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Baseline laboratory characteristics of the UK RAINBOW trial cohort: phenotypic and genomic features.

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The RAINBOW study is a phase 2-3 trial assessing 'chemotherapy free' treatment as primary therapy for Waldenström's macroglobulinaemia (WM), with the aim to improve response outcome and durability and also, importantly, reduce toxicity for WM patients. This will be done using Ibrutinib in combination with rituximab (RI) as the experimental arm. As there is no agreed standard on first-line therapy for WM, the control arm is the current frontline treatment based on most recently published clinical trial results at time of trial design. The control arm therefore consists of rituximab, cyclophosphamide and dexamethasone (DCR), and is a therapeutic combination widely recommended by international consensus as appropriate treatment for first-line therapy for WM. Primary objectives of the trial are to assess the efficacy of RI and determine whether progression-free survival is improved with RI vs DCR. There are also two exploratory objectives related to laboratory characterisation of bone marrow and peripheral blood samples. These are to investigate the effect of disease defining mutations (mutations *MYD88 L265P* (and variants for those WT for L265P)) and disease modifying mutations (*CXCR4, ARID1A, BTK C481S, PLCγ2, CD79, TP53* and *CARD11*) on response and survival outcome for patients treated with RI or DRC and to investigate (quantitatively by flow cytometry) response in blood and bone marrow and correlate this with conventional IgM responses as well as traditional survival outcomes.

It is anticipated that the study will complete recruitment (n=148) in September 2024. Laboratory studies are being delivered by a single, centralised laboratory. Bone marrow aspirate and peripheral blood samples are scheduled for baseline/screening, end of randomised treatment and 1 year after completion of randomised treatment. Screening bone marrow and peripheral blood samples have been received for 154 patients to date, the majority of which fulfilled trial eligibility criteria and were randomised.

Flow cytometry has been performed to enumerate and characterise neoplastic B-cells and plasma cells in both bone marrow and peripheral blood samples, utilising a previously published assay which demonstrated that depletion of neoplastic B-cells below the limit of detection of the assay (0.004%) was associated with improved progression-free survival(1). The assay will again be used to assess post-treatment samples for residual neoplastic B-cells but has also been used to quantify circulating levels of disease, both at presentation and follow-up. B-cell selection has also been performed on the bone marrow aspirate samples to provide 'tumour only' material for DNA extraction and subsequent sequencing. High-throughput sequencing with a panel of 33 genes has been performed on the majority of patients (118 + 8 pending), with *MYD88 L265P* mutation demonstrated in 111/118 (94%). Other

recurrent mutations are also seen, including *CXCR4* (45/118, 45%), *ARID1A* (9/118, 8%) and *TP53* (5/118, 4%). Full baseline flow cytometry and sequencing results (including VAF) will be presented at the workshop.

1. Long-term outcomes by bone marrow B-cell depletion from the R2W trial of bortezomib with cyclophosphamide and rituximab in Waldenström macroglobulinaemia
de Tute R, Counsell N, et al. Leukemia 2024 Apr;38(4):822-828.