EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 September 2021
EMA/49401/2022
CHMP

Reflection paper on the use of measurable residual disease as a clinical endpoint in multiple myeloma studies

Draft agreed by Oncology Working Party	23 September 2021
Adopted by CHMP	4 October 2021

Keywords	***Measurable residual disease, minimal residual disease, MRD, multiple myeloma***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction and problem statement

Multiple myeloma (MM) accounts for 1% of all cancers and 10% of all haematological malignancies. The incidence in Europe is 4.5–6.0/100 000/year with a median age at diagnosis of 72 years; the mortality is 4.1/100000/year.

The outcome of patients with MM has vastly improved over the last 15 years with the approval of more effective novel agents with different mechanisms of action. Longer remissions associated with new treatments have prompted research in early efficacy endpoints to speed up drug development.

In 2016, the International Myeloma Working Group (IMWG) defined new categories of response to treatment based on the detection of residual tumour cells by high-sensitivity techniques. Currently available data seem to suggest that the depth of response in terms of minimal residual disease (MRD) correlates with clinical outcome. There are a large number of studies, the majority in the newly diagnosed setting, showing that among patients achieving a complete response (CR), those with detectable MRD seem to have shorter progression free survival (PFS) and overall survival (OS) compared to those with undetectable MRD (MRD-negativity). Given this background, it is important to assess if the strength of the association between MRD-negativity and true clinical endpoints in predicting treatment effects is generally sufficiently robust for informing regulatory decisions, and whether MRD-negativity could generally be used as primary efficacy endpoint in main clinical trials to establish efficacy in the context of marketing authorisations.

This reflection paper discusses the current thinking about general use of MRD outcomes as endpoint in clinical trials to support the demonstration of efficacy and positive benefit-risk balance a marketing authorisation application. Throughout the text, the terms "measurable residual disease" and "minimal residual disease" are used interchangeably.

In short, the current thinking is that despite this correlation at the patient level, in view of the existing uncertainties about the quantitative aspects on the predictive association between MRD negativity and an effect on true clinical endpoints like OS and PFS, use of MRD outcomes as primary endpoint in clinical trials is currently unclear. Furthermore, whether this correlation is independent from type of treatment received, tumour burden, International Staging System (ISS or R-ISS) stage or cytogenetic characteristics is yet to be determined. Thus, at present time, MRD-negativity in MM clinical trials does not fulfil the general requirements of a surrogate endpoint for PFS and/or OS.

2. Additional considerations

It is recognised that the strength of evidence of surrogacy of MRD and PFS and OS is evolving. This reflection paper will be updated when significant new evidence emerges.

Further studies in MM are needed to ensure systematic collection of MRD data in terms of timing and methods (preferably NGS and NGF), and of results on the time-dependent endpoints PFS and OS. Such data could then be used for meta-analyses to establish MRD-negativity as a surrogate (at the trial level) for PFS/OS across treatment settings.

MRD assessment in patients with extramedullary disease and especially following novel immune therapies (e.g. CAR-T cells, etc) may present unique challenges for the detection techniques. Reassuringly, emerging data support the role of new functional imaging techniques to predict outcomes and evaluate response to therapy. Although there is lack of standardised imaging procedure for assessment, the use of ^{18}fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography – Computed Tomography (PET/CT) is currently recommended by the IMWG at diagnosis and also to evaluate treatment response. Clinical studies should try to adhere to recommendations by European and international working groups.

Assessment of MRD in peripheral blood (PB) is a future goal allowing serial sampling and avoiding the invasive bone marrow (BM) aspirate procedure. The sensitivity of MRD detection in PB samples and the optimal method to be used are currently under investigation. Clinical studies are recommended to explore the use of PB for the detection of MRD and compare it with results obtained in BM samples.

The current thinking addresses general use of MRD as an early endpoint for approval in MM trials aiming to establish efficacy. Outside the general situation, it is understood that there may be situations where results in terms of MRD and other variables measuring activity may be "dramatic" and, in the context of the totality of the supportive data and appropriate regulatory mechanisms, may be sufficiently informative for regulatory decisions. This reflection paper does not address such situations that require careful evaluation of all the available evidence in the relevant context.

Given the current uncertainty on MRD being a surrogate for PFS/OS, scientific advice is recommended in cases where MRD-negativity is proposed as primary endpoint in clinical studies intended for regulatory decision-making. During a MAA procedure, case-by-case assessment will be done, and limitations described above will be taken into account.

3. Summary

Currently, the quantitative relationship between MRD-negativity and clinical outcome, i.e. in terms of PFS/OS, is not robustly confirmed. There are several uncertainties that need further investigation. Sponsors are encouraged to seek scientific advice from the CHMP, if MRD-negativity is planned to be used as primary endpoint in studies intended for regulatory decision-making. The relationship between MRD and long-term outcome needs to be established for each disease setting – newly diagnosed transplant eligible, newly diagnosed transplant ineligible, relapsed and refractory and smouldering MM.

4. References

1. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncology 2016; 17 e328-46.
2. Landgren O. and Owen R.G; Better therapy requires better response evaluation: paving the way for minimal residual disease testing for every myeloma patient. Cytometry Part B 2016; 90B. 14-20.
3. B. Paiva *et al*; Minimal residual disease monitoring and immune profiling in multiple myeloma in elderly patients. Blood 2016; volume 127, number 25.
4. Multiple Myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow up. Annals of Oncology 2017.
5. Landgren O. and Iskander K.; Modern multiple myeloma therapy: deep, sustained treatment response and good clinical outcomes. Journal of internal medicine (2017), 281; 365-382
6. J. Lahuerta *et al;* Depth of response in multiple myeloma. Journal Clinical Oncology 2017; volume 35, number 25.
7. Munshi, N. C *et al;* Minimal residual disease predicts superior survival in patients with multiple myeloma: a meta-analysis. JAMA Oncology 3(1):28-35 (2017)
8. Flores-Montero J, et al. Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. *Leukemia* (2017) 31:2094-2103.

9. M. Cavo *et al*; Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. Lancet Oncol 2017; 18: e206–17.
10. Holstein, S.A. et al, Summary of the Third Annual Blood and Marrow Transplant Clinical Trials Network Myeloma Intergroup Workshop on Minimal Residual Disease and Immune Profiling. *Biol Blood Marrow Transplant 000 (2019) 1_9*