Abstract ID: 2439307

Abstract Title: Marrow immune features are most informative of sustained MRD negative response in newly diagnosed standard risk TE patients: findings from the UK MRA RADAR study

Abstract Track: Myeloma Genomics and Microenvironment and Immune Profiling

Abstract Type: Translational

Authors: Emma J. Lyon[1], Stephen Henderson[1], Elise Rees[1], Amatta Mirandari[1], Annabel Laidler[1], Dipal Mehta, Jessica Kimber[1], Alice Lefever[1], Kara-Louise Royle[3], David A. Cairns[3], Ceri Bygrave[4], Guy Pratt[5], Rakesh Popat[6], Christopher Parrish[7], Gordon Cook[7], Mike A. Chapman[8], Martin Kaiser, Matthew W. Jenner, Eileen Boyle[1,6], Ruth De Tute[7], Sergio A. Quezada[1], Karthik Ramasamy[11], Lydia Lee[1,6], Kwee Yong[1,6].

[1] University College London, UCL Cancer Institute, London, United Kingdom, [2] St. Bartholomew's Hospital, London, United Kingdom, [3] Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom, [4] University Hospital of Wales, Cardiff, United Kingdom, [5] University of Birmingham, Birmingham, United Kingdom, [6] University College London Hospitals, London, United Kingdom, [7] Department of Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [8] University of Cambridge, Cambridge, United Kingdom, [9] The Institute of Cancer Research; The Royal Marsden Hospital, London, United Kingdom, [10] University Hospital Southampton, Southampton, United Kingdom, [11] University of Oxford, Oxford, United Kingdom.

Abstract Body

Introduction: Achieving sustained MRD negative (MRD-neg) response is a major determinant of survival outcomes, and is influenced by the intersection of disease, host and regimen related factors. We investigate the role of bone marrow (BM) immune profiles in MRD responses in standard risk (SR) patients on RADAR, utilising a modelling approach to integrate disease and clinical features.

Methods: RADAR is a multi-centre, risk-adapted phase II/III trial for NDMM eligible for ASCT. Standard risk (SR) is defined as < 2 of t(4;14), t(14;16), del(17p), 1q+, 1p-. SR patients received 4 cycles of bortezomib, lenalidomide, cyclophosphamide and dexamethasone (VRDc) followed by ASCT and MRD test (flow, 10^{-5}) at D100 and 15m post ASCT. MRD-neg patients at D100 receive isatuximab alone, while MRD-pos receive multi-drug consolidation and maintenance. The MRD-pos cohort comprise those who were MRD-pos at D100 post ASCT, plus MRD-neg pts who relapsed or were MRD-pos at 15m. MRD-neg cohort was MRD-neg at both D100 and15m.

Immune and CD138+ cells were analysed in fresh BM by flow, and 36 marker CyTOF lymphoid panel on thawed samples. We analysed baseline clinical, disease and immune features associated with sustained MRD-neg. We used an Elastic Net

penalised regression model with a 20/80 test/train split to model MRD prediction. The test set was tuned using 5-fold cross-validation repeated 20 times. Missing values were imputed, and numeric variables normalised within the tuning process. In practice tuning tended to collapse to a Ridge Regression as the best model.

Results: We studied 377 patients (median 61y, male 60%, white 86%;), MRD-pos=66%. Using a penalised logistic regression model, we predicted MRD outcome on holdout test data with ~70% accuracy. We found that clinical parameters such as B2M and paraprotein had little prognostic value for sustained MRD-neg, but Albumin had some predictive value (OR 1.23, binomial p-value 0.07). Among the immune biomarkers a higher fraction of myeloid cells (OR 0.7, p = 0.002) and CD4 cells (OR 0.77, p = 0.02) were associated with MRD-neg, while a higher CD8 (OR 1.29, p = 0.03) as well as double-negative (DN, CD4-CD8-) T-cells (OR 1.23, p = 0.1) were associated with MRD-pos response.

CyTOF analysis on 18 patients (MRD-pos=8, neg=10) resolved T cell states from naïve (CCR7+CD27+) to terminally differentiated (GzmB+CD57+) CD4+ and CD8+ cells. Consistent with our predictive model, CD4+ T-cells were enriched in MRD-neg patients, mainly driven by naïve (CD27+CD45RO-CCR7+) cells, while differentiated effectors (CD28+GzmB+) were enriched in MRD-pos (p=0.0031). MRD-pos was associated with terminally differentiated CD8 cells (GzmB+CD57+KLRG1+) and DN T cell clusters that are CD57+GzmB+, indicative of terminal differentiation.

Conclusion: At baseline and pre-treatment, variables indicative of the state of the patient's own immune system are the most informative of sustained MRD-neg response in SR patients receiving induction and ASCT.