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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN
MAN**

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GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN

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Glossary and Abbreviations

Data maturity: A clinical study is considered mature if the distribution of events over time (early – late) makes it feasible to estimate the treatment effect in the full study population. This refers to the assumption that there is a biological difference between e.g. tumours progressing early and late and that the treatment effect might differ. The number of late events should therefore be large enough for study data to be stable. In practice, if a treatment difference has been established and the majority of events expected over long term has occurred, the study may in most cases be regarded as “mature”.

Chemosensitizer (or drug resistance modifier): A compound without own anti-tumour activity which increases the activity through pharmacodynamic interaction with anti-tumour compound(s).

Chemoprotectant: A compound which counteracts the activity of anti-tumour compounds on normal tissue without (or clearly less) affecting the anti-tumour activity.

Cytostatic: Anticancer compound shown to inhibit cell division without direct effects on tumour cell viability in non-clinical studies.

Cytotoxic: Anticancer compounds inducing irreversible lethal lesions through interference with DNA replication, mitosis, etc. following short term exposure in non-clinical studies.

Non-cytotoxic: Anticancer compounds not belonging to the class of cytotoxic compounds.

Primary resistance: Progression without prior objective response or growth inhibition.

Secondary resistance: Progression after documented objective response or period of growth inhibition.

Randomised phase II trial: Randomised exploratory study designed to provide data of importance for the design of Phase III confirmatory studies, e.g. with respect to the effect size using a clinically relevant measure of activity and/or biomarkers.

Window of opportunity: Under certain well-defined conditions it is acceptable to conduct a clinical study with an experimental compound in settings (line of therapy, stage, etc.) where available data for this compound normally would be regarded as too limited. The conditions for conducting such a study must be set rigorously so that the interest of the patient is guaranteed. Circumstances to take into account include benefit-risk of available therapies, available safety/activity data for the experimental compound, tumour-related symptoms (in most cases absent), expected evolution of the disease if left untreated or treated with available therapies, ease of frequent monitoring of tumour evolution (including use of biomarkers), planned intervention post chemotherapy, etc.

PK: Pharmacokinetics

PD: Pharmacodynamics

ANC: Absolute neutrophil count

MTD: Maximum tolerated dose, often defined by dose-limiting toxicity occurring in at least 2 of 6 patients so that further dose-escalation is not undertaken.

DLT: Dose limiting toxicities

RP2D: Recommended phase 2 dose

CR: Complete response

PR: Partial response

ORR: Objective response rate (the proportion of patients in whom a CR or PR was observed)

TTP: Time to tumour progression (time from randomisation to observed tumour progression, censoring for death without progression)

TTF: Time to treatment failure (time from randomisation to discontinuation of therapy or add-on of new anti-cancer therapy for any reason including death, progression, toxicity)

EFS: Event-free survival (variable protocol specific definitions, e.g. time from randomisation to objective tumour progression, secondary malignancy, or cancer-related death)

PFS: Progression-free survival (time from randomisation to objective tumour progression or death from any cause)

DFS: Disease-free survival (time from randomisation to recurrence or death from any cause)

OS: Overall survival (time from randomisation to death from any cause)

ADCC: Antibody dependent cellular cytotoxicity

MoAb: Monoclonal antibody

BSC: Best supportive care – include antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including radiotherapy), etc. and does not include tumour specific therapy

BSA: Body surface area

CRF: Case report form

HRQoL: Health Related Quality of Life

I. INTRODUCTION

This guideline is intended to provide guidance on the clinical investigation of anticancer agents and should be read in conjunction with Directive 2001/83/EC, as amended. Applicants should also refer to other relevant European and ICH guidelines on the conduct of clinical trials, including those on:

- Note for guidance on the pre-clinical evaluation of anticancer medicinal products (CPMP/SWP/997/96),
- Note for guidance on statistical principles for clinical trials, ICH topic E9 (CHMP/ICH/363/96),
- Note for guidance on choice on control group in clinical trials, ICH topic E10 (CHMP/ICH/364/96),
- Points to Consider on application with 1. Meta-analyses; 2. One Pivotal study (CPMP/EWP/2330/99),
- Points to Consider on the choice of non-inferiority margin (CPMP/EWP/2158/99),
- Concept Paper on the development of a CPMP note for guidance on the clinical pharmacokinetic investigation of the pharmacokinetics of peptides and proteins (CPMP/EWP/226/02),
- Reflection Paper on the regulatory guidance for the use of Health-Related Quality of Life (HRQL) measures in the evaluation of medicinal products (CPMP/EWP/139391/04)₂,
- Note for Guidance on general considerations for clinical trials, ICH topic E8 (CPMP/ICH/291/95),
- Draft Guideline on clinical trials in small populations (CPMP/EWP/83561/2005),
- Note for Guidance on evaluation of anticancer medicinal products in man: *Addendum* on Paediatric Oncology (CPMP/EWP/569/02),
- Points to Consider of diagnostic agents (CPMP/EWP/1119/98),
- Points to Consider on Adjustment for baseline Covariates (CPMP/EWP/2863/99).
- Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Topics E2A
- Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports, ICH Topic E2B
- Note for Guidance on Structure and Content of Clinical Study Reports, ICH Topic E3

The guideline on anticancer medicinal products adopted in 1996, and revised in 2001 and 2003, focused on conventional cytotoxic compounds. Although the main subject matter of a guideline from a regulatory perspective should be on confirmatory studies where the class of drug, whether it be cytostatic or cytotoxic, for example, is less important, this focus on cytotoxic compounds has been regarded as a deficiency. This revised version, therefore, aims to cover anti-cancer compounds more comprehensively.

There are numerous possible ways to classify anti-cancer drugs such as direct anti-tumoural vs. indirect anti-tumoural, or based on pharmacology or molecular target (*e.g.* hormones, immune modulators, nuclear-targeting, signal-transduction targeting, etc.). As this document is meant to provide guidance on clinical drug development, the aim has been to classify compounds according to reasonable designs of exploratory studies, i.e. cytotoxic compounds where toxicity and ORR are considered suitable markers of activity in drug development vs. non-cytotoxic compounds where ORR and/or toxicity may not serve this purpose.

A very large number of anti-cancer compounds have been and currently are under development. Only a minority, however, have completed the clinical development and reached a marketing authorisation, due to insufficient evidence of efficacy or evidence of a detrimental safety profile. Until non-clinical models with good predictive properties have been defined, this situation is likely to remain essentially unchanged and the absence of such models is considered to constitute the greatest hurdle for efficient drug development within the foreseeable future.

Since chemoprotective agents and drug resistance modifiers are used as part of anticancer regimens, some guidance on these agents will also be provided in appropriate sections of this guideline. Anti-emetics and haematopoietic growth factors, however, are covered in separate documents.

Additional recommendations of relevance for childhood malignancies and paediatric drug development are provided as a separate “*Addendum on paediatric oncology*”(CPMP/EWP/569/02).

This document is meant for guidance only, but deviations should be justified. It is fully acknowledged that the current rapid development with regard to basic understanding of tumour biology, targets for anti-cancer therapy, imaging techniques, etc. makes the field highly dynamic. When established approaches to drug development are considered suboptimal and in need of revision, it is advisable to seek regulatory scientific advice, especially prior to the conduct of Phase III studies.

II. PHASE I/II EXPLORATORY TRIALS

The distinction between Phase I/II exploratory and Phase III confirmatory trials has been adhered to in this Guideline. This does not mean that exploratory aims should not form an important part of Phase III trials. Similarly, hypothesis generation and hypothesis testing may form parts of Phase II trials, e.g. with respect to defining a suitable target population for Phase III studies, whether based on conventional criteria, biomarkers, or pharmacogenomics.

Although efforts to identify target structures and explain variability in PK and PD are encouraged, the need to confirm the findings should not be overlooked in the planning of the drug development programme. It is also acknowledged that at the time of first submission for marketing authorisation, there will be many unresolved issues, e.g. new identification of important pharmacological factors to explain the outcome of the confirmatory studies.

The use of reasonably justified markers of activity, etc. in early drug development is supported in general, but it is essential that technical/quantitative reliability is assured. For confirmatory studies, the approach is much more strict, e.g. with respect to measures of efficacy or methods to identify suitable patients for therapy. Changes late in drug development or after marketing authorisation are especially sensitive issues. Some relevant regulatory guidance on these aspects may be found in the Points to Consider of diagnostic agents (CPMP/EWP/1119/98).

II.1 Cytotoxic Compounds

This refers to conventional cytotoxic agents, i.e. compounds inducing irreversible lethal cellular lesions following short-term exposure through interference with DNA replication, mitosis, etc. For these compounds, toxicity and tumour response are considered suitable indicators of activity. Under some circumstances, tumour stabilisation for a defined period of time is considered a more appropriate measure of anti-tumour activity than tumour response, for guidance please refer to II.2.2 “Exploratory trials with time-related endpoints”.

As for non-cytotoxic compounds, studies encompassing aims to characterise prerequisites for activity and to identify markers of resistance are encouraged. This may include investigating target expression, pharmacogenomics, use of microarray techniques, etc.

II.1.1 Phase I, single agent dose and schedule finding trials

The basic assumption governing the design of these trials is that, for dose finding purposes, toxicity is an acceptable endpoint. The main objective is to define dose-limiting toxicities and the dose to bring forward into further trials. While meeting this objective is generally straightforward, in spite of the fact that the inter-patient variability in PK might be large, it is often more complex to define reasonable dose schedules to study further.

It is accepted that the dose initially is calculated per body surface area (BSA), but the empirical support for the notion that this approach meaningfully reduces inter-patient variability in exposure is weak. Whether a flat dose or a dose calculated according to BSA or weight is used, it is recommended that the importance of BSA or weight for variability in exposure is explored through modelling. This may be done as soon as available phase I/II PK data make such analyses meaningful and the information may be used to define whether a flat dose or a dose calculated per BSA, e.g. should be used in further drug development.

Objectives

- MTD, DLT and a recommended Phase II dose (RP2D) (usually one dose step below MTD) should be identified for defined schedules and modes of administration. Supportive measures used as part of the treatment should be accounted for as well as the treatment status of the patients (prior chemo/radiotherapy).
- Frequent side effects and target organs for toxicity should be characterised as regards relationship to dose and schedule. Extent, duration and reversibility should be determined.
- Main PK parameters should be determined.

In addition

- Tumour measurement and response evaluation should be carried out whenever possible. The absence of measurable disease should not be a contraindication to participation in these studies, however. Use of sensitive measures of activity such as functional imaging or biomarkers is encouraged and may be of particular interest for schedule finding.
- Implementation of population-based PK/PD modelling is encouraged, e.g. exploring the relationship between exposure and a toxicity parameter such as ANC.
- For orally administered drug, food (e.g. American breakfast)-drug interaction should be studied.
- PK mass balance studies are encouraged.

Eligibility of patients

These trials should normally be undertaken in cancer patients without established therapeutic alternatives. The possible role for “window of opportunity” studies in late dose/schedule finding studies (but mainly in Phase II) is recognised, however.

Provided that safety is reasonably established and that there is a scientific rationale, it might be appropriate to conduct further dose and/or schedule finding studies also in patients for whom alternative therapies are available. This includes the neo-adjuvant setting in treatment naïve patients scheduled for surgery, provided that patient benefit has not been established for other neoadjuvant therapies and that delay in surgery cannot be detrimental to the patient. The safety and interests of the patient must always be guaranteed and a detailed justification should be provided in the study protocol. In these cases, the use of sensitive measures of anti-tumour activity is expected. Similarly, patients with diseases where the tumour activity is low (defined by minimal symptoms and expected slow progression) and where anti-tumour activity is easily measured and with no available curative treatment options may be included in this type of studies. An example could be clinically indolent, chronic lymphocytic leukaemia.

Routes of administration and schedules

In most cases, intravenous administration, when feasible, is advisable for first use in man studies since it eliminates variability related to bioavailability. The oral or alternative routes such as s.c administration may be further explored when predictable bioavailability and acceptable variability in exposure have been demonstrated.

For schedule finding, experience related to class of compounds is helpful. Non-clinical data with respect to cycle dependency and the ratio tumour / normal tissue cytotoxicity *ex vivo* may be of some interest.

Dose escalation

When no prior experience exists in humans, the starting dose is normally based on the dose devoid of severe toxicity in animal studies (CPMP/SWP/997/96). The smallest possible number of patients should be exposed to each dose level of the agent under study. Adequate data should be obtained for each dose level before escalation takes place. The methodology and scheme used for dose escalation should be described (e.g. modified Fibonacci scheme, pharmacokinetically-guided dose escalation, accelerated titration, etc.). Dose increments will usually vary from 100% at first dose level to 20-25% of the previous dose at the end of the trial.

In case of minimal toxicity, or occasionally in case of non-significant toxicity, within-patient dose escalation may be appropriate in order to reduce the number of patients exposed to non-active doses, but is acceptable only if non-clinical data provide no evidence of cumulative toxicity.

If toxicity is acceptable, the patient may be re-exposed upon recovery and preferably should receive at least 2 cycles at the same dose level.

Treatment shall be discontinued:

- If there is evidence of disease progression
- If non-acceptable side-effects have occurred. In patients benefiting from therapy, dose reduction may be undertaken.
- Upon request of the patient

Three or more fully evaluable patients are normally studied at each dose level if no severe adverse effects have occurred, but fewer than 3 patients per dose level may be acceptable if there is no/minimal toxicity at that dose. The number of patients within a given dose-level should be increased in case of overt toxicity and dose escalation should be stopped when MTD has been defined.

Evaluation of toxicity

The minimal requirements for evaluation of adverse effects include assessment of symptoms, physical examination, ECG, blood and urine laboratory analyses and radiological assessment as appropriate. Preclinical data should be used to guide the need for further examinations. If there are no signals with respect to QTc in preclinical studies or related to class of products, no formal QTc studies are expected, but inclusion of ECG as part of routine monitoring is recommended. Local toxicity at the site of administration should be specifically recorded. The toxicity should be graded according to a generally recognised system (e.g. WHO toxicity criteria, Common Terminology Criteria for Adverse Events, CTCAE).

Factors influencing toxicity (organ dysfunction, concomitant therapy) should be explored as appropriate. These factors should be further elucidated in Phase II/III.

If death occurs during the study, the cause of death and its possible relationship to the medicinal product under study, including autopsy whenever possible, should be assessed. As appropriate, blood and tissue material should be collected for pharmacokinetic, biochemical and microscopical studies.

Evaluation of all Adverse Events (ICH E3) and expedited reporting during study conduct should be performed according to ICH E2A and E2B. In parallel (or in the final study report), CTCAE/WHO toxicity criteria should be used to grade toxicity of all adverse drug reactions

Termination and conclusions

A Phase I study should be terminated when the MTD, target organs for toxicity and RP2D have been identified.

The report should describe all encountered toxicities, their severity and reversibility, dose (exposure) relationship and symptomatic measures if available. All observed tumour responses should be reported.

For each schedule and/or route of administration, the report should encompass:

- MTD and DLT
- RP2D (according to known risk factors if possible e.g. heavily pretreated patients)
- Where specific toxicity is identified, tests to evaluate this toxicity and testing interval
- Main PK parameters
- Recommendations for further non-clinical studies, as appropriate
- Recommendations for preventive measures to be used in future studies

II.1.2 Phase II, Single agent therapeutic exploratory studies

Phase II trials have different aims, such as to investigate single-agent activity in a variety of tumour types, or in a selected tumour type, or to investigate activity and feasibility of combination or multimodality regimens.

This section is focused on trials where the primary objective is to estimate single agent antitumour activity in patients with a defined tumour type in order to identify compounds to bring forward to confirmatory trial.

Objectives and design

Phase II trials may be conducted with or without a randomised reference but are generally conducted without a randomised reference with the limitations for statistical inference that this implies. The studies are intended to:

- Determine if significant responses can be achieved with the agent under study in the target tumours at doses and schedules defined in prior Phase I/II studies, or whether to stop investigating that specific tumour type
- To assess the probability of response in the target tumour type and conclude on the need for further studies (investigate earlier stages of the disease, combinations, compare with standard therapy)
- Further characterise the PK profile
- Further characterise dose and schedule dependency, with respect to safety and activity
- Further characterise the side-effects of the medicinal product:
 - detection of less common manifestations of toxicity
 - assessment of cumulative/sub-acute toxicity
 - assess possible measures to manage the toxicity
- When applicable, further characterise the best route of administration

Selection and number of patients

Exact definition of the target disease, previous therapy (if any) and stage should be given.

Each eligible patient should have at least one measurable or evaluable indicator of disease.

In most cases, patients with advanced disease and no available established treatment options constitute the target population for these trials. Use of an experimental compound in patients with available treatment options may be appropriate when there is prior evidence of activity in patients failing the available treatment option. However, there are complex medical and ethical issues to be addressed when including these patients into Phase II trials. If appropriately justified from the patient's perspective, window of opportunity studies may be acceptable as previously discussed.

Recruitment should be conducted according to a predefined plan that allows the objectives to be achieved with the smallest possible number of patients. Frequently it is appropriate to apply predefined stopping rules for activity which is deemed too low and toxicity if deemed too high and to power the study to obtain a sufficiently precise estimate of antitumour activity to decide whether further studies are indicated.

Dose and schedule

The dose and schedule should be clearly defined. Details on the administration of the medicinal product with special precautions (hydration of patients, protection against light and temperature, etc.) should be stated as well as other agents, which are contraindicated during the study period.

- Guidance should be supplied outlining dose modifications related to the severity of the observed toxicity.
- Rules for dose escalation in case of low toxicity should be considered.

- Consideration should be given to study high-risk patients (e.g. high risk with respect to target organ toxicity or compromised metabolic or excretory mechanisms for the experimental compound) separately.

Other concomitant treatment

All chemopotentiator/chemoprotector/resistance-modifying agents, which are to be used as part of the protocol, must be clearly detailed.

Ancillary treatments may be given as medically indicated, but must be recorded in the CRF.

Any other antineoplastic therapy should be avoided during the study period. Should surgery or radiotherapy be used as specified in the protocol, the treated area cannot be used for response assessment.

Evaluation of toxicity

This should be conducted at predetermined intervals.

Any evidence of cumulative toxicity should be recorded and estimated as a function of total dose. This should be specifically studied according to target organ or function.

Evaluation of activity

The method(s) to be used to measure and evaluate activity should be stated and justified in the protocol. For multicentre trials, imaging techniques and image analysis procedures should be standardised as far as feasible and meaningful. When possible, cytological/pathological characterisation of (a) representative lesion(s) should be obtained. Previously irradiated lesions (and new lesions) within irradiated fields are considered valid for the assessment of progression.

An objective response is defined as a measurable reduction in the tumour burden, assessed by reduction of the target lesion/other indicator using justified imaging procedures. When multiple lesions are present, representative lesions may be selected for the measurement and assessment of objective response, but progression of other lesions and the development of new lesions should be assessed during the study period. It is recognised that imaging techniques may be inappropriate for the assessment of certain tumours, e.g. superficial lesions where photo documentation and callipers may be used. For exploratory studies, this is acceptable without further measures aimed at reducing possible bias.

The ORR should be documented according to international standards (e.g. RECIST, or WHO criteria). Modifications of these criteria may be appropriate in certain situations, e.g. RECIST and mesothelioma, but should be justified. The protocol should provide details as regards criteria for response/progression and timing of response assessments. As ORR is used to define whether the activity is promising in a historical context, it is noteworthy that differences between RECIST and WHO criteria may give rise to apparent differences in activity. In most cases, however, the problems related to the interpretation of historical data more relate to differences in patient characteristics, the rapid evolution of imaging techniques, etc.

External independent review of tumour response is encouraged, according to the objectives of the trial.

In evaluating ORR, data for all patients entered into the trial should be reported. Where ORR in the per-protocol analysis set is considered to be of primary interest, then data for all patients included into the trial should also be reported.

Data on TTP/PFS and available data on OS should normally be reported.

The use of tumour markers and other dynamic measures of activity is encouraged.

In patients with symptomatic disease at base line, the assessment of symptom control is encouraged, if a randomised phase II trial is undertaken.

Termination and conclusions

The study should end when the experimental plan has been fulfilled.

The report should encompass:

- Whether the antitumour activity is of interest to study further

- Adequacy of the studied dose/schedule
- Adequacy of rules for dose reduction and dose escalation
- Main PK parameters
- Toxicity, including cumulative toxicity

Early termination may occur

- When too low anti-tumour activity is observed
- When non acceptable toxicity has occurred;
- When evidence of cumulative toxicity preventing further use of the agent has emerged.

II.2 Non-cytotoxic Compounds

This refers to a very heterogeneous group of compounds ranging from antihormonal agents to antisense compounds, signal transduction, angiogenesis or cell cycle inhibitors, immune modulators, etc. The common element affecting the design of clinical trials is that toxicity may not be an appropriate endpoint in dose and schedule finding trials and ORR may not be an appropriate measure of anti-tumour activity, while prolonged exposure may be needed in many cases.

For these reasons, the early stages of clinical drug development are more complex and have to be tailored according to the assumed pharmacology of the individual compound as defined in non-clinical studies. The rather strict delineation between Phase I and II trials, as for conventional cytotoxic compounds, may be less relevant as measures of anti-tumour activity, e.g. based on assessment of biomarkers might be needed early in order to define dose and schedule.

Otherwise, most of the elements discussed in relation to cytotoxic drugs are of relevance also here such as restrictions with respect to patient eligibility, recommendations as regards routes of administration, evaluation of toxicity and anti-tumour activity, etc. These issues will not be further discussed here.

II.2.1 Phase I/II single agent dose and schedule finding trials

Based on preclinical tolerability and toxicology findings and the assumed pharmacology of the compound, early trials may sometimes be conducted in healthy volunteers. Tolerability, safety, PK and, if at all possible, PD measures of activity are appropriate objectives.

Non-clinical data and, when available, data from healthy volunteers should be used to design the studies to be conducted in patients, e.g. as regards eligibility criteria and starting dose. In accordance with the guidance for cytotoxic compounds, availability of established therapies should normally be regarded as an exclusion criterion. Refractoriness to conventional cytotoxic compounds, however, may confer resistance also to some clearly non-related compounds. This obviously affects the possibility to define a dose/concentration – effect relationship. All sensible and ethically acceptable measures undertaken to increase the assay sensitivity of these clinical trials, including the conduct of window of opportunity studies are encouraged. Whenever appropriate, this includes measuring the expression of the assumed target for drug activity.

PD measures may include biochemical measures (receptor binding, enzyme inhibition, down stream events, etc. as validated in non-clinical studies), functional imaging, proteomics, immunological measures (antibody or T-cell response), etc. Population PK/PD studies are encouraged. For compounds shown to be cytostatic in non-clinical models, prolonged exposure may be needed to elicit tumour shrinkage in clinical studies. If unexpectedly early tumour shrinkage is observed this may constitute a signal indicating that further studies exploring the underlying mechanisms behind early response should be considered. This may include pharmacogenomics.

Even if, e.g. saturation of the target for drug activity, or a desired PD activity can be demonstrated without significant toxicity, it is still advisable to investigate higher dosages in order to better define the safety of the compound and possible irregularities in PK and PD. This may include defining DLT, when feasible and appropriate.

Biopsies from tumours (primaries and metastatic lesions), or in some cases normal tissues, might be needed to obtain data on target saturation or down stream events. If there are no other means to obtain

information on the drug exposure - activity relationship, such as functional imaging or blood biomarkers, this might be crucial and has to be considered in the recruitment of investigators and patients.

As for conventional cytotoxic drugs, the use of tumour markers and sensitive imaging techniques, in combination with conventional methods, are recommended in order to delineate possible antitumour activity. Also in exploratory trials it is recommended that technical standardisation of, e.g. functional imaging techniques, is implemented in order to reduce inter-centre variability.

Eligibility criteria and the number of patients should be defined according to the objectives of the study, also taking into account variability in PK and PD at doses and schedules selected for further studies.

II.2.2 Phase II, single agent therapeutic exploratory studies

For the purpose of simplification, it is assumed that a dose/exposure range has been defined that shows pharmacological activity/target occupancy with or without dose limiting toxicity. Similarly, that a target population has been selected as regards tumour type and preferably expression-level of the target for drug activity. Whether it is advisable or not to broaden the inclusion of patients beyond the postulated target population, depends on a critical assessment of available non-clinical and clinical data, including experience with similar compounds, acknowledging limitations as regards understanding prerequisites for anti-tumour activity

Study designs and measures of activity

Based on findings in currently available non-clinical models, it has been shown that it may be hard to predict whether a non-cytotoxic compound will act mainly through growth inhibition or will elicit early tumour shrinkage in patients. This is of importance as these anti-tumour properties determine whether TTP or ORR will be appropriate Phase II measures of anti-tumour activity. In this context and reflecting heterogeneity in the target population, it is acknowledged that a compound might elicit rapid tumour shrinkage in a subgroup of patients while growth inhibition might be the predominant effect in most responding patients. If available clinical data do not further elucidate this crucial issue for the proper design of Phase II trials, it is advisable to assume that TTP more appropriately reflects the anti-tumour activity and design the study accordingly. In these studies, it is recommended that documented progressive disease should be an inclusion criterion. In most cases it is advisable to apply short time intervals for tumour assessments on study. Throughout this section (II.2) TTP, instead of PFS, has been proposed as a measure of anti-tumour activity. If, however, PFS is found more appropriate, this does not constitute a regulatory concern, but early deaths, for example, might reduce the sensitivity of the studies with regard to defining anti-tumour activity.

ORR, despite all its shortcomings related to patient-selection, etc, is a rather convincing measure of activity as for most tumours, spontaneous regression fulfilling criteria for at least partial response is an uncommon phenomenon. For exploratory purposes, studies without a randomised reference are therefore considered interpretable. TTP, however, is in principle a function of underlying tumour growth rate and the activity of the anti-tumour compound. Also, if documented progressive disease is an inclusion criterion, underlying growth rate is hard to define in most patients and historical data will be even harder to interpret. Therefore, the interpretation of TTP data without a randomised reference is problematic.

Exploratory trials with time-related endpoints

There is probably no ideal yet feasible design of exploratory studies for compounds assumed to mainly elicit tumour growth control. In the following some design alternatives are discussed, all with pros and cons, but in principle acceptable from a regulatory perspective.

- A randomised, dose comparative trial, e.g. comparing the lowest dose likely to be pharmacologically active with higher dose(s), if showing a difference in TTP, will obviously provide evidence of activity, but not in absolute terms.
- Randomised withdrawal of therapy in patients with non-progressive disease after a defined period of time on experimental therapy. The acceptability of this design to patients and investigators, however, may constitute an obstacle and carry-over effects may be a reality for some compounds.

- In previously treated patients, a within patient comparison of TTP might provide evidence of activity. Here TTP on last prior therapy is compared with TTP on the experimental therapy. It should be noted, however, that the underlying assumption of non-decreasing growth rate over time cannot always be substantiated. For exploratory purposes this constitutes no major concern. It is advisable to recruit patients with secondary as well as primary resistance on prior therapy. This ensures at least to some extent, that the study population is representative. It should also be noted that patients with early failure (primary resistance) on prior therapy may show some inversions in terms of TTP just due to fluctuations in tumour growth rate and variability related to imaging techniques.

For certain indications, a within patient comparison may be justified also in treatment naïve patients.

- A randomised phase II study versus a compound known to be active in the selected population (or placebo/BSC if justified) provides another alternative. If such a study is regarded as exploratory, there is no need for, e.g. well-defined non-inferiority criteria. In a comparison in terms of TTP it should be noted, that a purely growth inhibitory compound is “favoured” compared with a compound inducing tumour shrinkage, as progression is defined in relation to best tumour response. At the time of tumour progression, the tumour burden in patients failing a purely growth inhibitory compound will therefore be higher than in patients where tumour shrinkage was elicited. .
- If no more refined techniques are applicable, TTP without an internal reference has to be accepted as a measure of Phase II anti-tumour activity. A systematic literature review is advised in these cases. Fixed-time related endpoints such as percentage of patients without progression after a predefined period of therapy may be used in order to define whether the apparent anti-tumour activity is sufficiently high to justify the conduct of, e.g. Phase III confirmatory studies.

In principle, a statistical approach similar to that for Phase II trials for cytotoxic compounds is applicable. It is harder to set up criteria for early termination, however. The number of patients should be sufficient to obtain a reasonably precise estimate of the percentage of progression-free patients at a predefined time point. As for cytotoxic compounds, the aim should be to achieve this objective with the smallest possible number of patients. The underlying assumptions as regards progression rate without therapy are more problematic and “promising activity” is harder to define.

For these studies, the use of conventional criteria for ORR and tumour progression is recommended and independent review is encouraged. It is recognised, however, that, e.g. an apparent increase in tumour size due to inflammatory oedema might be a first sign of activity for certain compounds. If prior trials indicate that this is the case, it is accepted that this is accounted for in the study protocol. The use of ORR and TTP as key measures of activity should not be regarded as contradictory to the use of tumour/PD markers in parallel. It is advisable though to use conventional measures to guide therapy, e.g. for withdrawal of therapy in case of progression.

If a randomised design is considered appropriate and if blinding is possible, the use of generally accepted instrument to estimate HRQoL or symptom control may provide valuable information.

For window of opportunity studies and if sensitive measures of pharmacological activity are available, e.g. functional tumour imaging, and a target population has been identified with tumours likely to be sensitive, placebo-controlled trials with one or preferably more doses of the experimental compound might be feasible. Sensitive measures, even if not fully validated with respect to relationship to ORR, are from a regulatory perspective acceptable for exploratory purposes and allow not only for refined dose comparisons, but also early escape in case of absence of activity. It is advisable though to clearly define in the protocol criteria for progressive disease, whether a composite (e.g. biomarkers, or imaging, or symptoms) is used or not.

Tumour tissue biopsy data may provide valuable information related to prerequisites for antitumour activity and resistance, primary or secondary.

II.2.2.1 Monoclonal antibodies (MoAb)

Monoclonal antibodies may affect tumour cells directly through ADCC and/or blocking of growth factor/anti-apoptotic receptor signalling, or through the targeting of growth factors for the tumour or tumour supportive structures.

Tumour cells should be screened for (over-) expression of the target and the relationship between target expression and activity should be investigated.

Tumour specificity is frequently not attainable, but it is possible to screen for “unwanted” targets in vitro, facilitating the safety assessment.

Understanding the PK provides some guidance for dose-finding as clearance may be related to target saturation.

If, e.g., a growth factor receptor is targeted and pending of the characteristics of the MoAb (Ig subclass, association with toxin, etc.) it might be of relevance to try to elucidate whether blockade of the receptor or ADCC is of prime importance for antitumour activity. Studies conducted in the neo-adjuvant setting allowing for repeated morphological examinations may in some cases provide a means of investigating this.

The experience as regards immunogenicity of MoAbs in other fields of clinical medicine should be taken into account with respect to choice of assays, markers for loss of activity and possible safety problems (CPMP/EWP/2330/99).

II.2.2.2 Immune modulating compounds including tumour vaccines

Immune modulating compounds, including so-called tumour vaccines and certain cytokines, constitute a special problem with respect to proof of concept studies. Nevertheless, evidence of anti-tumour activity is essential prior to the initiation of confirmatory studies.

Tumour response in patients with high tumour burden might constitute an insurmountable objective. On the other hand, it might be hard to justify the use of clearly experimental therapies in patients with limited and measurable disease, not heavily pretreated with cytotoxic and immunosuppressive regimens. Specific signs of immunisation should be investigated, including *ex vivo* studies using patient serum and designed to detect anti-target tumour cytotoxicity. If no other way forward is identified, tumour biopsy data showing signs of immune activation could serve as an early marker for possible anti-tumour activity. Regulatory scientific advice should be considered during the exploratory phase of drug development.

II.3 Phase I/II, combination therapy studies

Conventional cytotoxic compounds have for long been used in combination in order to increase the anti-tumour activity at acceptable levels of toxicity by combining compounds with partly non-overlapping toxicity and, perhaps, partly non-overlapping prerequisites for activity/resistance. Regulatory agencies, as well as learned societies, have accepted this approach. In principle, this should be applicable also for combinations including non-cytotoxic compounds.

II.3.1 Combining conventional cytotoxic compounds

In the selection of patients with available alternative therapies, the documented activity of the individual components of the combination regimen should be taken into account.

The exploratory phase encompasses the determination of MTD and RP2D for the combination and a preliminary assessment of anti-tumour activity in terms of ORR and PFS/TTP. While the degree of anti-tumour activity for a new combination relies on assumptions, it is often possible to predict toxicity, based on the toxicities of the individual components. If relevant PK interactions can be excluded, and pending on the dose-response/toxicity profiles, dose-finding studies may be initiated at about 1/2 of the recommended mono-therapy dose for each compound. It might also be appropriate to start at the full recommended mono-therapy dose for one of the compounds and reduced dose (50% or less) for the other compound. As the sequence of administration may be of importance with respect to potential PK interactions and anti-tumour activity, this has to be accounted for in the design of the studies. More patients on each dose level are normally needed compared with single agent dose finding studies.

Within patient dose-escalation may be appropriate if non-significant toxicity is observed in an individual patient and if monotherapy clinical and preclinical data indicate absence of cumulative toxicity. A justification in the protocol is expected in these cases.

There are no practical ways to balance dose intensity between components of a combination regimen to optimise benefit – risk. It is thus accepted that, e.g. priority in terms of dose intensity is given to the compound with the highest monotherapy activity.

If one of the components is regarded as an acceptable treatment regimen in monotherapy, a randomised phase II study comparing the monotherapy regimen with the combination might be informative prior to the initiation of confirmatory studies. As for all randomised trials and especially if possible to blind, the use of recognised instruments for the assessment of HRQoL or symptom control might be valuable.

II.3.2 Combinations involving cytotoxic and non-cytotoxic drugs.

Data from non-clinical studies are needed to design clinical combination studies for these compounds, but there are examples where non-clinical data have been misleading rather than informative with respect to the anti-tumour activity of these combination regimens. Exploratory clinical studies are therefore needed in order to demonstrate the possible add-on activity of the experimental non-cytotoxic compound to, e.g. a conventional chemotherapy regimen.

If there are no strong biological/pharmacological arguments to the contrary, the selected chemotherapy regimen should normally be “best available”. If the dose intensity of the chemotherapy regimen is unaltered it can be assumed that all patients will receive appropriate therapy. Therefore there is no need to restrict the eligibility of patients from this perspective.

Whenever previous non-clinical and clinical experience has suggested that PD markers, etc. might be informative with regard to anti-tumour activity, they should be part of the experimental plan. This may include investigations whether the expression of the target for the non-cytotoxic compound is affected by treatment with cytotoxic agents and if appropriate *vice versa*.

Given the current status with respect to predictability of add-on activity in non-clinical models, randomised phase II studies comparing the experimental regimen with the chemotherapy-alone regimen are advisable. For these studies, it is recommended that conventional anti-tumour activity data (ORR and TTP) are supplemented with tumour markers and sensitive measures of, e.g. tumour metabolic activity as appropriate.

Alternatively, the objectives of a randomised phase II trial may be investigated in a carefully justified phase II/III combination trial with an adaptive design. When add-on activity of the non-cytotoxic compound to a chemotherapy regimen has been demonstrated in clinical studies, the need for further randomised phase II studies when new indications are studied has largely been overruled. If the expression of the target for the non-cytotoxic compound may be differently affected by different chemotherapy regimens, it might be advisable to study target expression during treatment with a new chemotherapy regimen prior to the conduct of add-on studies.

Research aiming at understanding the mechanisms and prerequisites for the add-on effects is encouraged, while it may allow for an improved characterisation of target populations in future studies.

It is conceivable that for some non-cytotoxic compounds, combinations are needed not only to optimise anti-tumour activity, but actually are required in order to obtain activity. For such compounds, e.g. target saturation in monotherapy and, importantly, non-clinical toxicity for the combination may be used to define suitable starting doses and schedules. Otherwise dose/schedule exploratory and therapeutic exploratory studies may proceed essentially as for a monotherapy regimen.

III. PHASE III, THERAPEUTIC CONFIRMATORY STUDIES

Phase III 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.

Where an alternative to conventional pathology/anatomy-based indications is considered, regulatory scientific advice is recommended.

III.1. Design

III.1.1 Eligibility criteria

Prior experience with the experimental compound in terms of anti-tumour activity and safety in relation to dose and schedule should be sufficient to initiate phase III studies in the defined target population. As the aim of these studies should be to provide a basis for evidence-based clinical practice, any exclusion criteria, e.g. related to age, performance status, impaired organ function, or tumour localisation has to be well justified from the perspective of patients in the study and patients to be treated in clinical practice. Therefore investigators should be encouraged to include patients representative of those likely to be treated with the experimental compound in clinical practice. Restrictions as regards, e.g. performance status should be reflected in the SPC.

Patients are expected to be characterised by relevant tumour parameters, e.g. stage, grade, target expression, other biological markers of importance for prognosis and/or tumour sensitivity, prior therapy (responsive/refractory/resistant as appropriate), as well as performance status, co-morbidity, organ dysfunction, etc. Stratification based on important and well established prognostic covariates should be considered (CPMP/EWP/2863/99).

If exploratory studies provide a basis for including/excluding certain patients based on tumour phenotype/genotype, this is fully acceptable from a regulatory perspective and will be reflected in the labelling. As a corollary, even if patients with tumours not expressing the target for activity are eligible, a restricted labelling may still be appropriate if it has not been demonstrated that target expression is irrelevant for anti-tumour activity.

III.1.2 Randomisation and blinding

Randomisation and stratification should adhere to the general principles laid down in current guidelines (CHMP/ICH/363/96). In many cases, a double-blind design is no option due to obvious differences in toxicity between study regimens or due to safety concerns. Fully recognising this, a justification in the protocol is expected. If the study has to be conducted as an open label study, this has implications with respect to choice of study endpoints and conduct of sensitivity analyses and other measures to be undertaken to limit potential bias related to the open-label nature of the trial.

III.1.3 Study endpoints

While it is generally acknowledged that the aim of treatment is to improve quality of life and survival, restraints on the conduct of clinical trials may make these goals unattainable. It is thus recognised that investigators, patients and ethics committees may require, e.g. optional cross-over at time of tumour progression. Similarly, the use of active next-line therapies must be accepted. This may affect the possibility of detecting differences in OS as well as symptoms related to tumour progression.

Primary endpoints

Confirmatory trials should demonstrate that the investigational product provides clinical benefit. There should thus be sufficient evidence available demonstrating that the chosen primary endpoint can provide a valid and reliable measure of clinical benefit in the patient population described by the inclusion criteria (ICH E8 and E9).

Acceptable primary endpoints include OS and PFS/DFS. If PFS/DFS is the selected primary endpoint, OS should be reported as a secondary and *vice versa*. When OS is reported as secondary endpoint, the required number of events and duration of follow-up will depend on the results as regards the primary endpoint, availability and activity of next line therapies, expected survival after progression and safety results comparing test with reference. The estimated treatment effect on OS should be sufficiently precise, however, to ensure that there are no relevant negative effects on this endpoint. In situations where there is a large effect on PFS, a long expected survival after progression, or a clearly favourable safety profile, precise estimates of OS may not be needed for approval. When PFS is reported as secondary endpoint, consistency is expected as regards the treatment effect on OS.

If major differences in toxicity are expected in favour of the control regimen, OS should normally be selected as the most appropriate primary endpoint. Similarly, if there are no evidence based next line therapies available and if the period of time from disease progression to death is expected to be short, OS is considered to be the most appropriate endpoint; in most cases even if crossover is foreseen according to protocol. In cases where alternative endpoints are considered to adequately capture patient benefit, the choice has to be justified and scientific advice is recommended. PFS is an acceptable endpoint in situations where it is expected that further lines of treatment with effect on OS may importantly hamper the detection of a relevant treatment effect on OS. Similarly, if the aim is to show non-inferiority and if there are available evidence based next line therapies, PFS/DFS should normally be the selected primary endpoint provided that the quality of historical data is sufficiently high to allow an adequate definition of the non-inferiority margin.

Independent review and confirmation of best tumour response and progression should be undertaken if PFS is the primary endpoint.

Alternative primary endpoints, such as TTP, TTF or EFS might uncommonly be appropriate. This has to be fully justified and it is recommended that prior regulatory agreement is sought in these cases.

In patients with tumour-related symptoms at base line, symptom control, if related to anti-tumour effects, is a valid measure of therapeutic activity and may serve as primary endpoint in late line therapy studies, provided that the study can be conducted under proper double-blind conditions and that other sources of possible bias can be minimised. In certain cases, time to symptomatic tumour progression may also be an adequate primary measure of patient benefit.

There are also examples where tumour response-related activities, e.g. limb-saving surgery may be reasonable primary measures of patient benefit. Analyses of location- or cause-specific events, however, should in general be avoided as the focus may be drawn away from the main objective, namely the overall success of the treatment strategy in question.

Without further justification, ORR is not an acceptable primary endpoint for confirmatory trials. Patients with acute leukaemia destined for transplantation could serve as an example where CR is an acceptable primary endpoint, supported by data on successful transplantation and, e.g. leukaemia-free survival.

Tumour markers convincingly demonstrated to reflect tumour burden can be used, in combination with other measures of tumour burden, to define tumour response and progression, an example being multiple myeloma and the M-component. For new classes of compounds, however, it has to be demonstrated that the marker is a valid measure of tumour burden and that no bias in the assessment is introduced, e.g. through differential suppression of the tumour marker.

The first line of therapy administered after tumour progression on study drugs should be documented and when feasible further therapy. The putative effects of treatments after progression on study drugs on later events should be discussed in the study report.

Fully recognising all restraints, a justification is expected in the study protocol why endpoints such as survival benefit or symptom control cannot be used as a primary measure of patient benefit.

Secondary endpoints and exploratory analyses

Irrespective of the choice of primary endpoint OS/PFS, ORR and rate of tumour stabilisation for, e.g. 3 months should be reported.

In double-blind studies and especially in the palliative setting, HRQoL (CPMP/EWP/139391/04) using generally accepted instruments might be valuable.

The influence on study outcome of protocol defined baseline covariates selected amongst those generally recognised as relevant in the literature should be investigated. As appropriate and based on findings in exploratory studies the importance of, e.g. polymorphism for target expression or certain tumour mutations should be further investigated.

III.1.4 Reference therapy

The choice of reference regimen should be justified and normally this regimen should be selected from best available, evidence-based therapeutic options. Amongst best available references, regimens with

similar cycle lengths should be prioritised as it facilitates the identical scheduling of tumour assessments. In this context, “best available, evidence-based” should be read as a widely used, but not necessarily licensed regimen with a favourable benefit-risk convincingly documented through randomised trials and at least as good as alternative evidence-based treatment options. It is acknowledged that there are different, region-preferred standards. For superiority studies (ref. vs. test), this should normally not constitute a problem as long as the reference is evidence-based. For add-on studies (ref. + test vs. ref.), it might be possible to use a few, region-preferred references. Here a convincing clinical/pharmacological justification (cf. II.3.2) is needed, and EU scientific advice is recommended.

In most cases of advanced disease, the duration of therapy is until disease progression or non-acceptable toxicity/tolerability. It is accepted, however, that for certain therapeutic areas a fixed number of cycles is administered in accordance with clinical practice. For (neo)adjuvant therapy and in most cases where treatment is administered with curative intent, a fixed course of therapy is given. In active reference controlled trials, the assessment is facilitated if the duration of therapy is similar and deviations should be justified.

If, for a specific target population, there is no regimen with an evidence-based favourable benefit - risk relationship, a regimen used in clinical practice with a well-documented and benign safety profile is acceptable. Alternatively, “investigator’s best choice” among a few selected regimens with these characteristics (may include BSC) is acceptable. In these cases, superior efficacy has to be shown versus the pooled results in the reference arm.

In many cases, the absence of evidence-based therapies refers to patients who have failed several lines of therapy. In this situation, it might be easier to obtain the data needed for marketing authorisation based on a properly conducted randomised study in less advanced patients, supported by “salvage” studies, compared with conducting a last line, randomised BSC/investigator’s best choice comparative study.

Placebo, as add-on to BSC or active background therapy, is increasingly used as comparator in pivotal trials. To be meaningful, unblinding due to adverse reactions should not be a frequent event. If BSC or the selected active background therapy is otherwise acceptable, placebo add-on offers the possibility to reduce bias in general and to assess, e.g. symptom control in a fruitful way.

From a licensing perspective, non-inferiority results are acceptable only if a non-inferiority margin can be defined based on historical study results for the reference regimen (CPMP/EWP/2158/99). It is acknowledged, however, that even if historical data for the reference regimen may have shown, e.g. a survival benefit, the confidence interval may be too wide and close to null to allow for the proper construction of a non-inferiority margin. In these cases regulatory advice should be considered.

Single agent and combination therapies

Whether the experimental agent is used as a single agent or in combination, the experimental regimen should be compared with the “best available” comparator.

If the experimental agent (A) is added to an established regimen (B), superiority of AB vs. B should be demonstrated and benefit-risk should be shown to be favourable. A discussion is expected based on available data as regards dose intensity of B and benefit risk. If a major difference in toxicity is foreseen, it is in most cases advisable to design the study in order to show a survival benefit.

In case of substitution studies, i.e. studies where a component (C) of an established regimen (BC) is replaced with an experimental agent (A) and if non-inferiority (BC vs. BA) is the aim, the contribution of C to the activity of BC has to be well defined (CPMP/EWP/2158/99).

Uncommonly, an entirely new combination AB is tested against a reference regimen. In these cases, solid non-clinical and clinical phase I/II data should support the need for all components in the experimental regimen.

III.1.5 Drug resistance modifiers, radio/chemo sensitisers and chemoprotective agents

In principle, the design of confirmatory studies for experimental drug resistance modifying agents and radio/chemo sensitisers (A) is straight forward; AB should be demonstrated to be more active than an established regimen (B) in terms of anti-tumour activity and the benefit – risk for the combination

should be shown to be favourable. If there are PK interactions, or dynamic interactions not related to anti-tumour activity, dose adjustments of B in the combination arm might be needed in order to make the comparison AB vs. B at similar overall toxicity. If the full effects of the PK interaction is captured by changes in the plasma levels of B (e.g. no changes in distribution), however, dose adjustments of B in order to compare AB vs. B at similar exposure of B is preferred.

For a chemoprotective agent, it has to be shown that normal tissues are more protected from toxicity than tumour tissue. For most cytotoxic compounds, it is, however, easier to detect dose-related differences in toxicity than in efficacy. This means that in many cases very large studies are needed with tight confidence intervals around measures of anti-tumour activity in order to prove that normal tissue protection is achieved without loss of anti-tumour activity. Co-primary endpoints are thus needed, testing the hypotheses of improved safety and non-inferior anti-tumour activity. In a few cases, it might actually be easier to convincingly demonstrate differential tissue protection by increasing the dose of the cytotoxic compound in the experimental arm aiming to show enhanced anti-tumour activity without increased toxicity.

However, if it can be shown conclusively that there is no PK interaction and that the chemoprotective compound cannot interact with the tumour, e.g. by absence of target in tumour cells, it might be acceptable only to show reduced toxicity without formal non-inferiority testing of tumour protection. Regulatory scientific advice is recommended in these cases.

III.1.6 (Neo)adjuvant therapy

The objectives of neoadjuvant therapy may include improved overall outcome and organ preservation (e.g. more conservative surgery). If organ preservation is the main objective, at least non-inferior DFS/PFS should be documented. As for adjuvant therapy, a defined number of cycles is frequently administered. Pending on the objectives of the study it is accepted that treatment is withdrawn if tumour shrinkage is not observed after a defined treatment period.

In the adjuvant setting, effects on DFS are considered relevant to the individual patient. As the use of adjuvant therapy may limit therapeutic options at time of recurrence OS data should be reported. For established areas of adjuvant therapy, e.g. breast and colorectal cancer, and if benefit-risk is considered favourable for the experimental regimen based on DFS and available safety and survival data, mature survival data may be reported post-licensing. In some cases and due to toxicity concerns, favourable effects on OS have to be demonstrated.

III.1.7 Tumour prevention

The regulatory experience is limited, but conceptually the situation is rather similar to the adjuvant setting. Thus individuals at risk should be defined so that the observed risk reduction in tumour incidence outweighs the side effects of therapy. As tumour prevention may select for tumours with altered biological behaviour, data on OS may be needed. In the planning of these studies, regulatory scientific advice is recommended.

III.2 Methodological considerations

Frequently, only one single study is foreseen for a specific indication. Licensing based on one pivotal study, however, requires demonstration of efficacy at levels beyond standard criteria for statistical significance (CPMP/EWP/2330/99). This is of special relevance in non-inferiority trials and in a comparison with BSC/investigator's best choice. It is acknowledged that supportive evidence from confirmatory studies conducted in other indications should be taken into account in the assessment. The supportive value of these studies might vary and a discussion is expected as regards the relevance of these findings in relation to the application for the new indication.

III.2.1 Interim analyses

Interim analyses are frequently undertaken in Phase III trials, but early stopping whether for futility or difference is a sensitive issue. If the majority of the total number of expected events in the long term has been observed and a difference has been documented, this is normally accepted as an indicator that the study is reasonably mature and that the study results will remain stable over prolonged follow-up. The interpretation of interim analyses conducted on a less mature data set may be problematic. In cases where the treatment effect has been underestimated in the planning of the study, this may create

a dilemma if statistically convincing effects in terms of overall survival have been demonstrated too early. Interim analyses based on events of progression are not encouraged.

III.2.2 Time to event analyses and assessment of response and progression

For studies with PFS/DFS as primary endpoint, symmetry with respect to imaging and study visits is pivotal and adherence to protocol-defined schedules is essential and deviations should be reported. Sensitivity analyses are recommended to explore possible effects when events are detected between scheduled tumour assessments. (Appendix 1, "[Methodological considerations for using progression-free survival \(PFS\) as primary endpoint in confirmatory trials for registration](#)" is going to be published in 2 Q of 2006).

As discussed above (see II.2.2., Exploratory trials with time-related endpoints), a comparison in terms of PFS between a predominantly tumour shrinking compound and a predominantly growth inhibiting compound may "favour" the latter compound with respect to tumour burden at time of progression. Until now, there is no regulatory experience with respect to comparisons with clearly discordant outcomes in terms of ORR and PFS and there are no established ways to adjust for this. If exploratory studies indicate that this might become the case, alternative endpoints such as OS should be considered.

Differences in mode of action between the experimental and reference therapy might generate problems in relation to measurements of tumour burden and anti-tumour activity, one example being early tumour swelling as discussed previously. Whenever such problems are foreseen, which may require deviation from standard approaches (RECIST, WHO), it is recommended that agreement is reached with regulatory agencies prior to the initiation of pivotal trials. Similarly, if tumour assessment techniques cannot be used that allow for independent adjudication, it is advisable to discuss available alternatives with regulatory agencies.

III.2.3 Fixed-time endpoint

In open labelled studies and instead of PFS/DFS as repeatedly assessed, a fixed-time point comparison of the proportion of patients that are event-free has some merits as primary measure of efficacy in superiority studies. The fixed-time point comparison might provide an alternative for diagnosis where prior studies supply robust data as regards expected distribution of events of progression and where it is possible to define the proper time point for assessment of progression with confidence. The potential for missing a small treatment benefit at time points not captured in the single time point analysis is a caveat if the treatment effect of the experimental agent differs from what has been seen in historical studies.

From a statistical perspective, this reduces to some extent the sensitivity of the trial to detect differences in the distribution of the times to event between treatment arms, but the measure is less open to detection bias and reduces the need for resource consuming and frequent imaging. In this case "detection bias" refers to the investigators' and the patients' interpretation of clinical signs and symptoms, an interpretation that may or may not trigger diagnostic activities. As a secondary endpoint, PFS/DFS should also be presented as a conventional time to event analysis, based on assessment of tumour progression conducted as in clinical practice.

III.2.4 Non-inferiority studies

Given the importance of difference detecting ability for the assessment of non-inferiority trials where similar activity is assumed for test and reference, it is of relevance to plan for subgroup analyses excluding patients with poor prognostic factors at base line, such as poor PS, co-morbidities, etc. as in these patients it might be harder to detect a difference in activity between treatment regimens, if there were one. Similarly a per protocol analysis set should be defined so that protocol violations, compliance problems, etc. do not reduce the possibility to detect a difference.

III.2.5 Analyses based on a grouping of patients on an outcome of treatment

Comparisons of time-to-event variables (like OS, or PFS) by grouping patients on an outcome of treatment are problematic. Since outcomes like tumour response, dose intensity, toxicity, or compliance represent an interaction between therapy, patient and tumour the contribution of therapy cannot be disentangled. Nevertheless, certain unexpected outcomes such as clearly improved survival despite dose-reduction due to toxicity, or absence of prolonged survival in responding patients might

be informative. A search for unexpected findings constitutes a rationale for conducting these exploratory analyses.

Response duration comparing groups of patient on different therapies may be regarded as informative. Data should be reported with confidence intervals for the individual study arms, but significance testing comparing duration of response between study arms should be avoided as the comparison refers to non-randomised groups.

III.2.6 Studies in small study populations, very rare tumours

For some truly rare tumours or very narrow indications, whether due to tumour phenotype or restrictions related to target expression, it is simply not possible to recruit a sufficiently large number of patients to conduct reasonably powered, randomised studies in order to detect clearly relevant differences in anti-tumour activity. In some cases a small, randomised, reference controlled study is the best option, in other cases a within-patient TTP analysis (or the combination) might be a better alternative. In the latter case, TTP on last prior therapy is compared with time to progression on the experimental therapy as discussed above.

Problems related to studies in small populations are further discussed in the Guideline on clinical trials in small populations (CPMP/EWP/83561/2005). The importance of an integrated approach taking into account non-clinical data, effects of PD markers of activity, etc. in the assessment of efficacy in terms of clinical endpoints is emphasised.

As there is no general solution to the problem of how to document benefit – risk in these cases, regulatory scientific advice is recommended.

III.2.7 Use of external control

The use of external control (including historical control) is discussed in ICH Topic E10 (CHMP/ICH/364/96) and it is concluded that “the inability to control bias restricts use of the external control design to situations where the treatment effect is dramatic and the usual course of the disease highly predictable”. Dramatic effects are uncommonly documented in the treatment of malignancies, but it is acknowledged that such effects, obvious to any qualified observer, are seen occasionally. In these cases, prospective confirmation in randomised, reference-controlled studies is not only unacceptable to investigators, patients and ethics committees, but also unnecessary.

III.3 Special populations

III.3.1 Elderly and frail patients

In many indications elderly patients represent the majority of the patient population. If not reasonably reflected in the data base, this should be justified. Some compounds may be specifically suitable for the treatment of elderly, e.g. due to PK properties such as low sensitivity to impaired organ function. In these cases, dedicated studies in the elderly are encouraged. It is acknowledged that it may be hard to identify appropriate reference therapies in some of these cases and that other outcome measures than PFS/OS might become more relevant. In these cases it is advisable to seek regulatory agreement on the development program.

Frail patients, whether elderly or not, with clearly impaired PS constitute a vulnerable group of patients rarely included in conventional confirmatory studies. Clinical studies in this group of patients are encouraged from a regulatory perspective.

III.3.2 Children

See *Addendum* (CPMP/EWP/569/02).

III.3.3 Gender

For some tumours and/or therapies, a difference in antitumour activity related to gender has been reported. Where a priori it is likely that there may be a treatment by gender interaction, this should be taken into account in the design of the study. Otherwise it is expected that the proportion of females and males reflects the prevalence of the disease and that the sponsor provides subgroup analyses (efficacy and safety) by gender.

III.3.4 Patients with impaired organ function

Studies in patients with decompensated liver function are rarely indicated, but patients with liver metastases should normally be included in the development programme. For compounds metabolised by the liver, PK studies are expected, exploring the relationship between, e.g. enzyme levels, or bilirubin increase and exposure.

For compounds developed for use in late line therapies, the need for dose reductions in patients with impaired bone marrow reserve due to prior chemo/radio therapy may need special attention.

Exploratory studies, including PK, in patients with malignant ascites or other third space conditions are encouraged.

Effects of renal impairment should be studied as appropriate (CPMP/EWP/226/02).

If justified by the target indication, the studies referred to above may be conducted post licensing.

III.4 Safety

In addition to standard reporting of adverse events (see II.1.1 Evaluation of toxicity), it is expected that effects of preventive measures, such as antiemetics or use of growth factors are delineated. Acute, subacute and late toxicities should be described. Safety in special populations, as detailed above, should be summarised from the full studies programme.

For common events, safety in relation to treatment cycle, first, second, third etc., is of value. Similarly, timing and duration of some events such as nausea and vomiting, or cytopenias should be reported.

Where appropriate, pharmacogenomics may be used to identify patients at increased risk for severe toxicities.

Cumulative toxicity should always be investigated. If relevant, secondary tumours should remain an objective for post licensing pharmacovigilance activities.

IV. REQUIREMENTS FOR MARKETING AUTHORISATION

A favourable benefit risk relationship should have been established in studies designed in conceptual compliance with the guidance outlined in section III of this document (“Phase III confirmatory studies”).

For licensing under exceptional circumstances, please refer to Article 14(8) of Regulation (EC) No 726/2004 and paragraph III.2.6 of this document. It is acknowledged that in some of these cases, comprehensive data on safety and efficacy cannot be provided prior to licensing. In these cases approval may be associated with certain specific conditions.

The legislation opens for conditional marketing authorisation. Conceptually, this refers to situations of unmet medical need where a preliminary benefit – risk assessment based on early data is compatible with a favourable profile, but where there is a need to confirm that benefit –risk is indeed favourable in the target population. This means that finalisation of confirmatory trials in no way should be jeopardised by early licensing. Furthermore and in case the product proves harmful in the normal condition of use, or if therapeutic efficacy is lacking, revocation of marketing authorisation (or a revision of labelling) is foreseen as a viable option. Further guidance will be developed as appropriate, taking into account an implementation regulation and applicable guidelines, when available.

REFERENCES

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