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Guideline on the use of minimal residual disease as a clinical endpoint in multiple myeloma studies

Draft

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Executive summary

The aim of the guideline is to address the use of undetectable minimal residual disease (MRD) as an intermediate efficacy endpoint in controlled randomised clinical studies in patients with multiple myeloma (MM), adequately designed to demonstrate efficacy by relevant hard endpoints, that might allow earlier approval of new drugs pending final confirmatory data.

1. Introduction (background)

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 treatment of MM has been transformed over the last 15 years with the approval of more effective novel agents with different mechanisms of actions, including proteosome inhibitors, immunomodulators, monoclonal antibodies and histone deacetylase inhibitors. Treatment in MM is now recommended as multidrug combinations of these agents which have led to nearly all patients achieving a response and an improved survival.

For patients in good clinical condition, induction followed by high-dose therapy with autologous stem cell transplantation (ASCT) and subsequent maintenance is the standard treatment. Allogeneic SCT is not indicated as part of front-line therapy. For patients not eligible for transplant there are several drug combinations available as induction therapy. Consolidation therapy is not systematically given. MM remains an incurable disease and eventually nearly all patients relapse. In the relapsed and refractory setting, including very advanced stage disease, there are several combination therapies available.

Currently, progression-free survival (PFS) is considered an appropriate primary endpoint to demonstrate clinically meaningful patient benefit in randomised phase III studies. However, with such an endpoint the timeframe to achieve statistically and clinically meaningful results from pivotal studies with new therapies in earlier treatment lines is well over 5 years. There is a need to find alternatives to the currently used time-to-event variables so that the efficacy of novel therapies can be evaluated at an earlier time point.

The International Myeloma Working Group (IMWG) has recently defined new categories of response to treatment based on the detection of residual tumour cells that can identify deeper responses. The value of MRD following treatment in patients with MM has been revealed as one of the most relevant prognostic factors.

There are a large number of studies consistently showing that among patients achieving a complete response (CR), those with detectable MRD have an inferior PFS and overall survival (OS) compared to those with undetectable MRD.

Undetectable MRD has been associated with improved PFS and OS among patients in CR regardless of prior transplant, disease stage or cytogenetics.

The availability of MRD data shortly after treatment is important because with more effective treatment regimens PFS will be evaluable only after a long observation period.

The validation of MRD response rate as a surrogate endpoint requires that the treatment effect on this marker can predict quantitatively the treatment effect in terms of PFS. Qualitatively available data are sufficiently convincing for MRD response rate to be used as an intermediate endpoint in randomised controlled trials as long as the benefit in terms of long term efficacy can eventually be confirmed.

2. Scope

Guidance is provided on the basis and regulatory requirements for the use of MRD as an intermediate endpoint to predict clinical benefit in trials in MM and it is not applicable to other clinical settings.

Novel immune therapies present unique challenges with the techniques used to detect MRD and there are insufficient data available. At present, this guidance is not applicable for the use of MRD assessment in clinical trials with novel immune-therapies.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4).
- Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 (EMA/CHMP/509951/2006, Rev.1).

4. General aspects of MRD

Definition

Undetectable (also referred as negative) MRD implies less than 1 in 10^5 residual tumour cells detected in the bone marrow following treatment.

Sample

Tumour cells are restricted to the bone marrow (BM) although small numbers of malignant cells may be detectable in peripheral blood (PB) with highly sensitive techniques. The presence of detectable MRD should be conducted in BM aspirates while assessment in PB is considered exploratory at present.

Timing

Measurement of MRD should be conducted after each treatment stage and the timing of MRD testing depends on the type of treatment and if the patient is considered eligible for transplant.

The timepoints of the MRD test will depend on the administered treatment regimen and study objectives and should be justified by a biological rationale and appropriate data.

a) Non-eligible to transplant

   For patients non-eligible to transplant MRD testing should be done at the time a patient is expected to have the most optimal response following induction treatment.

b) Transplant eligible

   The significance of achieving undetectable MRD earlier versus later in disease course (i.e. before or after ASCT) is not known. For patients eligible to transplant, MRD testing should be done at two timepoints: at the time when a patient achieves the most optimal response following induction treatment and at day 100 following transplant.

c) Maintenance treatment

   For patients receiving maintenance treatment MRD testing should be conducted before the start of maintenance and at subsequent timepoints (e.g. every 6 months).

To study the duration of undetectable MRD, repeated MRD testing timepoints preferably every 6 months are recommended. Deviation of the selected timepoints may be acceptable if fully justified.

Laboratory methods

The following techniques have been described for the detection of MRD:

- Multiparametric flow cytometry (MFC): there is a validated Euro-flow method using 8 colour combinations.
- Allele specific oligonucleotide-qPCR.
- Next generation sequencing of VDJ sequences.

The optimal test should have a high applicability (useful in most patients), high sensitivity and specificity, reproducibility and proven clinical value by adequate clinical data. Currently no test fulfils all these criteria although next generation sequencing (NGS) and next generation flow fulfil most of them and the use of both methods simultaneously is recommended.

A quality management system that includes the laboratory organisational structure, responsibilities, policies and standards needed to ensure accuracy and satisfactory quality of the MRD evaluation assay would be required. It is recommended that MRD should be evaluated in accordance with Good Laboratory Practice (GLP) guidelines, or an equivalent quality management system, and that the analytical method should be appropriately validated.

The use of central laboratories is not considered a regulatory requirement provided a robust quality system is in place and that the same protocol is used for that particular analytical method. All local laboratories within a clinical trial should undergo inter-laboratorial comparisons in order to render the results comparable between different laboratories and may be between different trials.

In the case of monoclonal antibodies therapy the laboratory assay of MRD represents a challenge as low levels of antibody can lead to false-positive results. The use of NGS is not affected by antibody-based treatment. Other therapies including chimeric antigen receptor T cells may require other strategy yet to be defined.

5. MRD as an endpoint for licensure

Early approval of a medicinal product based on MRD as an intermediate endpoint may be considered due to medical need (e.g. comprehensive data on time-dependent endpoints would take a disproportionate long time) provided that confirmatory comprehensive data on PFS and OS from the same trial are submitted at a later stage. Therefore, confirmatory trials should be designed to demonstrate efficacy with regards to PFS and/or OS and pre-specify how any potential problems due to early licensure based on MRD as an intermediate endpoint (e.g. cross over) will be appropriately handled.

Ultimately, the suitability of MRD as an intermediate endpoint in MM clinical trials requires that the overall benefit risk balance is positive despite any uncertainties around the benefits and risks.

A difference in undetectable (negative) MRD response rates can be used as primary evidence of clinical benefit to obtain early licensure in randomised MM trials designed to show superiority in terms of PFS but where mature PFS data will only become available at a later stage. Regulatory considerations (e.g. legal basis of the marketing authorisation application or other considerations, for example conditional approval) will be decided on a case by case basis.

The following is required, and any deviations should be fully justified:

Study design and results

- The pivotal trial (s) will be randomised with the control regimen selected according to the criteria set out in the CHMP guideline on the evaluation of anticancer medicinal products in man.
- The trial should be prospectively powered for PFS and all patients should be followed up for OS. Depending on the target population and study objectives a trial may also require to be powered for OS.
- The statistical analysis and methods for assessment of MRD and PFS should be pre-planned and clearly described in the statistical analysis plan.
- The relevant treatment effect will need to be estimated and the trial design and statistical analysis will need to be aligned with the estimands.
- The difference in undetectable MRD response rate between study arms should be large enough to assume that a clinically meaningful PFS benefit will appear on mature data taking into consideration the clinical setting (e.g. newly diagnosed or relapsed refractory). Subgroups intended for confirmatory inference will be required to be pre-specified in the statistical analysis plan. In case of approval based on MRD response rate, PFS data confirming a positive benefit risk will be required from the marketing authorisation holder in an agreed timeframe.

MRD definitions as clinical endpoint and methods

- Undetectable MRD response rate following treatment is defined as the proportion of patients in the study population who achieve clinical complete response (CR) and undetectable MRD in BM at a pre-specified time-point after treatment.
- MRD status should be measured by a standardised method with a quantitative lower limit of at least $< 10^{-5}$ following guidelines that define specificity, sensitivity and reproducibility. MRD results should be reported by the laboratory method(s) used and the level of sensitivity (e.g. one in 10^5 cells). It is recommended to use two different methods within the same trial.
- If two laboratory methods are used for each patient within a clinical trial it should be pre-specified and justified in the protocol how the data will be handled including a strategy for dealing with differential outcomes.
- A quality control scheme for each laboratory providing MRD analysis in the clinical trial will be required.
- Measurement of MRD should be conducted after each treatment stage: at the time of suspected response (PR, VGPR, CR or sCR) following induction treatment and 100 days after ASCT in patients who receives transplantation. For patients receiving maintenance treatment MRD testing should be conducted before the start of maintenance and at subsequent timepoints. The timepoints of the MRD test will depend on the administered treatment regimen and study objectives, should be pre-specified in the protocol and justified by a biological rational and appropriate data on the mechanism of action of the drug and prior knowledge on the kinetics of responses.
- MRD will be considered undetectable if the proportion of malignant cells in the bone marrow is $< 10^{-5}$.
- In patients with undetectable MRD eradication of tumour cells needs to be confirmed in the extramedullary compartment. Total eradication of tumour cells from all compartments would imply

ruling out extramedullary disease (e.g. negative PET scan) and undetectable MRD in BM and should be reported as a secondary endpoint.

- Patients with missing MRD assessment (any cause) and patients with detectable MRD status will be counted as MRD non-responders.
- Duration of undetectable MRD endpoint is defined as duration from the start of undetectable MRD to the time of reappearance of detectable MRD. This endpoint (secondary) is applicable only to patients who achieve undetectable MRD.
- Sustained undetectable MRD would be defined as undetectable MRD in patients in CR and with normal imaging that has lasted a minimum of 1 year.
- The following exploratory analyses are recommended to inform on the prognostic value of MRD and its potential for regulatory purposes:

  a) Analyses using different cuts-off for undetectable MRD and analyses in patients who achieve VGPR or PR

  b) Comparison of the results observed using different laboratory methods for MRD assessment

  c) Total eradication of tumour cells by imaging, undetectable MRD in BM and recovery of normal plasma cells (normal heavy/light chain ratio).

5.1. Uncertain areas

Up to 10% of patients have extramedullary disease at diagnosis and a high proportion have these findings at the time of relapse. It is unknown if the detection of imaging positive (e.g. PET) lesions either at diagnosis or relapse has a prognostic significance.

Assessment of MRD in PB is the ultimate goal allowing serial sampling and avoiding the invasive BM procedure. The sensitivity of MRD detection in PB and the optimal method to be used are unknown. Clinical studies are recommended to explore the use of PB for the detection of MRD and compare it with results obtained in BM.

Assessment of MRD kinetics over the disease course instead of at a single time-point when CR is first documented may provide a better evaluation of disease control. Exploratory analysis of MRD in BM at more than one time point is recommended.

6. References

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