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MAGNAZ trial - A prospective phase II study in patients with monoclonal gammopathy of unknown significance (MGUS) and anti-Myelin Associated Glycoprotein (MAG) Neuropathy and Zanubrutinib Treatment

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Introdcution: Polyneuropathy (PNP) associated with IgM monoclonal gammopathy (MGUS), also called IgM-related PNP, is mediated by the anti-neural effect of the M-protein component and is classified as one of the MGUS-related diseases. In around 70% of patients with IgM-related PNP anti-myelin associated glycoprotein (MAG) antibodies are detected. There is no established treatment for IgM-related PNP except anti-CD20 monoclonal antibody treatment with 30% or less clinical responses. There is increasing interest to use Bruton's tyrosine kinase (BTK) inhibitors, approved for the treatment of Waldenstrom Macroglobulinemia, for IgM-related PNP treatment but a formal study is currently lacking. We therefore designed a phase 2 clinical trial to investigate the effect of zanubrutinib, a next generation BTK inhibitor, combined with anti-CD20 monoclonal antibody treatment, in IgM-related PNP with anti MAG antibodies. The primary study endpoint is change from baseline in the Rasch-built Overall Disability Scale (RODS) for inflammatory neuropathies (iRODS) at the end of Cycle 12. The main secondary endpoint is to assess the safety of zanubrutinib treatment in IgM-related PNP as measured by CTCAE, version 5.0. **Methods:** Patients will be treated for a minimum of 6 cycles; patients experiencing hematological response continue until 12 cycles of treatment. All patients will be followed for the duration of 12 cycles for the primary endpoint analysis. Patients who have an anti MAG titer > 10.000 BTU, adequate hematological, renal and hepatic function tests, no hemorrhagic disorder and no New York Heart Association (NYHA) grade 3 or 4 cardiac disease can be included after signing informed consent. Explorative analysis will consist of Next Generation Sequencing of MYD88 and CXCR4 mutations after CD19 selection of the bone marrow aspirate at start. During study participation extensive neurological testing and serum IgM and anti MAG testing will be performed. In total 40 patients will be included and the MAGNAZ study expects to start in Q4 2021.

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AI-based models for the identification of critical genetic biomarkers to distinguish MM from MGUS using the WES data

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Background: Multiple Myeloma (MM) is preceded by the premalignant stage of Monoclonal Gammopathy of Undetermined Significance (MGUS) and therefore, it is important to identify the genetic factors responsible for progression of MGUS to MM. We have built machine learning (ML) models to identify pivotal genetic biomarkers that distinguish MM and MGUS. **Methods:** Tumor normal matched paired Whole Exome Sequencing (WES) data of 1174 patients of MM and 61 patients of MGUS were analyzed. The data were obtained from dbGaP (phs000748; phs000348), AIIMS, Delhi, India, and EGA (EGAD00001001901). Variants were identified using four variant callers, namely, MuSE, Mutect2, VarScan2, and Somatic-Sniper and; SNVs were annotated using ANNOVAR. Pooled genomic annotations obtained were analyzed to derive significantly mutated genes with 'dndscv' tool. Union of top ranked 250 significantly mutated genes from each variant caller yielded 1316 genes. For each gene, variant count and (maximum, mean, median, and standard deviation of) VAF and AD were used as features which were reduced by principal component analysis (PCA) and only top-3 principal components were selected for each gene. Next, 5 ML classifiers (random forest, decision tree, logistic regression, XGBoost, and SVM) were used to distinguish MM from MGUS. Imbalance of data (95% MM and 5% MGUS cases) was handled by the cost-sensitive loss function in the classifiers. Permutation based feature importance was carried out on top two performing models to infer the most significant features that were mapped back to genes to obtain the top ranking genes for MM and MGUS. **Results:** Cost-sensitive SVM outperformed the rest of the models in balanced accuracy, weighted F1-score, Mathews correlation coefficient (MCC), precision, recall and area under curve (AUC) with values 95.5%, 94.82%, 0.8162, 76.49%, 98.33% and 95.5%, respectively. Top ranking genes identified for MM were: HLA-DQB1 IRF1, MUC6, FGFR3, MUC4, HOXA1, ITPR3, HIST1H1E, MUC12, ITGA2, HLA-DQA2, HUWE1, IGLL5, HLA-DRB5, HLA-DQB2, ILK. Top ranking genes identified for MGUS were: MUC3A, HLA-A, HLA-C, IRF4, JAK1, HDAC2, HLA-DQA1, FRG1, HS6ST1, H2AFV, and HLA-DRB1. HLA-DQB1, IRF1, ITPR3, HOXA1, HIST1H1E, HUWE1, IGLL5, HIPK3, HLA-DQA2, HLA-DRB5, and ILK were found significant for MM; and HLA-A, HLA-C, IRF4, JAK1, HDAC2 HLA-DQA1, HS6ST1, H2AFV, and HLA-DRB1 were found significant for MGUS by the top two ML classifiers. All these genes were found significant in the literature for MM and MGUS. **Conclusion:** MGUS and MM share many common features such as genomic biomarkers, structural variants etc. with the difference of having less impact of mutations in MGUS. Thus, it is challenging to distinguish MM from MGUS. Here, we utilized ML classifiers to distinguish MM from MGUS. Our classifiers are able to identify the significant genes that are helpful in MM vs. MGUS classification that can lead to a better understanding of progression from MGUS to MM.