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Committee for Medicinal Products for Human Use (CHMP)

Appendix 2 to the Guideline on the evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3) on Confirmatory studies in Haematological Malignancies

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CHMP, Haematological Malignancies

Superseded by "Evaluation of anticancer medicinal products in man - Appendix 4" published January 2013
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. The main guideline also provides some more details, e.g. with respect to choice of reference regimen and use of historical control and should thus be consulted. Based on regulatory experience since the release of the main document in 2005, this appendix contains some updated guidance of relevance also for solid tumours, e.g. with respect to maintenance therapy, use of “safety” as outcome measure and studies in small study populations.

2. General Principles

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. In general, these studies are expected to be randomised, reference-controlled and the target population, as well as the reference regimen (may be best supportive care (BSC)), are normally defined by disease, stage and prior lines of therapy.

While it is generally acknowledged that the aim of drug development within this field 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.

From a drug development perspective, haematological malignancies may in many aspects be viewed as similar to solid tumours. There are, however, some characteristics of possible importance from a study design perspective including:

• Treatment may encompass different phases: induction, consolidation and maintenance.
• Increasing use of allogeneic stem cell transplantation.
• Regimens with variable dose intensity are used in clinical practice, some without being formally licensed.
• Response may be determined at different levels of sensitivity, from imaging to molecular response.

As this appendix is focused on the design of confirmatory studies, the aim of therapy, curative versus non-curative including studies with palliative objectives 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 alternatives, in clinical practice still 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.

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, "major increase in toxicity", however, in most cases refers to a fear that treatment-related irreversible adverse events or severe impairment to patient condition will be increased in the experimental arm. Other issues to take into account include 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 measures in order to enable a proper benefit – risk assessment.

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, e.g. a fixed number of cycles of therapy may be administered, followed by watchful waiting.
In order to support licensure for maintenance/prolonged therapy, if not established, it should be demonstrated that this concept poses a favourable benefit risk. If the experimental agent is used as part of initial therapy with, e.g. a fixed number of cycles, it is normally expected that a favourable benefit/risk of prolonged therapy is demonstrated in comparison with stopping experimental therapy after a fixed number of cycles.

As disease progression on therapy at least signifies resistance to that regimen and might affect the activity of next-line therapies, progression free survival (PFS) is no an ideal endpoint in studies comparing prolonged therapy with BSC. If at all possible, these studies should therefore be designed with the aim to document patient benefit in terms of survival. Alternative endpoints, such as treatment-free survival (TFS, defined as time from end of therapy until need for next line treatment or death), overall response rate (ORR) or PFS on next-line therapy, etc. may be discussed in EU regulatory advice procedures.

In contrast to solid tumours, it is acknowledged that disease specific response criteria are unavoidable in many cases and that full harmonization has not yet been accomplished for some disease entities. Therefore it is of importance to follow the progress made by international working groups on these issues. Especially if less conservative disease specific response criteria are introduced in new guidelines, a justification with focus on aspects of drug development is expected from the sponsor. It is acknowledged that clinical guidelines may change over the course of the conduct of studies, e.g. with respect to response criteria or proper reference regimens. In these situations the version at time of study start is normally acceptable, but a justification is expected.

3. Design of confirmatory studies

3.1. Methodological and Regulatory Considerations

Patient population

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 and updated treatment guidelines are 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 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. In case adjusted analyses are to be undertaken for covariates other than those used for stratification, these factors should be pre-specified in the protocol or the statistical analysis plan (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 histological 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. 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, based on all available evidence, including non-clinical and pharmacological data, 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 advice should be sought.

Some possible target indications comprise very small groups of patients, so small that "exceptional circumstances" might apply. Unless the target for activity is expressed only in these rare conditions, sponsors are in general advised to initiate confirmatory studies in these patient groups 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 clinical response rate, duration of response as well as outcome
measures such as HSCT rate, use of minimal residual disease (MRD) to define response rate and recurrence of disease, as appropriate. Mature time to event endpoints such as PFS and OS should be reported even though it is acknowledged that formal statistical significance cannot always be expected, even if the experimental compound is relevantly efficacious.

**Reference therapy**

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 (including the objectives of the trial).

In some cases there is no well documented reference regimen, even though patients in clinical practice are treated with certain regimens. BSC is acceptable in these cases, but an active comparator, documented e.g. in terms of response rate, is often preferable. If a single reference regimen cannot be defined, investigator’s best choice is an option. 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.

**Endpoints**

The appropriateness of specific outcome measures such as cure rate, PFS etc. as primary endpoint is discussed later in this document.

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 reducing the possibility to show effects in terms of other endpoints, particularly overall survival (OS). This is of special relevance for applications including only one pivotal trial where data on overall survival and other secondary endpoints should be as exhaustive as possible to allow informed regulatory and clinical decisions to be made.

The intent-to-treat analysis based on all patients randomized who started the allocated randomized treatment is the preferred primary analysis for the efficacy endpoint (e.g. PFS). Patients withdrawn from therapy prior to progression, e.g. due to toxicity, should be followed until disease progression, whether a next line therapy has been started or not. This allows for alternative informative PFS analyses including: 1) censoring at time of withdrawal; 2) counting as event withdrawal prior to progression.

The schedule for response assessments should be well-defined, using the same intervals in control and experimental arms. As frequently studies cannot be conducted under proper double blind conditions, independent review of events of progression if based on imaging (or other sources of information suitable for “blinded” evaluation, e.g. bone marrow morphology and cytogenetics) is recommended, also if OS is the primary endpoint. 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 might be used as primary measure in these cases. When event rate at a single point in time is selected for the primary analysis, it is in most cases recommended that all patients should have been on study for that period of time and that the time point should be selected so that a majority of events in the long run should have occurred. PFS as assessed by the investigator should be reported as a secondary endpoint when a fixed time-point assessment is used as outcome measure. Events of progression occurring between scheduled response assessments should be subject to sensitivity analyses as discussed in appendix 1 of the anti-cancer NFG.

**Non-inferiority**

In case of improved (or similar) toxicity/tolerability, non-inferiority in terms of efficacy is sufficient. If, however, exploratory study data, e.g. a high and unprecedented complete response (CR) rate, indicate that 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 if non-inferiority in terms of progression-free survival (PFS) in a small study would formally be sufficient for licensure from an efficacy perspective.

In non-inferiority studies using a substitution design (AB vs. AX) it should be recognised, that the contribution of a substituted compound to the overall activity of a reference regimen might be hard to define (Main guideline, III.1.4). If the magnitude of the contribution of the substituted compound cannot be directly established based on historical data, also circumstantial evidence indicating that the substituted compound is of clear importance for the overall activity of the reference regimen should be
made part of the justification of the selected non-inferiority margin. In addition, absence of clinically important loss of efficacy of the experimental regimen relative to the reference regimen should be demonstrated (Choice of a Non-Inferiority Margin, CPMP/EWP/2158/99). Due to the uncertainties in establishing a proper non-inferiority margin in these cases, it is expected that a clinically meaningful reduction in toxicity is convincingly demonstrated.

### 3.2. Treatment administered with curative intent

The ultimate aim of developing new therapies in patients with, e.g. acute leukaemia 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.

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 the treatment of acute leukemia, lack of achievement of CR, relapse and death without relapse are counted as events in an event-free survival (EFS) analysis. Those patients who did not reach CR during the pre-specified induction phase will be considered as events at time 0. Those who reached CR will be considered at risk of relapse or death without relapse in the primary analysis. This definition of EFS applies to all sections of this document.

In case EFS is found to be a justified primary endpoint, it is of importance that study data are analysed only when sufficiently mature, i.e. when it is foreseen that the EFS plateau is stable or when additional disease recurrence is rare.

In patients with high grade lymphoma, PFS may be used as outcome measure. Not achieving at least partial response (PR) after a defined period/number of cycles may be regarded as treatment failure in some protocols and only those achieving at least PR continue on therapy. In the primary analysis it is recommended that patients not reaching PR are followed off or on next-line therapy until an event of progression or death is reached.

When cure is the objective of therapy, it is advised that disease-free survival at a pre-specified time point is used as outcome measure (see above with respect to timing).

### Haematopoietic Stem Cell Transplantation

If allogeneic stem cell transplantation (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 (e.g. patient eligibility, patient matching, conditioning regimen, graft versus host disease prevention, etc) vary between institutions and regions. Nevertheless, these criteria should be defined as far as possible in the protocol and reasons for performing or not performing 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 for the primary analysis as, despite censoring, efficacy endpoints (response rate, EFS) 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 EFS, disease-free survival and OS should be reported without censoring for HSCT.

As treatment administered prior to transplantation, for example, might affect outcome of HSCT, 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.

Autologous stem cell transplantation constitutes less of a concern from an assessment perspective and may be viewed as intensified consolidation therapy where the consequences on short-term mortality and possible long-term benefit are less pronounced than after HSCT. Nevertheless, heterogeneity in the conduct of autologous transplantation should be avoided as far as possible, but censoring should normally not be undertaken.

If an experimental compound is to be studied as part of HSCT, the general guidance provided in this section applies. Due to the complexity of the clinical setting, EU regulatory advice is recommended.
**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 EFS or PFS, as appropriate, are acceptable primary endpoints.

Confounding effects of therapies administered after the end of experimental therapy may make endpoints other than PFS or EFS more appropriate. This means that CR (and CR + PR, if specifically justified) after end of experimental therapy could be an acceptable primary endpoint when further therapy is scheduled, such as when induction is followed by consolidation therapy. In these cases, the possible influence of the experimental compound on the activity of consolidation therapy should always be addressed and outcomes with respect to CR should be supported by EFS or PFS data.

It is recommended that CR is defined according to established clinical criteria, but supportive evidence in terms of Minimal Residual Disease (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.

**Increased Toxicity Expected**

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

A major increase in CR associated with trends in PFS or EFS, and survival, however, might be sufficient if treatments administered after the end of the experimental therapy are likely to confound overall outcome. This is of special relevance if the target population is small.

**Major Increase in Toxicity Expected**

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

### 3.3. 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, a distinction 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 intention to achieve long-term disease control**

Typical conditions include low-grade lymphomas, multiple myeloma and chronic leukaemias for which established reference therapies are available and next-line treatment options are likely to be meaningfully active.

**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. In case of relevantly reduced toxicity, mature survival data may be submitted post licensure if justified by study data.

**Increased Toxicity Expected**

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

Survival data should be made available at the time of submission. It is acknowledged that mature survival data cannot be expected in all cases, though a justification explaining 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.

It is acknowledged that alternative endpoints may be more appropriate in certain situations, i.e. when maintenance therapy is investigated in areas where this has not established (see general principles). The wish may also be to enable a long treatment-free interval after intense induction therapy. In these cases, or if a not currently established surrogate for long term benefit is planned to be used as primary endpoint, EU regulatory advice is recommended prior to the initiation of confirmatory studies.

**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 the 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 for the assessment of possibly therapy-related fatalities. Absence of mature survival data at the 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 for 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 therapy, the objective should be to demonstrate prolonged OS and/or improved symptom control or quality of life (QoL). The latter requires that the study is conducted under proper double-blind conditions. If the reference regimen is known to be active, but not established, 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 PFS benefit over the reference regimen, 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. Safety

Also from a safety perspective the expected prognosis should be considered in the planning of the studies. The following issues should be taken into account:

**Acute toxicity:** Bone marrow failure is often a presenting symptom in haematological malignancies and is frequently aggravated by treatment. In contrast to the approach in solid tumours, dose reduction for this reason is often not indicated, in particular if the aim is curative.

Monitoring of frequency and type (viral, bacterial, fungal) of possible, probable or proven infections should be undertaken.

**Acute, non-haematological toxicity** should be evaluated as in patients with solid tumours.

**Sub-acute toxicity:** Sub-acute toxicity of special interest includes immunosuppression which may continue for months after end of therapy. Monitoring for opportunistic infections for up to one year after the end of therapy should be considered for compounds known or suspected to cause long term immunodeficiency.

**Late toxicity:** A substantial percentage of patients with haematological malignancies is cured or achieve long-term disease control after therapy. Long term follow up for toxicity is therefore relevant. Late toxicity includes secondary malignancies and certain organ toxicities (e.g. CNS, cardiovascular). The number of patients suffering from late toxicities increases over time and is therefore an objective for post licensure pharmacovigilance activities.

If the aims of the study include demonstration of improved safety, the protocol should specify how this should be accomplished. It is not acceptable to focus on one toxic effect only. The outcome measure(s) should provide unbiased information on overall toxicity and tolerability, perhaps in addition to a specific item such as neuropathy where a clinically relevant improvement is expected. As there is limited experience with this type of studies, EU regulatory advice should be considered.
5. Disease specific guidance

5.1. 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. guidelines defining treatment failure criteria.

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. Events of failure to achieve response and progression should be defined in accordance with updated treatment guidelines.

Due to limited regulatory experience, BCR-ABL transcript level ("molecular response") is yet not an acceptable primary outcome measure, but its use as secondary endpoint is non-controversial. Techniques and response criteria should be justified and should comply with updated guidelines and consensus documents. When new scientific data (including generally acknowledged standardized techniques for assessment) become available justifying use of molecular response as primary endpoint, acceptance from a regulatory perspective is foreseen. EU regulatory advice should be sought to confirm the choice of the endpoint.

In patients failing a licensed TKI, studies may be undertaken in all patients fulfilling established criteria for non-response or secondary failure; alternatively patients may be enrolled also taking into account mutation patterns if properly justified. In the second-line setting where licensed products are available, randomised trials vs. an active comparator are expected. 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 induction 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.

These recommendations may apply also for a non-TKI intended for late line therapy, but mechanistic studies are expected aiming at clarifying mechanisms of resistance to the experimental compound. As the target population is small, EU regulatory advice is recommended prior to the initiation of pivotal trials.

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 documented in detail (including grading) prior to inclusion in the study. As class related adverse reactions are common, it is of importance that "cross-intolerance" is excluded as objectively as possible due to the subjective nature of "tolerance" in many cases.

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 that is active in patients with CML will be undertaken. Superiority 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 long term follow-up.

Accelerated Phase, Blast Crisis

It is foreseen that the vast majority of these patients have been treated with a TKI. For accelerated phase the guidance given above with respect to patients after failure on a TKI therefore may apply. However due to the rarity of blast crisis and the foreseen complexity of the therapeutic situation, EU regulatory advice should be considered. This applies also to accelerated phase if the guidance related to chronic phase is considered non-applicable.
5.2. 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, low dose Ara-C, intensive chemotherapy or HSCT were the only available treatment options. HSCT 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 the 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 the percentage of bone marrow blasts, cytogenetics and number and degree of peripheral cytopenias at diagnosis, enabling identification of four risk 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 the 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).

Inclusion Criteria in Exploratory and Confirmatory Trials

Since evolution of bone marrow failure and survival depend 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 prognostic score, 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.

Treatments Aiming at Symptom Improvement

Alleviation of symptoms related to cytopenia is an acceptable aim of treatment in patients with low risk MDS. In most cases this means reduction of anaemia-related symptoms. Due to prevalent comorbidities in this elderly population, symptom scales, even if properly validated, may be too insensitive to capture also relevant differences between treatment groups especially 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 hemoglobin) is therefore considered an acceptable outcome measure.

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 Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3) do apply. Haematological or cytogenetic 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 purposes (and detection of a clinical benefit).

Confirmatory studies are expected to be randomised and well controlled using a licensed or evidence based medicinal product as reference. In principle, PFS is an acceptable primary endpoint, but survival data are needed in order to exclude with reasonable certainty detrimental effects on survival. In high risk MDS, however, survival is the preferred measure of patient benefit. In the case HSCT is a realistic treatment option in responding patients, please refer to the section "Treatment administered with curative intent". 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 also in trials aiming to establish a benefit in terms of survival and/or progression.