

Comparative study of minimal residual disease (MRD) in Waldenstrom macroglobulinaemia (WM): depletion of WM-phenotype B-cells assessed by flow cytometry and MYD88 L265P detection by digital droplet PCR

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Minimal residual disease (MRD) has been demonstrated as an independent predictor of survival outcomes in several mature B-cell malignancies, most notably myeloma and CLL. Rituximab-based regimens are widely used as primary therapy in WM and were included in both the R2W and RAINBOW UK trials. Many patients have excellent response durations to Rituximab-based treatment despite the apparent rarity of complete responses (CR). It is recognised that rituximab-based therapies can result in depletion of monoclonal B-cells but a persistence of CD20- plasma cells. This phenomenon can result in delayed serological responses and may also explain the low incidence of CR. Previous work by this group during the UK R2W trial has demonstrated flow cytometric assessment of bone marrow B-cell depletion is possible in WM and is an independent predictor of outcome. WM plasma cells cannot currently be assessed by flow cytometry as a WM-specific plasma cell phenotype has not been described, and therefore WM plasma cells cannot be reliably distinguished from normal plasma cells.

Droplet Digital PCR (ddPCR) is a DNA quantification technology that can provide absolute counts of target molecules with a specific molecular variant with high sensitivity. Several groups have assessed MYD88 L265P by ddPCR in the post-treatment setting for WM but published data showing the impact of molecular residual disease on progression-free survival (PFS) and particularly overall survival (OS) remains limited. It is possible that molecular based studies could demonstrate a residual molecular signal due to the residual plasma cell populations in a proportion of patients showing undetectable B-cells by flow cytometry. This could potentially lead to an inferior prediction of PFS in this setting. There has been limited work correlating molecular evidence of the MYD88 mutation with direct assessment of bone marrow and peripheral blood cellular burden by flow cytometry. It is possible that combining both these modalities may lead to a better understanding of the biological response to treatment and suggest which populations are best targeted by novel therapies.

The R2W and RAINBOW trials represent a cohort of 219 well-characterised patients, of which 95% of those assessed demonstrated the MYD88 L265P mutation at baseline. Alongside the previously reported B-cell flow cytometry assay, we have performed validation of a MYD88 L265P ddPCR assay to reach a sensitivity of 0.01%. Data is available on bone marrow aspirate and

peripheral blood samples collected at baseline, post 3 cycles of treatment and at 3 months following the end of therapy (EOT) for R2W. For the RAINBOW trial, timepoints for bone marrow aspirate and peripheral blood sample collection were end of randomised treatment and 1 year after completion of randomised treatment. Flow cytometric analysis to determine B-cell depletion was performed at all time points for both bone marrow aspirate and blood samples. This data will be presented for both trials, accompanied by MYD88 L265P ddPCR performed on DNA extracted from leucocytes from bone marrow aspirate or peripheral blood. The study aims to demonstrate the impact of both B-cell depletion and molecular evidence of residual disease on patient outcome.

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