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Appendix 4 to the guideline on the evaluation of anticancer medicinal products in man

Condition Specific Guidance

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1. Non-Small Cell Lung Cancer

NSCLC is a leading cause of cancer morbidity and mortality. Most patients diagnosed with NSCLC present with advanced disease and many of the patients who do present early will go on to develop metastatic lung disease. Common disease related symptoms include pulmonary effects (cough, dyspnoea) and general symptoms of pain, anorexia and high degrees of psychological distress.

Recent developments in the knowledge of NSCLC biology have uncovered targets for therapeutic agents, creating new opportunities but also adding complexity to the interplay between potential biomarkers and drug candidates and consequently, to the assessment of their value in the management of this disease

These factors warrant a specific guidance for the assessment of medicinal agents directed at the management of NSCLC in the context of the present guideline. Namely, criteria, definitions, and other reflections are provided for the use of biomarkers, the systematization of therapeutic phases in the course of the disease, and the endpoints applicable to the assessment of clinical benefit.

Classification of NSCLC

NSCLC must be classified using pathological and molecular features. The importance of consistent, accurate and reproducible histological subtyping cannot be understated.

Pathological evaluation using internationally agreed criteria should determine the histological classification (WHO Classification) and the extent of the disease (UICC TNM Classification). Immunohistochemical analysis may improve pathological diagnosis, particularly for small biopsies.

Pathological evaluation to determine the molecular features of the tumour is highly recommended, and should be carried out in line with current scientific knowledge (see section 5).

Stratification according to disease and patients characteristics

Exploratory trials should clearly test hypotheses of activity in accordance with known or presumed biological roles of their intended molecular targets. For this purpose, trial subjects must be constituted by patients with disease that is well characterized according to relevant biomarkers. Subsequently, the same applies to confirmatory trials which must restrict inclusion to categories of patients with clinical and molecular characteristics that increase the likeliness of response and hence clinical benefit.

It is particularly important to perform specific trials, or at least to stratify patients based on baseline characteristics such as tumour histology and expression of predictive molecular biomarkers. Such markers help delineate distinct disease entities, enriching the patient population to those with the target of interest and defining subsets of patients most likely to benefit from therapy. However, the success of such an approach depends heavily on having an accurate diagnosis.

At least a third of lung cancer patients are 70 years or older, older patients should be actively recruited into clinical trials. Other variables such as smoking status, performance status and geographical origin should also be considered in the recruitment of patients.

Treatment definitions

Adjuvant or neoadjuvant therapy may improve survival in certain groups of patients by decreasing the risk of metastatic disease (see section 7.5.2). For adjuvant therapy, patients should generally be relatively young without significant co-morbidities who have undergone complete resection by lobectomy. The tolerability of any adjuvant therapy must be considered. Neoadjuvant therapy may reduce tumour volume, control micrometastasis and if adequate tumour samples are obtained may provide valuable information regarding tumour response and tumour biology.

The concept of maintenance therapy should be considered for well tolerated medicinal products and a maintenance approach may represent an effective way of delivering second line therapy. Maintenance therapy is the prolongation of treatment at the end of a defined number of initial treatment cycles following tumour control (tumour response or stable disease). Continuation or true maintenance therapy refers to the continuous administration of at least one of the agents given in first line therapy (either at the same intensity or at a lower intensity). Switch maintenance or early second line therapy refers to the immediate administration of a different agent not included as part of the first line regimen following completion of therapy.

Efficacy endpoints

For exploratory studies, ORR may be an acceptable endpoint for early evaluation of new medicinal products in NSCLC (see section 6), though modest response rates may in fact underestimate patient reported benefits. In light of this, endpoints which also capture clinical benefit and record palliative control (pain control, weight loss, performance status) may be included in the study design. Prognostic and predictive molecular markers and mechanisms of resistance should be actively investigated.

Improving survival remains the principal objective for patients with NSCLC and in many cases OS should be selected as the primary endpoint for confirmatory studies. If, however, the experimental regimen is likely to be well tolerated, PFS benefit might enable a proper benefit – risk assessment, especially if supported by data on HRQoL/PRO (Appendix 2).

For maintenance studies, if conducted versus placebo/BSC, the recommended endpoint is OS (see section 7.1.5).

2. Prostate Cancer

The proper design of prostate cancer studies is a challenge since there are several complicating issues.

Firstly there is a large variability in the biology of prostate cancer. Autopsy analyses show that almost every man will ultimately develop prostate cancer, the majority being slowly progressive, and only a minority aggressive with fatal outcome. There is thus a risk related to the detection of indolent tumours and a challenge to identify clinical significant prostate cancer of importance to treat. Treatments with curative intent include surgery and/or radiotherapy but active surveillance is an alternative and reduces the risk for overtreatment and side effects related to radical therapy.

Secondly, metastatic prostate cancer is frequently found in the bone only, and imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), radionuclide imaging and positron emitting tomography (PET) with different traces are less suitable to estimate bone disease and soft tissue metastases are uncommon clinical presentation of prostate cancer.

Prostate specific antigen (PSA) is not cancer specific, but changes in PSA levels during different therapies are used as a biomarker. Individuals' PSA values are not comparable to each other but changes and nadir are prognostic.

Prostate cancer is diagnosed on histopathology of core biopsies, but the likelihood to detect a cancer is dependent on number of biopsies, the prostate volume and the cancer location (anterior cancer and cancer located near the urethra is difficult to biopsy using transrectal technique).

Cancer prevention studies

The recommended primary outcome measure in prostate cancer prevention trials is disease free survival or the rate of diagnosed prostate cancer at a predefined point in time. Baseline risk factors of likely prognostic importance include age, ethnicity, family history of prostate cancer, serum PSA, normal/abnormal digital rectal examination or transrectal ultrasonography.

It is crucial to have identical diagnostic procedures between active and placebo groups in order to avoid sampling bias. Additionally, long observation periods are needed as both the induction period and the latency period to detect a prostate cancer are long. Even small differences in management between the treatment groups may harbour confounding factors of importance.

It is crucial to assess the clinical relevance of the diagnosed cancer, i.e. the diagnosed cancer should be clinically significant. Stage, Gleason score and PSA level are regarded as the most appropriate prognostic factors of outcome of new diagnosed prostate cancers.

Minimally invasive treatment

Since available treatment options with curative potential for localized prostate cancer are associated with side effects that interfere with HRQoL, a concept of minimal invasive treatment, i.e. focal therapy, has been introduced. The aim is to delay or avoid the need for, e.g. surgery using techniques and/or medicinal compounds that offer low risk of side effects.

As a first step, anti-tumour activity has to be proven. This may be achieved in trials using subjects planned for radical surgery where one lobe containing cancer is treated with the minimally invasive concept before radical surgery.

For confirmatory trials, an acceptable primary end point is time to need for radical therapy, or proportion of patients in need for such therapy at a predefined point in time. Until now, however, there is no consensus as regards criteria defining need for radical therapy. Clinical guidelines developed by European Urology Association (EAU), National Cancer Comprehensive Network (NCCN) and National Institute for health and clinical excellence (NICE) suggest several options. This unfortunate situation is acknowledged; nevertheless clear criteria defining need for radical therapy should be in place in study protocols, especially if the study cannot be conducted under double-blind conditions. Independent adjudication is recommended.

PROs and genitourinary function preservation should be reported as secondary endpoints.

Prognostic factors of relevance in the planning of the study include: age/life expectancy, disease stage, Gleason score and PSA.

Neoadjuvant and Adjuvant therapy

As more effective treatment options become available in the metastatic setting, more trials are expected also in the (neo) adjuvant treatment.

Adjuvant endocrine treatment has been proven effective in patients receiving radiotherapy or surgery in terms of improved progression free survival; however adjuvant androgen deprivation has improved overall survival only for patients receiving radiotherapy. Neoadjuvant hormonal treatment prior to radiotherapy improves progression free survival but prior to surgery hormonal treatment only reduces the number of positive surgical margins without any favourable outcome on progression free survival.

The definition of progression-free survival is usually based on PSA, and differs between radiotherapy and surgery groups. After successful surgery the PSA levels is immediately <0.2 ng/ml and a commonly used definition of relapsed disease is any measurable PSA levels above 0.2 ng/ml confirmed by two consecutive measures. But after successful radiotherapy a decrease in PSA is observed over several months not always reaching levels <0.2 ng/ml.

There have also been cases of demonstrated “PSA bounce” in patients proven relapse-free with long-term follow-up. This type of PSA kinetics after radiotherapy has urged for a consensus and a definition of relapse after radiotherapy is an increase from nadir of 2.0 ng/ml (RTOG-ASTRO criteria Phoenix).

It is acknowledged, however, that there is an ongoing debate on how to best define relapse. Irrespective of this, criteria defining progression and need for treatment of recurrence should be clearly stated in the protocol. PSA measurement and any other clinical assessment should be done at the same pre-specified time-point in experimental and control groups. The rate of biochemical, local and systemic failure should be reported separately, as well as the rate of secondary treatment.

Therapy for high-risk localized disease and locally advanced disease

Clinical stage, Gleason score and PSA level should all be considered in the evaluation of risk of recurrence in patients with localized disease. High-risk localized prostate cancer, includes either locally advanced disease, i.e. a bulky tumour with growth outside the prostate capsule (T-stage 3-4) based on per rectal assessment, or a tumour that express several high-risk factors indicating a more advanced tumour stage. Common is the absence of distant metastases; however this is a function of which diagnostics is performed.

The protocol should define methods to be used to exclude distant metastases. Digital rectal examination is still considered the most appropriate method to assess local progression. If studies cannot be conducted under proper double blind conditions, examination by two independent urologists is recommended. Response criteria are otherwise similar to those for metastatic disease presented below.

Distant metastases-free survival, PFS including local progression, genitourinary function and validated PRO questionnaires constitute relevant outcome measures.

Therapy for metastatic disease

Hormone naive

During more than 60 years the treatment of choice in metastatic prostate cancer has been androgen depletion therapy. More than 90% of the cancers are androgen dependent, but eventually the disease becomes castration refractory. Currently androgen depletion is often introduced in the adjuvant setting or at PSA relapse without detectable metastases. The first sign of castration refractory state is often detected as PSA increase despite serum testosterone at castration levels.

Several definitions have been discussed, but a consensus has been reached during the work of The Prostate Cancer Clinical Trials Working Group (PCWG2). The PCWG2 proposes that subjects should be categorised according to rising PSA state (non-castrate or castrate) and the occurrence of clinical detectable metastases (non-castrate or castrate) throughout the natural prostate cancer history.

It is foreseen that active medicinal agents in late castration refractory state of prostate cancer will challenge the use of androgen depletion therapy in order to avoid the symptoms associated with castration treatment.

The use of anti-androgens provides an additional treatment option in the hormone naive status. The anti-androgens treatment has both a direct effect and a withdrawal effect. This has to be taken into account when designing clinical trials and it is often stated that anti-testosterone treatment should have been removed at least 4-6 weeks before inclusion to avoid PSA decrease from withdrawal effect.

For medicinal products aiming at achieving medical castration, it is sufficient to convincingly demonstrate the achievement and maintenance of castrate levels of testosterone in the absence of

breakthroughs and micro-surges. If the aim is to achieve “surgical level” of castration, 20 ng/dL and below, clinical benefit should be demonstrated in a randomized trial vs. standard therapy (target 50 ng/dL and below) if the benefit of a lower serum testosterone target level cannot be demonstrated by other means.

For non-hormonal products to be used as add-on or instead of, it is expected that favourable effects on PFS (see below) and/or OS are demonstrated in-line with the main guideline text.

Castration refractory

In the castration refractory state of the disease, there is still some hormonal treatment available including CYP-17 inhibitors, anti-androgens, oestrogens and corticosteroids before the disease is classified as androgen refractory. Androgen depletion should continue during the disease course as androgen sensitive clones are assumed to prevail.

It is important to emphasise that castration-resistant prostate cancer is a heterogeneous group of disease and today known prognostic factors include: Gleason score, PSA levels and kinetic, tumour stage at diagnose (including bone only, nodal visceral spread), primary treatment, time to relapse, duration of androgen depletion therapy, time to castration refractory disease, time with clinical detectable metastatic disease, use of cytotoxic compounds and the response.

Additionally, general performance status, age and co-morbidity are important prognostic factors. From this perspective, it is advisable to consider whether it is more informative to conduct separate studies in high and low risk patients.

The evaluation of response is performed according to RECIST criteria when soft-tissue metastases are detectable. However, prostate cancer is characterised by osteblastic bone metastases not always suitable to assessment according to RECIST. Therefore the occurrence of new bone lesions as a marker for progressive disease might be considered acceptable, provided that pre-specified criteria (an example being the PCWG2 criteria) adequately addressing the possibility of a flare reaction or trauma are defined in the protocol. Indeed, subclinical lytic bone lesion successfully treated may firstly responds with an osteoblastic reaction before restitution. Specifically for bone scan it is also of importance to consider uptake caused by trauma and other benign conditions such as osteoporotic fractures. Medicinal compounds acting as inhibitors of osteoblast activity may confound the assessment of disease activity by bone scans.

Progression in bone metastases is often accompanied by PSA increase. PSA increase may thus be taken into account in the definition of progressive disease based on imaging, although PSA increase alone cannot serve as primary end point in confirmatory studies. PSA, however, can even decrease in progressive late castration refractory state due to a dedifferentiation of the cancer cells making them unable to produce PSA.

Concomitant radiation therapy to prevent fractures may confound the efficacy evaluation, but should not be considered as an event in the efficacy analysis.

Currently a large number of new medicinal products are under late clinical development or have recently been marketed. Guidance is therefore not provided as regards suitable reference therapies in patients with castration resistant tumours.

Time to symptomatic progression, PFS and OS are considered appropriate outcome measures and the overall guidance provided in the general section apply.

3. Chronic Myeloid Leukaemia

CML is uniquely well characterised among human malignancies with respect to underlying molecular cause, course of disease, response to BCR-ABL tyrosine kinase inhibitors (TKI) and

molecular events causing drug resistance. Due to the continuous scientific advance in this field it is of major importance to follow the progress with respect to standardization of laboratory techniques used in the assessment of the disease. Generally acknowledged clinical diagnostic and treatment guidelines should also be followed and CHMP regulatory advice is recommended particularly when new diagnostic techniques or treatments emerge.

The diagnosis and stage of the disease should be well documented in any clinical study. Diagnosis of CML should be based on investigation of full blood count (FBC), bone marrow, cytogenetics and real time quantitative reverse transcriptase (RQ-PCR) for BCR-ABL transcripts.

When assessing the response to treatment there are three aspects that should be evaluated:

1. Haematological response
2. Cytogenetic response
3. Molecular response

The degree and timing of haematologic, cytogenetic and molecular responses provide very important prognostic information as time-dependent variables. Additionally, other prognostic scores such as age, spleen size and FBC should also be considered when defining high risk groups. The Sokal and Hasford scores are considered validated predictors of response in newly diagnosed patients.

Current international practice guidelines classify response to first line standard treatment into three categories and this approach including future updates should in general, be followed. An example as described by the ESMO is shown in Table 1. Other international practice guidelines, for example, those provided by the US National Comprehensive Cancer Network or the European Leukaemia Net may also be acceptable. For newer drugs whose response may be faster, landmarks and standards of success and failure may need to be reassessed.

Table 1 Definition of response to imatinib

	Optimal	Suboptimal	Failure
3 months	CHR	<CHR	No HR
6 months	≥PCgR	<PCgR	No CgR
12 months	CCgR	<CCgR	<PCgR
18 months	≥MMolR	<MMolR	<CCgR
Any time	No response loss	Loss of MMolR	Loss of CHR
	Mutations[a]	Loss of CCgR	Mutationsb

CHR, complete haematological response (WBC <10x109/l, differential with no immature granulocytes and <5% basophils, platelet <450x109/l, spleen non palpable);
PCgR, partial cytogenetic response (Ph+ metaphases 1%–35%); CCgR, complete cytogenetic response (Ph+ metaphases absent);
MMolR, major molecular response (BCR-ABL:ABL <0.10% by International Scale, on RT-Q-PCR).
aBCR-ABL KD mutations still sensitive to imatinib.
bBCR-ABL KD mutations still insensitive to imatinib.

[Chronic Myeloid Leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up; *Annals of Oncology* 21 (supplement 5); v 165-167, 2010]

Monitoring the therapeutic response and level of residual disease is essential and the following guide is recommended. However, if responses with a new therapeutic agent are more rapid testing at more frequent intervals may be required.

1. During the first 3 months clinical, biochemistry and haematological monitoring should be assessed every 2 weeks.
2. From the third month on:
    - cytogenetics (chromosome banding analysis of marrow cell metaphases) should be performed at least every 6 months until a complete cytogenetic response has been confirmed

- RT-Q-PCR (BCR-ABL:ABL % on blood cells) should be performed every 3 months until a major molecular response is confirmed.

3. Once a complete cytogenetic response and major molecular response have been confirmed:
    - Cytogenetics every 12 months
    - RT-Q-PCR every 6 months

Screening for BCR-ABL KD mutations will be expected in cases of failure or suboptimal response.

Measuring drug concentration in blood may be required in some cases, such as failure, suboptimal response, dose-limiting toxicity and adverse events.

More frequent monitoring may be advisable in certain cases, for example when studies are conducted on a high risk population.

It is recommended that monitoring will take place in specialised central laboratories.

Whenever possible, it is expected that the mechanisms contributing to the lack or suboptimal response will be explored and may include the following:

- Mutations in the BCR-ABL kinase domain
- Clonal evolution, defined as the presence within CML cells of additional translocations that are thought to drive disease progression
- Pharmacokinetic variability (poor compliance, drug interactions, variability in metabolic enzymes etc)
- Amplification of the BCR-ABL fusion gene
- Overexpression of drug transporter genes and tyrosine kinases such as the SFKS
- Toxicity leading to dose interruptions or reductions

Chronic Phase (CP)

More than 90% of patients are diagnosed in CP.

As there are currently several medicinal products approved for the treatment of CML in CP a comparative trial should be undertaken against a licensed reference product.

If the aim is to show superiority versus a licensed comparator the recommended primary endpoint is major molecular response at 18 months. Appropriate secondary endpoints include complete cytogenetic response at 12 months, PFS and overall survival. The choice of alternative time-points for primary or secondary endpoints may also be acceptable if fully justified, for example if a response to treatment is expected to occur earlier during therapy Long term follow up of at least 8+ years is expected.

In the case of non-inferiority trials, a longer follow up will be required in order to evaluate the primary endpoint and major cytogenetic response after at least 2 years is recommended.

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.

When studies are conducted in special groups such as patients intolerant to prior TKI therapy, resistant to prior treatments (primary or secondary resistance), high risk patients or with new secondary mutations baseline characteristics should well defined before enrolment. 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 “intolerance” in many cases.

It is acknowledged that mutation analysis remains an essential assessment for patients in second line treatment and beyond. 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.

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 may be undertaken. Superiority should be demonstrated comparing the combination regimen with a single TKI. In studies exploring the combination of two TKI the potential of additive toxicity should be fully addressed.

In cases where the target population may be small, for example patients who have no other available treatments, EU regulatory advice is recommended prior to the initiation of phase II/III trials.

Advanced disease (Accelerated Phase, Blast Crisis)

It is foreseen that the vast majority of these patients have been treated with a TKI.

For those patients that are on accelerated phase (AP) but had prior treatment for chronic phase a trial versus another TKI may be conducted if possible. In the case presentation at diagnosis is accelerated phase without prior chronic phase a trial versus a first line TKI will be expected. In general, as treatment on AP depends on type of prior therapy the comparator used will be defined by prior patient treatment history.

Patients on blast crisis receive conventional chemotherapy with or without allogeneic SCT. Due to the rarity of blast crisis and the foreseen complexity of the therapeutic situation, EU regulatory advice should be considered.

4. 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 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 the time of diagnosis. The following disorders belong to this category: chronic myelomonocytic leukaemia (CMML), atypical chronic myeloid leukaemia, 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 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 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 haemoglobin levels) 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 therefore be prospectively assessed to exclude detrimental effects of the test drug that would outweigh documented benefits.

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 this guideline 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.

MDS is a condition that irrespective long-term prognosis severely can compromised patients QoL. With respect to the possible role of PRO/QoL outcome measure, please refer to appendix (X to be released for comments next year). The influence of treatments aiming at symptom improvement as part of background SOC on parameters relevant for the evaluation of safety and efficacy of the experimental drug should be carefully addressed.

5. Haematopoietic Stem Cell Transplantation

Drug development in relation to HSCT can be conducted as part of conditioning treatment for HSCT and also for the mobilisation of peripheral blood (PB) stem cells that will be utilised in a peripheral blood stem cell transplant (PBSCT). Immune therapy in relation to HSCT, however, is not covered in this appendix.

a) Conditioning treatment

Whenever possible, conducting comparative studies against accepted standard conditioning treatment(s) will be expected and the choice of endpoints and time points will depend on the specific clinical condition. The outcome measures will need to focus on two aspects, engraftment (short term outcome) and a long term outcome which depends on the indication and type of transplant. In addition long term follow up will be required and its duration will depend on the clinical setting.

If autologous HSCT is established in a certain condition such as in multiple myeloma, a randomised comparison with an established conditioning regimen is expected. The guidance as regards long term endpoints provided in the general guideline document applies. If not established, a comparison with standard of care with survival as outcome measure is expected.

In allogeneic HSCT, standardisation as far as possible as regards immune suppressive therapy and post transplant infection prophylaxis is warranted.

In both cases it is advisable to restrict inclusion so that variability in prognosis is reduced, not least if the primary aim is to show improved tolerability and safety and non-inferiority in terms of efficacy.

b) Treatment prior to high dose therapy

The aim should be to improve overall outcome and the principles of ITT should be adhered to, i.e. also patients not undergoing (autologous) HSCT should be followed for PFS/EFS and OS, prioritized as regards primary outcome measure as recommended in the main guideline. Quality of response prior to high dose therapy may be reported as a secondary endpoint.

c) PBSC mobilisation

This section reflects use of medicinal products for the mobilisation of autologous PBSC. The target population in terms of the condition to be treated, prior therapy etc. should be reflected in the eligibility criteria. Extrapolation to other patient populations will in general not be acceptable.

Endpoints should include short term and long term outcome. A target number of CD34 cells that translates into a successful engraftment together with long term data on the engraftment will be required for approval. Possible effects on the underlying condition should also be addressed.

Details on engraftment (time to engraft, outcome of engraft etc) will be expected. The potential for tumour stem cell mobilization, including tumour stem cells, and graft contamination should be addressed.

In cases where the PBSC mobilisation is intended for use in allogeneic transplant a safety assessment of the donor including short and long term data will be expected.

Specific short and long term safety data in relation to the HSCT should be submitted. Data on early complications such as mucositis, infections, sinusoidal obstruction syndrome (also known as hepatic veno-occlusive disease) and transplant-related lung injury will be required. Delayed complications including fertility toxicity, secondary malignancies and impaired growth and development in children will also need to be collected.

In the case of allogeneic HSCT particular attention should be given to data on acute and chronic graft versus host disease including details on specific prophylaxis and treatment measures and donor type (related or unrelated HLA matched transplant).