observed that overall mutational load is also associated with disease outcome. We detected chromothripsis in ~25% of newly diagnosed samples; and katagous hotspots on chromosome 3q27-3q28 (24%), 11q13 (5.8%) and 12q24 (5.3%).

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S121 SINGLE-CELL CHARACTERIZATION OF THE MULTIPLE MYELOMA (MM) IMMUNE MICROENVIRONMENT IDENTIFIES CD27- T CELLS AS POTENTIAL SOURCE OF TUMOR-REACTIVE LYMPHOCYTES


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Background: The broad use of immunomodulatory drugs (IMiDs) and the breakthrough of novel immunotherapies in MM urge the optimization of immune monitoring for tailored treatments based on better prediction of patients’ response. For instance, current T cells immune monitoring is of limited value because the phenotype of tumor-reactive T cells is uncertain.

Aims: To characterize the MM immune microenvironment at the single-cell level and to identify clinically relevant subsets for effective immune monitoring.

Methods: We used a semi-automated pipeline to unveil full cellular diversity based on unbiased clustering, in a large flow cytometry dataset of 86 newly-diagnosed MM patients enrolled in the PETHEMA/GEM-2012MENO065 clinical trial, including evaluation at diagnosis, after induction with bortezomib, lenalidomide, dexamethasone (VRD), allogeneic transplant and VRD consolidation. Immunophenotyping was performed using the first 8-color combination (CD19, CD27, CD38, CD45, CD36, CD81, CD117, CD138) of the next-generation flow (NGF) panel for single cell validation. Results were modeled in an advanced 145 patient cohort followed for 2 years. We performed single cell RNA sequencing (10xGenomics).