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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 ONCWP	7 March 2013
Adopted by CHMP for release for consultation	15 July 2013
Start of public consultation	31 July 2013
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Comments should be provided using this template. The completed comments form should be sent to ONCWPsecretariat@ema.europa.eu

Keywords	Breast cancer, pCR, neoadjuvant treatment, MRD, CLL, haematological malignancies

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1. Introduction

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

During the rev. 4 consultation period, stakeholders expressed an interest in further condition specific guidance, but importantly also in relation to specific issues such as the use of pathological complete remission (pCR) in neoadjuvant studies in breast cancer and minimal residual disease (MRD) in CLL and other haematological malignancies as primary endpoints in pivotal studies. This concept paper describes and discusses the basis for this revision to the existing guideline in relation to pCR and MRD.

2. Problem statement

Currently, the CHMP guideline states that "the objectives of neoadjuvant therapy may include improved overall outcome (OS, DFS/PFS), enabling surgery and organ preservation (e.g. more conservative surgery). When pathological CR at time of surgery is reported as secondary endpoint, patients withdrawn should be considered as non-responders." Use of pathological complete remission (pCR) as primary endpoint in neo-adjuvant trials for high-risk early-stage breast cancer has been subject to CHMP/EMA advice procedures and the acceptability, or not, of this outcome measure is considered to be of major importance[3-7].

Another novel endpoint which has been recognised as potentially important is the minimal residual disease (MRD) in CLL and other haematological malignancies. Large prospective randomized phase III trials have reported that MRD negative status is prognostic for both progression-free survival and overall survival (references)[8-12]. Thus there is a need to reflect on the utility in the development as primary efficacy endpoint.

3. Discussion (on the problem statement)

Adjuvant systemic therapies for breast cancer historically have been administered following definitive breast surgery. Preoperative or neoadjuvant systemic chemotherapy, once reserved for patients with locally advanced breast cancer in whom the goal was to render large breast cancers operable, has become increasingly common for a number of reasons (i.e. breast conservation, evaluation of tumour response to enable appropriate effective treatment, may provide prognostic information and provides the opportunity to examine modulation of tissue biomarkers from the time of biopsy to the time of definitive breast surgery). The possible use of pCR as primary endpoint has been introduced in neo-adjuvant trials for high-risk early-stage breast cancer. If this point is confirmed as a possible primary efficacy endpoint leading to a conditional approval, it could speed up the development in early breast cancer.

Acceptability of novel endpoints in other disease settings, such as Minimal Residual Disease (MRD) in CLL and other haematological malignancies, also needs to be discussed. A step forward in evaluating the response in CLL is the assessment of MRD by either allele-specific polymerase chain reaction or multicolor flow-cytometry. Both methods are considered to be similarly useful from the clinical point of view and standardized. Importantly, it has recently been demonstrated in large prospective randomized phase III trials that achieving MRD negative status is qualitatively predictive of progression-free survival and overall survival. These results have been preceded by many phase II studies pointing to the importance of achieving MRD-negative status in patients with CLL and also to some of the weaknesses of current methods for evaluating response to therapy in CLL. Until now,

however, further data are most likely needed to show that a certain difference in MRD can be used to estimate a difference in PFS.

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 6 months after adoption of the Concept Paper to be later released for 3 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 and, prior to release, the Scientific Advisory Group Oncology. It is anticipated that at least two 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 and its 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.

9. References to literature, guidelines, etc.

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2. SAG response to questions on the Guideline http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137129.pdf

3. Guidance for Industry: Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf)

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