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DRAFT

APPENDIX 2 TO THE GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN (CPMP/EWP/205/95 REV. 3) ON HAEMATOLOGICAL MALIGNANCIES

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1. SCOPE

The aim of this appendix is to provide guidance on the design of confirmatory studies in patients with haematological malignancies. With respect to exploratory studies, reference is made to the main guideline text.

2. GENERAL PRINCIPLE

The general principles as laid down in the main document apply. Thus confirmatory trials should be designed with the aim to establish the benefit - risk profile of the experimental medicinal product, including supportive measures, in a well-characterised target population of relevance for clinical practice. These studies are randomised, reference-controlled in nature and the target population, as well as the reference regimen (may be BSC), are normally defined by disease, stage and prior lines of therapy.

While it is generally acknowledged that the aim of treatment is to improve cure rate, survival, quality of life/symptom control, or to reduce toxicity without loss in efficacy, restraints on the conduct of clinical trials may make it hard or impossible to demonstrate relevant effects on some of these endpoints. For instance, use of active next-line therapies must be accepted and this may affect the possibility of detecting differences in OS as well as symptoms related to disease progression.

As this appendix is focused on the design of confirmatory studies, the aim of therapy, curative versus non-curative, and not the underlying disease has been used to structure the discussion in the general part of the document.

For haematological malignancies where treatment is administered without curative intent, there are often alternative, in clinical practise well established regimens, showing major differences in efficacy and toxicity indicating that efficacy in these cases is considered to parallel toxicity. It is therefore of relevance in the planning phase, to take into account the expected tolerability/toxicity profile of the experimental regimen compared with the selected reference regimen. It is fully acknowledged that safety data may be rather limited prior to the conduct of the first confirmatory trial, but main toxicities should normally have been identified and this should be sufficient for a rough estimate of the expected relative toxicity of the experimental regimen compared with alternative reference regimens. Toxicity is thus another factor used to structure the discussion in order to provide guidance with respect to requirements for licensure from a regulatory perspective. If, however, exploratory study data indicate that, e.g. a survival benefit is a realistic aim also for a compound with similar or reduced toxicity, it is strongly recommended that the study is designed to demonstrate this, even in situations where non-inferiority in terms of PFS would be sufficient for licensure.

Three categories are used in this document: Reduced or similar toxicity, increased toxicity and major increase in toxicity. No precise definition is given here due to the heterogeneity of the conditions with respect to prognosis and therefore acceptability of toxicity. ”Major increase in toxicity”, however, in most cases refers to a clear that treatment-related SAE.s will be relevantly increased in the experimental arm. However, in comparison with a well tolerated reference regimen of low toxicity, for example, sustained immune suppression with infectious complications and need for prophylaxis could also be regarded as a major increase in toxicity. Other issues to take into account include risk for non-reversible toxicities and risk for secondary tumours. This categorisation is mainly meant for guidance in the planning of confirmatory studies and in order to provide advice on regulatory expectations with respect to study outcome in order to enable a proper benefit – risk assessment.

For children, toxicity data should be considered with special emphasis on long-term toxicity and in relation to projected life expectancy and risks of interference with QoL. Therefore confirmatory studies should entail measures to generate data on long-term safety and toxicity. Toxicity in respect to impediments of organ- and neurological and psychosocial development should be under special focus.

The benefit – risk of the reference regimen should be well documented and the regimen should be considered a first choice in clinical practice. Among such regimens, a regimen with similar expected toxicity to the experimental regimen is preferred if available and suitable from a design perspective. In some cases there is no well documented reference regimen, even though patients in clinical practice

are treated with certain regimens. Formally, BSC is acceptable in these cases, but an active comparator, e.g. in terms of response rate, may include investigators best choice, is often preferable. In these cases reference regimens with low toxicity are favoured and superiority in terms of patient relevant endpoints should be demonstrated. Cross-over to the experimental arm should be avoided.

For many solid tumours, treatment is administered until treatment failure, either due to tumour progression or unacceptable toxicity. This, however, is frequently not the case in haematological malignancies where a fixed number of cycles of therapy may be administered followed by watchful waiting, or, in some cases, allogeneic haematopoietic stem cell transplantation (HSCT). As the meaning of disease progression on and off therapy differs, this should be taken into account in the planning of studies with a fixed maximum number of treatment cycles and is of special relevance if the experimental regimen is more toxic than the control regimen and in case retreatment with the same regimen is an option after a sufficiently long period of time of non-active disease.

For conditions where maintenance therapy is normally not administered, a claim for treatment until progression should be supported by study data showing a relevant benefit of prolonged therapy with the experimental regimen over a fixed number of cycles with the same regimen.

In contrast to solid tumours, it is acknowledged that disease specific response criteria are unavoidable in many cases and that full harmonization has yet not been accomplished for some disease entities. Therefore it is of importance to follow the progress made by international working groups on these issues.

Some possible target indications comprise very small groups of patients, so small that "exceptional circumstance" might apply. As a general recommendation, sponsors are advised to initiate studies in these patient groups only when benefit – risk is established in indications allowing for a more comprehensive evaluation, especially with respect to safety. In these small target populations all evidence with respect to efficacy and safety must be taken into account. This encompasses outcome measures currently viewed as supportive only, such as HSCT rate, use of minimal residual disease to define response rate and recurrence of disease.

The time point of and the need for initiating confirmatory studies in the paediatric population have to be seen in relation to any development for adults. Acknowledging the general principles of ICH E11, haematological malignancies in children represent life-threatening diseases with - for many risk groups - still limited therapeutic options requiring an early initiation of an informed paediatric development, including confirmatory studies when extrapolation of efficacy is not possible. In general, extrapolation from young adults may more likely be possible for CML and for AML, than for non-Hodgkin lymphomas or ALL. However, even when the aetiology, disease course and pharmacological action seem similar in children and adults, confirmatory studies are not *a priori* unnecessary, as there might be unknown, non-controllable factors.

For some individual disease entities more disease specific guidance is provided, but the general part of this appendix is meant to cover conditions such as AML/ALL, lymphoma and multiple myeloma.

3. DESIGN OF CONFIRMATORY STUDIES

With respect to diagnosis, criteria for initiation of treatment, eligibility, response criteria and choice of reference therapy, a justification based on scientific evidence and/or generally acknowledged guidelines is expected.

There is a general wish to reduce heterogeneity of study populations in order to increase the ability of the study to detect differences between study arms. This, however, has to be balanced against the availability of patients for inclusion and the wish to enrol a clinically representative selection of patients. Stratification of the randomisation for baseline covariates of major prognostic importance should be considered. Whether stratification is undertaken or not, this should be discussed in the study protocol and in case adjusted analyses are to be undertaken, co-variates for such analyses should be pre-specified in the protocol (Points to Consider on Adjustment for Baseline Covariates CPMP/EWP/2863/99).

As some of the conditions are rare, it is understood that the sponsor might wish to define the target population using alternative criteria to those commonly employed. It is also acknowledged that a priori

it cannot be assumed that use of, e.g. conventional diagnostic criteria or eligibility according to line-of-therapy best reduce heterogeneity with respect to the efficacy of administered therapies. For example, in studies investigating the activity of a compound targeting a specific, molecularly well-defined structure assumed to be pivotal for the condition(s), it might be possible to enrol patients with formally different diagnosis, but expressing this target. This should be addressed in exploratory studies, but it is accepted that formal testing with adequate statistical power of such a hypothesis cannot always be done during phase II. Possible consequences with respect to selection of proper reference therapy(ies) must also be considered and the study should be designed so that it is possible to conclude on the benefit – risk in the different subgroups of patients for which a claim is to be made, taking into account multiplicity issues (Points to Consider on Multiplicity Issues in Clinical Trials CPMP/EWP/908/99).

Prior to the initiation of confirmatory studies using non-conventional criteria for eligibility, EU regulatory agreement should be sought.

There are conditions where efficacy failure is defined by not achieving CR after a defined number of treatment cycles ("induction"). In these cases non-response, relapse and death are counted as events in a disease-free survival (DFS) analysis. During the pre-specified induction time period, these events should be regarded as events at randomisation in the primary analysis.

In cases where PFS is as an acceptable primary endpoint for marketing authorisation, the consequences for the data collection on other endpoints must be carefully considered. Meeting a primary endpoint on PFS followed by a submission for marketing authorisation might result in cross-over to the experimental compound, thereby jeopardising the possibility to show effects in terms of other endpoints, particularly overall survival. Even when PFS is an acceptable primary endpoint and the effect shown is of clinical significance, sufficient data on overall survival should be available at the time of marketing authorisation. In general, when PFS is chosen as the primary endpoint, the data on overall survival and other secondary endpoints should be as exhaustive as possible to allow informed clinical decisions to be made.

In children PFS is only suitable if an anatomical remnant without proliferative capacity is to be expected. This can be the case in, e.g. intrathoracic Hodgkin's disease, intrathoracic B-cell lymphoma and bone localizations of lymphomas.

The schedule for response assessments should be well-defined, using the same intervals in control and experimental arms. As frequently these studies cannot be conducted under proper double blind conditions, independent review of events of progression is expected. For some conditions, events of progression will be observed at a slow rate making frequent assessments of events of progression a burden to the patients. Event rate at a pre-specified and justified fixed point in time, e.g. at 2 years might be used as primary endpoint in these cases. Alternatively, events falling between scheduled response assessments should be assigned to the end of the assessment interval in the primary analysis. PFS should be reported as a supportive endpoint when a fixed time-point assessment is used as primary outcome measure. Sensitivity analyses should be undertaken as discussed in appendix 1 of the anti-cancer NfG.

3.1 Treatment administered with curative intent

The ultimate aim of therapy in patients with, e.g. acute leukaemia and being suitable for intensive therapy is to improve cure rate and survival. In some cases, however, and due to the complexity of administered therapies, the impact of a relevantly active experimental compound on these endpoints may be hard to demonstrate. For example, in case the experimental compound is used only as part of an induction regimen to be followed by consolidation therapy and possibly HSCT.

It is foreseen that the experimental compound rarely will be used as single agent therapy, but will be used as add-on to an established, perhaps modified regimen, or as substitution for a compound being part of the established regimen. In this context, maintenance therapy may be regarded as add-on therapy if maintenance therapy is considered non-established.

In case DFS is found to be a justified primary endpoint, it is of special importance that study data are analysed only when sufficiently mature, i.e. when it is foreseen that the DFS plateau is stable and cure rates can be estimated.

Haematopoietic Stem Cell Transplantation

If HSCT is a foreseeable treatment option, it is of importance to define how transplantation should be handled in the analysis plan. It is fully acknowledged that criteria for HSCT vary between institutions and regions. Nevertheless, these criteria should be defined as well as possible in the protocol and reasons for HSCT should be captured by the CRF.

If the decision to transplant is purely defined by baseline characteristics, availability of donor, response or not to therapy and the proportion of patients transplanted is likely to be small, censoring at time of transplantation is acceptable in the primary analysis as response rate and DFS, despite censoring, sufficiently well capture possible differences between study arms. If, however, the proportion of patients transplanted is substantial, or if time to CR or quality of CR, for example, might influence the decision, censoring due to HSCT is considered inappropriate. In these cases DFS or OS should reported as primary endpoint without censoring for HSCT.

As treatment administered prior to transplantation, for example, might affect outcome, proportion of patients undergoing HSCT is not considered to be a suitable primary outcome measure even if all patients responding sufficiently well to treatment are scheduled for transplantation.

Due to the lower complication rate in children and longer life expectancies as compared to adults; the donor sources of stem cells, in respect to HLA matching and donor-patient relation, are highly variable in childhood HSCT. Separate analysis in respect to the (projected) type of donor source should be done. This should also be considered in relation to adult patients.

Reduced or Similar Toxicity Expected

In most cases, a substitution design is foreseen. From a regulatory perspective, a non-inferiority design is acceptable and in most cases DFS is the preferred primary endpoint. It should be recognised, however, that the contribution of a substituted compound to the overall activity of a reference regimen might be hard to define. Therefore a full justification of the selected non-inferiority margin is expected, establishing the absolute efficacy of experimental treatment and the absence of clinically important loss of efficacy relative to reference treatments (Choice of a Non-Inferiority Margin, CPMP/EWP/2158/99).

Confounding effects of therapies administered after end of experimental therapy may make other endpoints than DFS more appropriate. This is of special relevance for non-inferiority studies. This means that CR could be an acceptable primary endpoint in case further therapy is scheduled after end of experimental therapy, one example being induction followed by consolidation therapy. Possible influences of the experimental compound on the activity of consolidation therapy should always be addressed and outcome with respect to CR should be supported by DFS data. It is recommended that CR is defined according to established clinical criteria, but supportive evidence in terms of MRD as defined by molecular criteria should be sought when applicable. MRD data, however, should only be used after proven intra- and inter-laboratory validation.

In children reduced or similar toxicity should refer to short time, long time and developmental toxicity.

Increased Toxicity Expected

Substitution or add-on designs may apply. In most cases, superiority in terms of DFS should be demonstrated and the benefit in terms of prolonged time to event should be sufficiently large to balance increased toxicity.

Major Increase in Toxicity Expected

The aim should be to demonstrate increased cure rate or improved survival. In some cases a major increase in DFS and supportive data to rule out relevant negative effects on survival may be acceptable, but in these cases EU regulatory advice is recommended prior to the initiation of the confirmatory study.

3.2 Treatment administered without curative intent

Treatment is administered without curative intent in a wide variety of conditions and lines of therapy. While “palliation” may be used to cover all situations where “cure” is not the objective, difference is made here between situations where the realistic objective is to achieve long-term disease control and cases where the prognosis is poor and where only short-term disease control is expected (“palliation”).

Treatment administered with the intent to achieve long-term disease control

Typical conditions include low-grade lymphoma, multiple myeloma and the chronic leukaemias and lines of therapy where there are well established reference therapies available as well as at least likely meaningfully active next-line treatment options.

Reduced or Similar Toxicity Expected

Substitution or single agent studies are foreseen. From a regulatory perspective, a non-inferiority design is acceptable and PFS is considered an appropriate primary endpoint.

Patients withdrawn from therapy prior to progression, e.g. due to toxicity, should be followed until disease progression whether on next line therapy or not. This allows for informative alternative PFS analyses including censoring at time of withdrawal, counting as event withdrawal prior to progression and progression off study therapy as event, which in most cases is the preferred primary analysis.

Increased Toxicity Expected

The aim should be to demonstrate superiority in terms of at least PFS.

Survival data should be available at time of submission. It is acknowledged that mature survival data cannot be expected in all cases, though a justification why this is the case should be provided. Post approval follow-up with respect to survival is expected in these cases. If absence of an increase in treatment-related mortality is not established with reasonable certainty, mature survival data should be available for the assessment of benefit – risk prior to licensure.

Major Increase in Toxicity Expected

The principal objective should be to demonstrate improved survival. In individual cases, however, this might be non-achievable due to expected good prognosis with respect to survival and availability of numerous active next line regimens, including experimental therapies, at time of disease progression.

If PFS is the selected primary endpoint for the study, this requires a thorough justification. Even though only a major benefit in terms of PFS prolongation would be acceptable, it is advised that the number of patients included should be sufficient to obtain a precise estimate of possible effects on overall survival. A careful discussion at the planning stage is also needed as regards the assessment of therapy-related fatalities. Absence of mature survival data at time of submission should be carefully justified.

Palliative therapy

In the context of this appendix, this mainly refers to last line settings where the prognosis as regards survival is poor and where it might be problematic to identify sufficiently documented reference therapies. In other cases, patients are considered not suitable for intensive, potentially curative therapy as defined by clear and as far as possible unambiguous criteria.

In cases where there is no established reference therapy, BSC or investigator's best choice are acceptable.

In a study conducted with BSC as reference regimen, the objective should be to demonstrate prolonged survival and/or improved symptom control or QoL. The latter requires that the study is conducted under proper double-blind conditions. If the reference regimen is known to be active, superiority in terms of PFS might be acceptable. In these cases, the following will be taken into account in the benefit – risk assessment: the evidence showing activity of the reference therapy, the magnitude of the benefit over the reference regimen shown in terms of PFS, the tolerability/toxicity profiles and the prevalence of the condition.

It is acknowledged that patients may be considered suitable only for palliative therapy at baseline due to, e.g. poor performance status, but may respond so well that further therapy can be administered with curative intent, including, e.g. reduced intensity HSCT. How to handle these patients should be defined in the analysis plan.

4. DISEASE SPECIFIC ISSUES

4.1 Chronic Myelogenous Leukaemia

CML is uniquely well characterised among human malignancies with respect to underlying molecular cause, evolution of disease, response to BCR-ABL tyrosine kinase inhibitors (TKI) and molecular events causing drug resistance. Due to the dynamics of the field it is of major importance to follow the evolution with respect to standardisation of molecular techniques used in the assessment of the disease. Generally acknowledged clinical treatment guidelines should also be followed, e.g. as regards criteria defining treatment failure.

Chronic Phase

In the first-line setting, comparative trials should be undertaken against a licensed reference product. Currently, complete cytogenetic response rate at 1 year is an acceptable primary objective in superiority trials. Long-term follow-up (5+ years) is expected with respect to duration of response/resistance development. For non-inferiority trials, prolonged follow-up is needed prior to licensure and PFS is the preferred primary endpoint. Progression should be defined in accordance with updated treatment guidelines.

Due to too limited experience, *BCR-ABL* transcript level ("molecular response") is from a regulatory perspective yet not an acceptable primary outcome measure, but its use as secondary endpoint is non-controversial. Technique and response criteria should be justified and comply with updated guidelines and consensus documents.

In patients not responding to a licensed TKI or after secondary efficacy failure, studies may be undertaken in an unselected patient population fulfilling established criteria for non-response or secondary failure, alternatively patients with progressive disease may be enrolled taking into account pattern of mutations if properly justified. In the second-line setting where licensed products are available, randomised trials vs. an active comparator are expected. As the target population is small, EU regulatory agreement is recommended prior to the initiation of pivotal trials.

For a new TKI and provided that activity in terms of cytogenetic response and duration of response is convincingly high and tolerability and toxicity are well documented and acceptable, single arm studies may still be adequate to support licensure in case a third or later line indication is targeted. Enrolled patients should be well characterised with respect to secondary mutations and an important aim is to confirm activity in relation to relevant mutations. If justified by data, patients with certain mutations associated with low activity for the experimental compound may be excluded, but this will be reflected in the labelling.

For a non-TKI, randomised comparative trials with a licensed compound are expected.

Patients intolerant to prior TKI therapy might also be enrolled in these studies, but efficacy should be reported separately. Symptoms and signs defining intolerance to the prior TKI should be reported and should be followed and reported on therapy with the experimental compound.

If patients with increased risk of efficacy failure to TKIs are identifiable at baseline, it is foreseen that add-on studies with a non-TKI being active in patients with CML will be undertaken. Superiority in terms of PFS should be demonstrated comparing the combination regimen with a single TKI. Pending the effect size of the add-on activity, superiority in terms of complete cytogenetic response at 1 year might be acceptable, subject to follow-up as regards PFS.

Accelerated Phase, Blast Crisis

It is foreseen that the vast majority of these patients has been treated with a TKI. The guidance given above with respect to patients after failure on a TKI therefore applies.

4.2 Myelodysplastic Syndromes

Myelodysplastic Syndromes (MDS) are a heterogeneous group of malignant clonal disorders which share two main features, i.e., progressive cytopenia and risk for transformation to AML. Until recently, supportive care or allogeneic stem cell transplantation (ASCT) were the only available treatment options. ASCT is potentially curative, but poses high mortality risk in the predominantly

elderly MDS population. Supportive care options include blood transfusions, antibiotics, erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF).

Diagnosis and Classification of MDS

Many patients with MDS are asymptomatic at time of diagnosis, but eventually develop symptomatic anaemia, thrombocytopenia and neutropenia alone or in combination. The clinical course is highly variable and several classification systems have been developed, including FAB, WHO and the International Prognostic Scoring System (IPSS).

IPSS is based on percentage bone marrow blasts, cytogenetics, and number and degree of peripheral cytopenias at diagnosis, enabling identification of four risks groups: low, intermediate-1, intermediate-2, and high risk. Recently, new clinical and laboratory variables were identified that might add prognostic information to the IPSS (red blood cell transfusion dependency, high levels of LDH). Sponsors are therefore advised to follow closely the expected refinement of prognostic scores to be used in the design of clinical trials when sufficiently validated

The WHO classification of myeloid neoplasms encompasses disorders that show both dysplastic and proliferative features at time of diagnosis. The following disorders belong to this category: chronic myelomonocytic leukaemia (CMML), atypical chronic myeloid leukemia, juvenile myelomonocytic leukaemia, and myelodysplastic /myeloproliferative disease, unclassifiable (MDS/MPD, U).

In childhood, MDS should be discerned in adult MDS and paediatric MDS. Juvenile myelomonocytic leukaemia (JMML) is the specifically in childhood occurring proliferative disease assumed to be a MDS. Studying JMML patients should be classified as genuine JMML, neurofibromatosis-, Noonan syndrome- and trisomy 8 mosaicism-related. Other entities labelled as MDS in childhood are, constitutional bone-marrow failure syndromes (such as Fanconi anaemia, Kostmann syndrome, Shwachmann-Diamond syndrome, Diamond –Blackfan anaemia), trisomy 8 mosaicism, familial MDS (first –degree relative with MDS/AML). Studies should consider these differences. The IPSS scoring is of limited value in children and cannot be used as such

Inclusion Criteria in Exploratory and Confirmatory Trials

Since evolution of bone marrow failure and survival depends on patients' baseline characteristics, any efficacy or safety conclusion may apply only to patients sharing similar prognostic features. It is, however, also acknowledged that pharmacological activity may vary in relation to, e.g. cytogenetic characteristics. There is thus a need for rather extensive exploratory studies in order to identify the proper target population for confirmatory studies.

Even though it is unwise in general to include patients with highly variable prognosis if left untreated, this might become necessary if exploratory studies indicate similar activity irrespective of prognosis, e.g. due to common expression of a certain drug target. Stratification using a well established prognostic score such as IPSS is recommended in such cases.

Central read of bone marrows and cytogentics should be undertaken at least in confirmatory trials.

Treatments Aiming at Symptom Improvement

Alleviation of symptoms related to cytopenia is an acceptable aim of treatment in patients with low grade MDS. In most cases this means reduction of anaemia-related symptoms. Due to prevalent co-morbidities in this elderly population, symptom scales, even if properly validated, may be too insensitive to capture also relevant differences between treatment groups not least as transfusion of red blood cells must be individualised due to e.g. concomitant cardiovascular disorders. Loss of need for transfusion for a defined period of time (in combination with improved Hb) is therefore considered acceptable outcome measures.

These trials, however, must investigate the impact of treatments (test and reference) on safety and on more global outcome variables, including disease evolution. OS and disease evolution must be prospectively assessed to exclude detrimental effects of the test drug that would outweigh documented benefits.

If studies can be undertaken under proper double blind conditions, effects of treatments on MDS-related symptomatic burden and QoL are welcomed.

Placebo on top of best supportive care based on currently available treatment options is an acceptable comparator if no specific active drug is available to treat the targeted symptoms. It is acknowledged that EPO is not licensed within the EU for the treatment of anaemia in patients with MDS, but subgroups of patients are identifiable with an increased likelihood of meaningful response. For these patients EPO may serve as comparator. Alternatively, patients non-responsive to EPO may be enrolled.

Treatments aiming at reducing risk for disease progression

Since progression to more severe stages of MDS and to AML is common and signals poor prognosis, any treatment that could delay or avoid progression is expected to have a positive impact on clinical outcome. Concerning the respective merits of disease progression-related endpoints and OS, all recommendations expressed in the main text of the Notes for Guidance on Anticancer Products do apply. Haematological responses cannot be accepted a priori to assess efficacy, and response rate is more suitable for exploratory trials (detecting activity and dose-effect relationships) than for efficacy purpose (and detection of a clinical benefit).

Confirmatory studies are expected to be randomised and well controlled using a licensed medicinal product as reference. In principle, PFS (e.g. leukaemia-free survival) is an acceptable primary endpoint, but survival data are needed in order to exclude with reasonable certainty detrimental effects on survival. The definition of progression must be based on a combination of standardised clinical and biological data and centralised blinded review is needed in order to establish progression.

Since symptom burden is of major concern in all stages of MDS, QoL assessment in properly double blind studies are welcomed as secondary endpoint also in trials aiming to establish a benefit in terms of survival and/or progression.