EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/102314/2017
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need to revise Condition – Specific guidance, Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

Agreed by Oncology Working Party (ONCWP)	November 2016
Adopted by CHMP for release for consultation	23 February 2017
Start of public consultation	01 April 2017
End of consultation (deadline for comments)	30 June 2017

Comments should be provided using this template. The completed comments form should be sent to ONCWPsecretariat@ema.europa.eu

Keywords	***MRD, Multiple Myeloma (MM), haematological malignancies***

30 Churchill PLace ● Canary Wharf ● London E14 5EU ● United Kingdom

1. Introduction

The guideline on anticancer medicinal products as revised in early 2010 (rev.3)[1] included disease specific guidance which was later expanded (rev. 4 published January 2013) to constitute a separate appendix (Appendix 4). The Appendix 4 was recently revised (rev 2 published February 2016).

This concept paper describes and discusses the basis for the revision to the existing Appendix 4 in relation to the use of minimal residual disease (MRD) as a clinical endpoint in multiple myeloma (MM) clinical studies.

2. Problem statement

MRD has been recognised as potentially important clinical endpoint in MM and other haematological malignancies. Several clinical trials have reported that non detectable MRD status is prognostic for both progression-free survival and overall survival in MM. In addition, the International Myeloma Working Group recently published consensus criteria for response and MRD assessment in myeloma[2]. Thus there is a need to reflect on the utility of MRD in the development of medicinal products for treatment of MM as primary intermediate efficacy endpoint.

3. Discussion (on the problem statement)

Treatment of MM has changed dramatically over the last decade with the introduction of novel drugs that has led to higher rates of response to treatment and prolonged progression free survival and overall survival.

In addition the definition of complete response (CR) has evolved over time with the introduction of stringent CR (sCR) and very good partial response (VGPR) by the International Myeloma Woking Group (2011) and more recently, with the consensus criteria for response and MRD (2016). Given the high rates of CR seen in patients with the new treatment approaches, new response categories need to be defined that can identify responses that are deeper than those conventionally used[2].

Improvements in technology have led to the development of sensitive assays that can detect minimal residual myeloma cells following treatment, including multiparametric flow cytometry, allele-specific oligonucleotide (ASO)-qPCR and next generation sequencing of VDJ sequences. The prognostic value of achieving non-detectable MRD status is undoubted. This type of analyses, however, is unsuitable to disentangle the treatment factor from the patient factor and the correlation between a difference in MRD negativity and a difference in PFS is currently less well understood. If a good correlation is demonstrated, superiority in MRD negativity, if sufficiently large, should be given special consideration as a potential intermediate endpoint for early licensure with confirmatory follow-up with PFS as outcome measure.

4. Recommendation

The Working Party recommends revising the Appendix 4 of the guideline in line with the above discussion.

5. Proposed timetable

It is anticipated that a draft updated appendix 4 may be available 12 months after adoption of the Concept Paper to be later released for 6 months external consultation and, thereafter, finalised within 4 months.

6. Resource requirements for preparation

The update of Appendix 4 will involve the Oncology Working Party. It is anticipated that at least three Working Party meetings will be needed.

7. Impact assessment (anticipated)

The aim of updating the Appendix 4 to the guideline is to facilitate discussions within the CHMP, other scientific Committees and Working Parties and to keep up with evolution of science and increase transparency of requirements in relation to drug development and licensure.

8. Interested parties

EORTC, ESMO, IMWG, HARMONY

9. References to literature, guidelines, etc.

1. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000406.jsp&mid=WC0b01ac0580034cf3
2. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma (The Lancet Oncology, Vol 17, August 2016)
3. 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)