What are the lessons learned for evaluating depth of response in myeloma?

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Today, over 500 publications focusing on minimal residual disease (MRD) testing in multiple myeloma are available in www.pubmed.gov. In mid-2016, the International Myeloma Working Group (IMWG) published updated criteria for the assessment of treatment response in patients with multiple myeloma. The updated 2016 IMWG response criteria defines MRD negativity the following way: (1) the patient has to be in clinical complete response (CR); (2) a bone marrow aspirate test has to show absence of aberrant clonal plasma ruled out by an assay with a minimum sensitivity of 1 in 10^5 nucleated cells or higher (i.e. 10^{-5} sensitivity). By the 2016 IMWG response criteria, permitted assays to define MRD negativity include either multi-parametric flow cytometry or next generation sequencing (NGS); multi-parametric flow cytometry can be done by the EuroFlow method or other validated equivalent methods; NGS can be done by the LymphoSIGHT method or other validated equivalent methods.

The 2016 IMWG response criteria are the first uniform MRD response criteria for multiple myeloma. They are timely and support the development of modern, effective combination therapy for patients with multiple myeloma. Importantly, recent meta-analysis shows that MRD negativity is associated with longer progression-free survival and overall survival in multiple myeloma. Furthermore, ongoing randomized clinical trials suggest that reaching MRD negativity is more important than the therapy given in order to become MRD negative. Currently, several ongoing clinical trials include MRD testing in parallel with conventional clinical end-points to correlate MRD negativity and clinical outcomes.

Based on these facts, the anticipation is that MRD negativity (eventually) will become a valid regulatory end-point for drug approval. Clearly, when MRD becomes a regulatory end-point for drug approval in multiple myeloma, the speed of drug development will increase significantly and it will give patients access to new drugs faster. Remaining important issues to address before MRD will become a regulator end-point include, for example: the value of MRD negativity in the setting of newly diagnosed versus relapsed multiple myeloma; the value of MRD negativity in relation to disease biology (e.g. high-risk versus standard-risk myeloma); and sustained MRD negativity.

This presentation will review and discuss current insights on MRD testing in the setting of standard of care, clinical trials and also regulatory aspects with regards to drug approval. Also future directions will be included. Focus will be to integrate cutting-edge research and clinical data with the aim to deliver clinically useful information for treating physicians.