27 November 2012
EMA/768937/2012

Answers from the CHMP Scientific Advisory Group (SAG) for Oncology for Revision of the anticancer guideline

Chair: Jan Schellens

Vice-Chair: Jonas Bergh

Secretary: Francesco Pignatti

Participants

Steinar Aamdal, Jonas Bergh, Jan Bogaerts, Laurence Collette, Marina Chiara Garassino, Rocio Garcia Carbonero, Christian Gisselbrecht, Rosa Giuliani, Steen W Hansen, Edward Laane, Jonathan Ledermann, Jan Schellens, Jean Tredaniel

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

Minutes from the SAG meeting

The meeting started at 9:30 am and was chaired by Jan Schellens.

In preparation of the meeting it was identified whether there was any restricted involvement of members taking into account the topics (medicinal products, guidelines) listed on the Agenda (see outcome of this check below). The same check was carried out for observers as well as invited expert(s) regardless of them taking part in person or via teleconference. The relevant participants were informed of any restricted involvement prior to the start of the meeting.

At the beginning of the meeting, prior to any discussion of the agenda topics, information on the restricted involvement of members and/or experts was read out. In addition, the EMA reminded all parties concerned of their obligation to declare their interests (in particular any changes, omissions or errors to the already declared interests).

Outcome of the check on Declaration of Conflict of Interest was the following:

No relevant interests were declared for this meeting.

SAG QUESTIONS AND ANSWERS:

1) When using PFS as primary endpoint for confirmatory studies, there is a risk that the tumour's drug resistance profile is affected by therapy. This might be of relevance for the activity of next-line therapies (see chapter 7.1.5 Endpoints). This risk has mainly been emphasised in settings where a new concept is introduced such as maintenance therapy or an increased number of "induction" cycles. In such situations, OS rather than PFS is the preferred endpoint. However, when this is not deemed to be feasible, endpoints such as PFS on next-line therapy (PFS2) should be determined. In fact, in general, it is recommended that in most studies time on next-line therapy is collected. The SAG is asked to discuss the proposed approach, particularly in terms of feasibility (standardisation of next-line therapies, follow-up) and usefulness of second progression-free survival.

In most settings OS is the most important and convincing clinical benefit endpoint for confirmatory trials. Where PFS is considered to be a clinically relevant endpoint for the current-line therapy, it is necessary to at least rule out a detriment in terms of OS. If this is not feasible then as an alternative PFS2 (Time from randomisation to objective tumour progression on next-line treatment or death from any cause) should be available. If progression after next-line therapy cannot be measured, time from randomization until treatment discontinuation, progression or death after next-line therapy should be measured. Whether such endpoints are sufficiently useful to provide reassurance about subsequent treatment(s) will depend, among other aspects, on the magnitude of the effect, data availability and quality, and possible bias.

Standardisation of next-line therapies is considered often feasible although not a strict requirement in randomized trials as long as systematic bias is absent.

2) The note for guidance continues to recommend that an improvement in PFS should be considered to be a clinically relevant endpoint *per* se, even in the absence of a documented improvement in OS, provided that there is no detriment in terms of OS (see chapter 7.1.5 Endpoints). This is implicitly justified by the delaying of symptoms and next–line therapy. Is this view generally agreed? Is it possible to generally define what is the minimum clinically relevant difference in PFS when this is the primary clinical benefit endpoint?

Although OS is generally the most important and convincing clinical benefit endpoint for confirmatory trials, the view is maintained that an improvement in PFS is a less important but still clinically relevant endpoint *per* se (even in the absence of a documented improvement in OS but provided that there is no

detriment in terms of OS). This is justified based on the importance of delaying the onset or worsening symptoms and the need for next–line therapy that are often associated with progression.

Progression is generally determined based on objective imaging criteria (RECIST). Thus, the effect on symptoms is generally not included as part of this endpoint and the clinical importance of PFS is often difficult to establish. Assessment of symptomatic progression ("clinical progression") would allow a better interpretation of the clinical importance of this endpoint, assuming that well defined, robust and reproducible methods to demonstrate clinical progression can be applied. It should be explored if, from a regulatory perspective, clinical progression could be adequately defined and recorded as secondary endpoint, to provide corroborative evidence of benefit.

Biomarker-driven patient selection and biological plausibility may add to the strength of evidence of an effect in terms of PFS.

In general, when designing studies aiming to show a difference in PFS in the metastatic setting, if the prognosis is in the order of 2-3 years OS or less, an improvement in median progression-free survival in the order 3-4 months or larger is considered adequate. However, in terms of assessment of the results, it is not considered useful to establish a minimum clinically relevant difference, as any positive difference could be viewed as still worthwhile from a patient perspective. However, the clinical importance of the observed benefit in terms of PFS needs to be balanced against the clinical importance of the unfavourable effects.

3) The note for guidance does not address the possible use of pathological complete remission (pCR) as primary endpoint in neoadjuvant trials for high-risk early-stage breast cancer. Should this endpoint be recommended as a possible primary efficacy endpoint leading to a conditional approval, and pending confirmation on DFS/PFS? See draft FDA guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf)

Currently, there is little regulatory experience with this endpoint and the published data are limited. Further experience and robust prospective clinical data are warranted before firm recommendations can be made.

4) Serum testosterone consistently below 50ng/dL is considered sufficient for licensing, for example, for a new GnRH agonist. If a product shows in a non-comparative trial that levels below 20ng/dL ("surgical castration") are achievable, can claims as regards superiority be accepted, even in the absence of a randomized GnRH agonist controlled trial?

Claims of superiority should be established based on randomized active-controlled trials due to issues of assay sensitivity. The results of previous studies are based on testosterone immunoassays that have insufficient accuracy in the low range; the target castrate testosterone level in patients on androgen deprivation therapy remains to be properly defined (see e.g., van der Sluis et al., 2012).

5) Are there any additional points that should be covered in this note for guidance or any of the appendixes?

The wording of the guideline should be strengthened where possible, giving clear recommendations where needed and otherwise avoiding areas where only weak recommendations can be provided.

The disease-specific appendix 4 is rather vague in terms of recommendations and the fields addressed are very dynamic. For instance, the prognostic scorings described are quickly outdated –unnecessary detail should be avoided. This should be reflected in an introduction.

Consider expanding the guidance for inclusion of elderly patients, stressing the importance of external validity, and the need for exploratory studies in the elderly (safety).

Mention Phase 0 studies for completeness.

Describe strategies for exploratory studies as basis for approval in rare diseases.

Consider the need to study PK changes over time to ensure adequate exposure over time.

Discuss pros and cons of adaptive designs (in particular, seamless phase II-III).