The acceptance of minimal residual disease (MRD) as a clinical endpoint in multiple myeloma (MM): *A targeted literature review*

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OBJECTIVES

The need to bring innovative drugs to market has spurred the need for surrogate endpoints that can predict PFS and OS outcomes in patients, and when measuring these endpoints, this is not optimal. MRD has emerged in recent years as a potentially viable alternative to PFS and OS in various hematologic malignancies. The objective of this work was to assess the status of MRD as a clinical endpoint in MM and its acceptance in current and future decision making from a regulatory and HTA standpoint.

METHODOLOGY

A targeted literature review was conducted to understand the current level of usage and acceptability of MRD as an endpoint in MM from multiple perspectives. The review included a thorough examination of academic articles in PubMed, clinical trials from clinicaltrials.org, FDA and EMA regulatory guidance, selected HTA bodies (ICER [US], NICE [UK], pCODR [Canada], PBAC [Australia], HAS [France], G-BA [Germany], and SMC[Scotland]), and clinical societies (IMF, IMWG). The search strategy combined terms for MRD and/or MM and the selected resources were reviewed by the authors.

RESULTS

MRD refers to small numbers of cancer cells that remain in patients with cancer during or after treatment or when the patient is in remission.[1] MRD testing provides an important readout of cancer treatment efficacy, monitoring patient remission, and detecting recurrence. It can also be used as a prognostic factor to determine treatment options. [2]

MRD appears in 29,169 articles in PubMed, with 885 articles also concerning MM. Since 2018, there has been a steady increase in the number of articles published, with the highest number in 2020 (131 articles) showing an increasing interest in MRD in MM from academic circles. A total of 612 clinical trials include MRD as an endpoint, with 141 of those coming from MM. MRD first appeared as an endpoint in a MM trial in 2013 (NCT01702831) and has since become commonplace as a secondary or even primary endpoint.[3]

Both the FDA and EMA have published targeted guidelines regarding the use of MRD in clinical trials for MM, signaling the need for standardization of practices, although neither body officially supports the validation of MRD as a surrogate for PFS/OS at this time.[4-6]

HTA bodies remain skeptical. Out of all reported HTAs analyzed (>80), approximately 15% reported MRD data and even less discussed the importance of the endpoint or included it in its decision making. The G-BA, HAS, and NICE have all been openly critical of MRD as an unvalidated surrogate endpoint for PFS and/or OS, even when published oral hearings confirmed significant clinical acceptance. Finally, both the IMF and IMWG are openly in favor of MRD as a clinical endpoint and continue to push for its acceptance by regulatory and HTA bodies.[7-9]

Brand name	Compound name	ICER[10]	NICE[11]	pCODR[12]	PBAC[13]	HAS[14]	G-BA[15]	SMC[16]
Blenrep®	belantamab-mafodotin							
Darzalex®	daratumumab							
Empliciti®	elotuzumab							
Sarclisa®	isatuximab							
Ninlaro®	ixazomib							
Pepaxto®	melphalan flufenamide							
Farydak®	panobinostat							
Xpovio®	selinexor							
Velcade®	bortezomib							
Kyprolis®	carfilzomib							
Abecma®	idecabtagene vicleucel							

Legend

- MRD influenced HTA decision (positively/negatively)
- MRD was mentioned in HTA report but did not influence the decision
- MRD was not mentioned in the HTA report
- MRD was not an endpoint in the clinical trial
- HTA assessment ongoing
- No HTA assessment available

CONCLUSIONS

While substantial academic and clinical support for the use of MRD as an endpoint for decision making in clinical trials for MM exists and is steadily growing, both regulators and especially HTA bodies are skeptical of this endpoint. This is a situation that Is unlikely to change until enough evidence amounts to confirm its status as a surrogate for PFS and/or OS.

References:

1. Luskin, Marlise R., et al. "Targeting minimal residual disease: a path to cure?." Nature Reviews Cancer 18.4 (2018): 255-263.
2. Kostopoulos, Ioannis V., et al. "Minimal residual disease in multiple myeloma: current landscape and future applications with immunotherapeutic approaches." Frontiers in Oncology 10 (2020): 860.
3. https://clinicaltrials.gov/ct2/show/NCT01702831?term=NCT01702831&draw=2&rank=1
4. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and
5. https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure
6. https://www.ema.europa.eu/en/guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies
7. https://www.myeloma.org/blog/key-trends-myeloma-care-2021
8. IMWG. International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. 2010.
9. IMWG. Multiple Myeloma Response Criteria. 2016
10. https://icer.org/
11. https://www.nice.org.uk/
12. https://www.cadth.ca/
13. https://www.pbs.gov.au/medicinestatus/home.html
14. https://www.has-sante.fr/jcms/pprd_2986129/en/home
15. https://www.g-ba.de/
16. https://www.scottishmedicines.org.uk/

Abbreviations: **EMA**: European Medicines Agency, **FDA**: Food and Drug Administration, **G-BA**: Gemeinsamer Bundesausschuss, **HAS**: Haute Autorité de Santé, **HTA**: Health technology assessment, **ICER**: Institute for Clinical and Economic Review, **IMF**: International Myeloma Foundation, **IMWG**: International Myeloma Working Group, **MM**: Multiple myeloma, **MRD**: Minimal residual disease, **NICE**: National Institute for Health and Care Excellence, **OS**: overall survival, **PBAC**: Pharmaceutical Benefits Advisory Committee, **pCODR**: pan-Canadian Oncology Drug Review, **PFS**: progression-free survival, **SMC**: Scottish Medicines Consortium