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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

APPENDIX 1 TO THE GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN (CHMP/EWP/205/95 REV. 3)

METHODOLOGICAL CONSIDERATIONS FOR USING PROGRESSION-FREE SURVIVAL (PFS) AS PRIMARY ENDPOINT IN CONFIRMATORY TRIALS FOR REGISTRATION

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Introduction

The use of PFS or DFS as a primary endpoint in clinical efficacy trials presents several methodological issues which need to be addressed prospectively. This appendix provides some general regulatory guidance on issues to consider relating to definitions, frequency and methods of assessment, ascertainment bias, handling of deviations and missing data, and radiology review. Guidance on the choice of primary endpoints, and appropriateness of using PFS/DFS as primary endpoint, is outside the scope of this appendix.

Endpoint definition

PFS is traditionally defined as the time from randomisation (or registration, in non-randomised trials) to objective tumour progression, or death from any cause, whichever first. DFS is defined as the time from randomisation to objective recurrence or death from any cause.

Disease progression and recurrence are typically assessed based on objective radiological findings. Whenever possible, the definition of progression should follow established response evaluation criteria (e.g., RECIST or WHO criteria, EBMT criteria). However, it is acknowledged that, depending on the type of agent, the site and type of lesion, and the objectives of the trial, modified criteria might be more appropriate. For instance, additional objective clinical and biochemical or radiological criteria may be used to assess progression. In all cases, it is important that the criteria for definition of a progression event are as objective as possible, and that the definitions be clearly and prospectively defined in the protocol.

Data analysis considerations

In practice, complete follow-up of all randomised subjects for study outcomes will rarely be available. Furthermore, deviations and withdrawal from the protocol treatment occurring after randomisation may have an impact on the trial data and, consequently, on the trial conclusions, particularly if they are related to treatment assignment. Subjects may, for example, receive the wrong study medication or none at all, may withdraw from treatment prior to scheduled completion, may be lost to follow-up, may change treatment before evidence of progression or may present with missing evaluations followed by evidence of progression.

Events of withdrawal from study therapy prior to independently adjudicated progression cannot automatically be regarded as non-informative and the adequacy of censoring these events in the statistical analysis may therefore be questioned. There is no way to handle this problem that is optimal for all anti-cancer studies, but the principles of intention-to-treat provide a reasonable approach and should be followed as far as possible when defining the analysis set for the primary analysis of PFS/DFS. In particular, for all randomised patients, outcome data should be collected according to the intended schedule of assessment and the date of progression or recurrence should be assigned based on the time of the first evidence of objective progression or recurrence regardless of violations, discontinuation of study drug or change of therapy. If, for a particular study, a different approach is considered to be more appropriate, a justification is expected and CHMP Scientific Advice agreement is recommended at the planning stage.

Even if foreseen in the study protocol, it may at times be difficult to collect reliable data on progression for patients withdrawn from study therapy. For this, and for other reasons, there is a need to predefine and justify methods for handling missing data, including rules of censoring. These methods should be chosen so as to minimise bias and loss of information, while being adequate for the aim of the trial. This may include approaches that consider withdrawal or change of therapy prior to adjudicated progression / recurrence as events in an analysis of PFS/DFS. Potential biases should always be addressed and sensitivity analyses should be undertaken using different approaches. Supportive analyses may include for example an approach that assigns the progression date to the date of the scheduled clinic visit, interval-censored analysis, single time point analysis, with progression being assigned at one pre-specified time after randomisation.

At present, from a regulatory perspective there are several possible approaches that can be recommended for sensitivity analyses. The range of sensitivity analyses should be sufficient to

demonstrate that the trial results are robust and will depend on the clinical situation and nature of the trial data observed (e.g., patterns of patient withdrawals).

Any differences in conclusions from the range of analyses presented will need to be explained. The importance of different analyses and analysis sets will also depend on the design of the trial (superiority or non-inferiority).

The strategy for the primary analysis should be clearly written before the trial starts. It is important that due consideration is given to the statistical analysis plan, including sensitivity analyses to address the handling of deviations and missing data, at the planning stage of the trial. In blinded trials, conducting a blind review at the end of the trial may offer a valuable opportunity to review the data handling methods selected and the range of analyses proposed so that unforeseen issues can be addressed. How to deal with and document these data analysis issues should follow general guidance provided in the note for guidance on statistical principles for clinical trials, ICH topic E9 (CHMP/ICH/363/96). A similar approach will not be welcomed for open-label trials. For such trials, utmost diligence is required when writing the study protocol and statistical analysis plan as amendments to important aspects of the analysis made in the knowledge of accruing data would give rise to concern.

The general approach to handling missing data should follow available guidance on points to consider on missing data (CPMP/EWP/1776/99).

Frequency and methods of assessment

Evaluation of PFS requires that all sites of possible disease specific to that tumour type be assessed at baseline, and that involved sites be systematically assessed during follow-up together with other sites, as clinically and radiologically indicated, ideally using the same methods. Similarly, evaluation of DFS may require that likely sites of disease be systematically assessed at follow-up assessment.

The frequency of assessment should therefore be adequate to detect the expected treatment effect. The optimal frequency for assessing progression needs to be determined on a trial by trial basis, taking into account the aims of the trial and the treatment schedules and the patient setting. A balance needs to be found between the need to assess progression as precisely as possible and the need to minimise exposure of patients to invasive and resource-intensive diagnostic procedures.

The estimated time of progression / recurrence can vary simply as a result of the frequency of assessments with longer PFS/ DFS resulting from less frequent assessments. Therefore, the methods and frequency of tumour assessment should be symmetric across study arms in a randomised trial, even when treatment cycles are of different lengths. Clinical trials that are not adequately blinded are particularly at risk of ascertainment bias when a change in the clinical status of the patient prompts an unscheduled assessment of disease status. Adherence to protocol-defined schedules is essential and deviations should be reported. Compliance with the visit schedule should be descriptively investigated at the time of the analysis and any impact on the trial results should be explored.

Handling deviations from scheduled assessment

For the purpose of the primary analysis, the timing of a progression that is detected between two scheduled tumour assessments should be assigned based on the documented time of progression and not, for example, based on either scheduled time of assessment. Alternative analyses based on scheduled time of assessment could be included as sensitivity analyses. Deviations from the timings of scheduled assessments are of concern due to the potential for introducing a detection bias.

Problems of bias due to differing follow-up visit schedules and/or different patterns of follow-up should be minimised by proper trial design and conduct. If differing follow-up visit schedules are unavoidable, methods to investigate the bias introduced must be outlined in the trial protocol.

For example, in neo-adjuvant studies surgery is a key time point where disease recurrence or progression may be observed. However, it might be unavoidable that the time of surgery be different in the two treatment groups. One possible solution in such a case may be to choose arbitrarily a fixed time just after the last scheduled time of surgery, and use that fixed time point as the time for all events occurring prior to it (including those at surgery).

Various approaches have also been proposed on how to handle unexpected differences in the patterns of follow-up in supportive analyses, aiming to minimise bias whilst preserving accuracy of the estimated time of progression, and consideration should be given to the pre-specification of such analyses. *Post hoc* data analyses are, however, of limited value in compensating for biased data collection,. In general, if there is a major discrepancy in the follow-up visit schedule between the treatment arms, it is unlikely that any approach will convincingly establish the absence of important bias.

The sensitivity analyses should be planned and described in the protocol or the statistical analysis plan and any changes must be justified in the study report.

Independent review

Assessment of disease or progression can potentially be subject to investigator bias, particularly in clinical trials that are not properly double-blinded and especially in trials in advanced disease where many lesions need to be followed. In these situations, where PFS or DFS is the primary endpoint, independent and blinded radiological evaluations and assessment of clinical tumour progression data as reported in the case report forms may provide some reassurance about the quality of the data if there are reasons to suspect investigator bias. This source of bias may not be a major issue in properly double-blinded randomised trials where PFS or DFS is the primary endpoint. The role of the outcome assigned through independent evaluation should be pre-specified in the protocol. In general, where independent evaluation is appropriate, the primary analysis should be based on the outcome assigned through independent evaluation. Data on PFS/DFS will be more persuasive if the trial results from the independent, blinded evaluation does not differ from the investigator assessments to any important degree. The procedures for independent review shall be defined prospectively described in the clinical trial documentation.

Regulatory guidance

In situations where DFS or PFS is used as the primary endpoint in a confirmatory trial to support a marketing authorisation application, it may be appropriate to consider CHMP Scientific Advice on methodological issues related to the definition and assessment PFS or DFS, and handling of deviations.