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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need to revise the guideline on the evaluation of anticancer medicinal products in man

Agreed by Efficacy Working Party	July 2010
Adoption by CHMP for release for consultation	22 July 2010
End of consultation (deadline for comments)	1 January 2011

The proposed guideline will replace guideline CPMP/EWP/205/95/Rev. 3.

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

Keywords	*Cancer, malignancy, lymphoma, leukaemia*

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1. Introduction

The current revision 3 of the Notes for Guidance "EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN" came into operation in 2006 and was followed by an appendix covering methodological issues related to Progression-free Survival and finally in 2010 an appendix on Haematological Malignancies. In addition a paediatric appendix was released in 2003.

The main text and the appendices are partly over-lapping and, e.g. some issues covered in the haematology appendix are of relevance also for the main text. There is thus a need to revise the main text and to incorporate elements of the appendices in order to provide more comprehensive and harmonised guidance documents. Furthermore, the methodology and paediatric appendices also need some revision. In addition the increase in tumour immunotherapies having entered advanced stages of clinical development and requiring specific methodology needs to be considered.

2. Problem statement

About one third of new chemical or biological entities under clinical development are aimed for the treatment of malignancies. This both reflects the need for improved treatment and a deeper understanding of the biology of tumours. The diversity of mechanistically different treatment modalities may need a more judicious approach with respect to inclusion criteria and end points for exploratory as well as confirmatory studies. Thus, in addition to the aim to harmonise the main document and its appendices, it is foreseen that an update is needed on certain specific topics related to drug development as further discussed below.

3. Discussion (on the problem statement)

There is a common understanding that for treatment to be effective, whether "targeted" or not, drug development should aim at identifying patients with an increased likelihood to respond favourably to treatment. While this is the case and has been so for a long time, in practice medicinal compounds are still developed without this being an integrated part of the drug development from drug discovery, throughout non-clinical and clinical development.

There is an obvious and understood wish to use serum biomarkers in order to try to define the proper patients for therapy. However, it is foreseen that tumour biopsies also within a foreseeable future will play a central role in identifying target expression, etc. As rarely it will be possible to achieve complete sampling and valid analyses, this merits a discussion about missing data, use of data derived from several independent studies, etc.

For classical cytotoxic compounds there has often been a foreseeable relationship between response rate (ORR), progression-free survival (PFS) and survival (OS). This appears less frequently to be the case for so called targeted compounds. PFS is also a composite endpoint: new lesions, increased size of existing lesions and death. To what extent this pattern may differ comparing classes of compounds is not well understood. Other topics related to PFS are the use of independent review and the weight that should be put on investigator's assessment and also to what extent the meaning of "progression" might differ in relation to prior/ongoing therapy.

The use of PFS or OS as primary endpoints will also be re-discussed taking elements from the haematology appendix into account, as well as the problems to conduct last-line studies in a competitive environment without accepting cross-over.

Tumour “vaccines” and other immune therapy approaches are rather sparsely covered in the current guideline and may need further development.

There is also a perceived need to expand the section on disease specific guidance as well as the paragraph about quality of life/patient reported outcome. The current paediatric appendix is focused on early drug development. This is not considered satisfactory and it is foreseen that, e.g. the experience gained from paediatric investigation plans will provide incentives to revise this appendix.

4. Recommendation

It is proposed to prepare revised guidance documents on the clinical investigation of medicinal products for the treatment of cancer.

5. Proposed timetable

It is anticipated that a draft revised CHMP Guideline, including updated appendices, may be available 9 months after adoption of the Concept Paper to be later released for 6 months external consultation and, thereafter, finalised within 6 months.

6. Resource requirements for preparation

The preparation of the new Guideline 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. The PDCO will be primarily responsible for the revision of the paediatric appendix.

7. Impact assessment (anticipated)

The aim of revising the guideline is to facilitate discussions within the CHMP and its scientific Committees and Working Parties and to increase transparency of requirements in relation to drug development and licensing.

8. Interested parties

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