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4 **Guideline on the use of minimal residual disease as a**
5 **clinical endpoint in multiple myeloma studies**
6 Draft

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8 Comments should be provided using this [template](#). The completed comments form should be sent to ONCWP@ema.europa.eu

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24 **Executive summary**

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

29 **1. Introduction (background)**

30 MM accounts for 1% of all cancers and 10% of all haematological malignancies. The incidence in
31 Europe is 4.5–6.0/100 000/year with a median age at diagnosis of 72 years; the mortality is
32 4.1/100000/year.

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

38 For patients in good clinical condition, induction followed by high-dose therapy with autologous stem
39 cell transplantation (ASCT) and subsequent maintenance is the standard treatment. Allogeneic SCT is
40 not indicated as part of front-line therapy. For patients not eligible for transplant there are several drug
41 combinations available as induction therapy. Consolidation therapy is not systematically given. MM
42 remains an incurable disease and eventually nearly all patients relapse. In the relapsed and refractory
43 setting, including very advanced stage disease, there are several combination therapies available.
44 Currently, progression-free survival (PFS) is considered an appropriate primary endpoint to
45 demonstrate clinically meaningful patient benefit in randomised phase III studies. However, with such
46 an endpoint the timeframe to achieve statistically and clinically meaningful results from pivotal studies
47 with new therapies in earlier treatment lines is well over 5 years. There is a need to find alternatives to
48 the currently used time-to-event variables so that the efficacy of novel therapies can be evaluated at
49 an earlier time point.

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

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

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

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

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

65 **2. Scope**

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

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

71 **3. Legal basis and relevant guidelines**

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

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

80 **4. General aspects of MRD**

81 Definition

82 Undetectable (also referred as negative) MRD implies less than 1 in 10⁵ residual tumour cells detected
83 in the bone marrow following treatment.

84 Sample

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

88 Timing

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

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

93 a) Non-eligible to transplant

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

96 b) Transplant eligible

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

101 c) Maintenance treatment

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

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

106 Laboratory methods

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

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

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

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

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

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

129 **5. MRD as an endpoint for licensure**

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

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

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

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

145 *Study design and results*

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

161 *MRD definitions as clinical endpoint and methods*

- 162 • Undetectable MRD response rate following treatment is defined as the proportion of patients in the
163 study population who achieve clinical complete response (CR) and undetectable MRD in BM at a
164 pre-specified time-point after treatment.
- 165 • MRD status should be measured by a standardised method with a quantitative lower limit of at
166 least $< 10^{-5}$ following guidelines that define specificity, sensitivity and reproducibility. MRD results
167 should be reported by the laboratory method(s) used and the level of sensitivity (e.g. one in 10^5
168 cells). It is recommended to use two different methods within the same trial.
- 169 • If two laboratory methods are used for each patient within a clinical trial it should be pre-specified
170 and justified in the protocol how the data will be handled including a strategy for dealing with
171 differential outcomes.
- 172 • A quality control scheme for each laboratory providing MRD analysis in the clinical trial will be
173 required.
- 174 • Measurement of MRD should be conducted after each treatment stage: at the time of suspected
175 response (PR, VGPR, CR or sCR) following induction treatment and 100 days after ASCT in patients
176 who receives transplantation. For patients receiving maintenance treatment MRD testing should be
177 conducted before the start of maintenance and at subsequent timepoints. The timepoints of the
178 MRD test will depend on the administered treatment regimen and study objectives, should be pre-
179 specified in the protocol and justified by a biological rational and appropriate data on the
180 mechanism of action of the drug and prior knowledge on the kinetics of responses.
- 181 • MRD will be considered undetectable if the proportion of malignant cells in the bone marrow is $<$
182 10^{-5} .
- 183 • In patients with undetectable MRD eradication of tumour cells needs to be confirmed in the
184 extramedullary compartment. Total eradication of tumour cells from all compartments would imply

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

187 • Patients with missing MRD assessment (any cause) and patients with detectable MRD status will be
188 counted as MRD non-responders.

189 • Duration of undetectable MRD endpoint is defined as duration from the start of undetectable MRD
190 to the time of reappearance of detectable MRD. This endpoint (secondary) is applicable only to
191 patients who achieve undetectable MRD.

192 • Sustained undetectable MRD would be defined as undetectable MRD in patients in CR and with
193 normal imaging that has lasted a minimum of 1 year.

194 • The following exploratory analyses are recommended to inform on the prognostic value of MRD and
195 its potential for regulatory purposes:

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

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

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

201 **5.1. Uncertain areas**

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

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

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

212 **6. References**

213 1. International Myeloma Working Group consensus criteria for response and minimal residual disease
214 assessment in multiple myeloma. *Lancet Oncology* 2016; 17 e328-46.

215 2. Landgren O. and Owen R.G; Better therapy requires better response evaluation: paving the way
216 for minimal residual disease testing for every myeloma patient. *Cytometry Part B* 2016; 90B. 14-
217 20.

218 3. B. Paiva *et al*; Minimal residual disease monitoring and immune profiling in multiple myeloma in
219 elderly patients. *Blood* 2016; volume 127, number 25.

220 4. Multiple Myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow up. *Annals*
221 *of Oncology* 2017.

222 5. J. Lahuerta *et al*; Depth of response in multiple myeloma. *Journal Clinical Oncology* 2017; volume
223 35, number 25.

- 224 6. Munshi, N. C *et al*; Minimal residual disease predicts superior survival in patients with multiple
225 myeloma: a meta-analysis. *JAMA Oncology* 3(1):28-35 (2017)
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