Minimal Residual Disease

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- The challenge with MRD as an endpoint is trying to quantify a very complex biological event. The vast majority of data we have collected over the course of the last 20 years is confounded by treatment advances in the field.

- MRD positivity in PB correlates with MRD assessments in BM. Those patients could be spared painful BM biopsies.

- All hospitals at the present time could be expected to assess MRD at 10^{-4}, but 10^{-5} should be the target. MRD 10^{-6} is a better goal in the research setting. The oncology working party has agreed so far on a cut-off of 10^{-5}, which seems to be acceptable to the EMA.

- Regulatory agencies are not prescribing a specific technology, but whichever is used has to be standardized and validated. The EMA recommends using 2 different assays in the same trial.

- Currently, regulators are considering MRD only in the context of CR. This might need some further discussions, as does the need to exclude extramedullary disease.

- In the USA, MRD is accepted as a prognostic tool, and in the setting of regulation, for patient stratification and possibly for patient selection and risk-based treatment assignments, but not yet MRD as a surrogate endpoint.

- MRD negativity is predictive of long-term survival outcomes with consistent hazard ratios, reducing the risk of progression or death by half. The meta-analysis of MRD data across trials had large patient numbers (among patients in CR, 306 patients were MRD-negative and 178 were MRD-positive).

- There are large datasets of MRD data in the UK, Spain, France and other countries from the European Myeloma Network.

- The role of MRD assessment with CAR T-cell therapies, where the treatment goal will likely be cure, remains to be elucidated.

- The role of MRD assessment in patients with high cytogenetic-risk MM requires more data.

- There is a room for a pre-competitive initiative between the industry, academia, and regulators to align efforts in answering some of the key questions around MRD surrogacy. There is already a consortium in place led by the Mayo Clinic aiming to gather available MRD data.

- As there are a number of challenges to retrospective approaches (i.e. inconsistency in data collection), another approach can be to address the regulatory requirements for MRD surrogacy in prospective studies. An important prerequisite for this approach is that there are good definitions in place.

- It is unclear whether HTAs would accept MRD as an endpoint.