COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

DRAFT

GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL
PRODUCTS IN MAN

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Note:

Any comments to this Guideline should be sent to the EMEA EWP Secretariat by email: silja.sommer@emea.eu.int or by fax: + 44 207 418 8613 by the end of June 2005.
GUIDELINE ON THE EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN

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Glossary and Abbreviations

**Benchmark study**: Randomised exploratory study designed to provide data of importance for the design of Phase III confirmatory studies, e.g. with respect the effect size using a clinically relevant measure of 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. For these compounds, toxicity and tumour response are considered suitable indicators of activity.

**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

**PK**: Pharmacokinetics

**PD**: Pharmacodynamics

**MTD**: Maximum tolerated dose

**DLT**: Dose limiting toxicities

**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 (censoring for death without progression)

**TTF**: Time to treatment failure (death, progression, change of therapy)

**EFS**: Event-free survival (time to death, progression or e.g. secondary malignancy)

**PFS**: Progression-free survival (time to death, progression)

**DFS**: Disease-free survival (time to death, recurrence)

**OS**: Overall survival (time to death)

**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

**CRF**: Case report form
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),
- Draft 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),
- 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).

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 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. make the field highly dynamic. When established approaches to drug development are considered suboptimal and in need of revision, it is advisable to seek 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 or, e.g. micro array techniques.

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 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.

II.1.1 Phase I, 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. Toxicity, in this context, is therefore viewed as a surrogate for activity. The main objective is to define dose-limiting toxicities and the dose to bring forward into further trials. While meeting the first 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 administered per body surface area. Whether this reduces interpatient variability in exposure should be investigated in the exploratory studies programme and alternative dosing, e.g. per body weight, by gender or simply a non-adjusted dose should be examined.

These trials should be undertaken in cancer patients and should normally not be conducted in individuals for whom there exist 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.

Objectives

- MTD, DLT and a suitable dose for Phase II (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. Predictability, extent, duration and reversibility should be preliminary 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

➢ For orally administered drug, food-drug interaction should be studied.

➢ Mass balance studies are encouraged.

Eligibility of patients

Patients should have a confirmed diagnosis of cancer not amenable to established forms of therapy, i.e. cancer with demonstrated resistance to established forms of therapy or in which no therapy of proven efficacy exists, and in whom use of the investigational agent may be beneficial based on non-clinical data.

Provided that safety is reasonably established, 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 (“window of opportunity”), 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 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 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

The intravenous route should be used whenever possible since it eliminates variability related to bioavailability. The oral route may be further explored when predictable bioavailability and acceptable variability in exposure have been demonstrated.

For schedule finding, experience related to a class of compounds is helpful. Non-clinical data with respect to cycle dependency and the ratio tumour / normal tissue cytotoxicity may be of some interest. For first use in man it is, however, common to start with a single intravenous dose repeated every 3-4 weeks.

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, continuous reassessment methods, 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.

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

Treatment shall be discontinued:

- If there is evidence of disease progression
- If non-acceptable side-effects have occurred
- 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 should be increased in case of overt toxicity.

Evaluation of toxicity

The minimal requirements for evaluation of adverse effects include assessment of symptoms, physical examination, blood and urine laboratory analyses and radiological assessment as appropriate. Preclinical data should be used to guide the need for further examinations. 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, NCI Common Toxicity Criteria).

Reported data should allow for the evaluation not only of the medicinal product under study, but also for factors influencing toxicity (organ dysfunction, concomitant therapy). 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.
Termination and conclusions

A Phase I study should be terminated when the MTD and target organs for toxicity 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
- Dose to be recommended for Phase II trials (according to known risk factors if possible e.g. prior cytotoxic treatment)
- 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, Therapeutic exploratory studies

Phase II trials can 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.

Here we describe trials where the primary objective is to estimate 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 are generally studies conducted without a randomised reference. 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 stop investigating the 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 efficacy
- Further characterise the best route of administration
- 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

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 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 demonstrated 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 stopping rules for activity, which is deemed too low, 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 treatment**

All chemoprotector/drug 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. When possible, cytological/pathological characterisation of representative lesions should be obtained. Except for progression, lesions in previously irradiated fields should not be considered as measurable.

An objective response is defined as a measurable reduction in the tumour burden, assessed by reduction of the target lesion/other indicator using validated 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 callipers are 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). 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 relate to differences in patient characteristics, the rapid evolution of imaging techniques, etc.

External independent review of tumour response is recommended, 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 PFS and normally OS should be reported.

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

In patients with symptomatic disease at baseline, the assessment of symptom control is encouraged.

**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 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 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 will be needed in most 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 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 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 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 most compounds shown to be non-cytotoxic in non-clinical models, prolonged exposure is needed to elicit anti-tumour activity. If early tumour shrinkage is observed in clinical studies, however, this constitutes a signal indicating the need to further explore the underlying mechanisms of action.

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 a MTD.

Biopsies from tumours (primaries and metastatic lesions), or in some cases normal tissues, might be needed to obtain data on target saturation or downstream 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 encouraged in order to delineate possible antitumour activity. Also in exploratory trials it is expected that technical standardisation of, e.g. functional imaging techniques, is implemented.

Eligibility criteria and the number of patients should be pre-specified to ensure that the variability in PK and PD is adequately captured at doses and schedules selected for further studies.

II.2.2 Phase II, 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. Even though a mechanistic approach is encouraged in general, it seems advisable to broaden the scope outside the postulated target population for most experimental compounds in order to acknowledge the limitations as regards to obtaining basic understanding of 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. 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

- 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 made. For exploratory purposes this constitutes no major concern. It is advisable to recruit patients with secondary as well as primary failure 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 “benchmark” study with 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 well-defined non-inferiority criteria. From a methodological perspective, it should be noted, however, that a purely growth inhibitory compound is favoured as regards tumour burden in a comparison in terms of TTP with a compound inducing tumour shrinkage, as progression is defined in relation to best tumour response. Therefore tumour burden will tend to be higher in patients failing a growth inhibitory compound.

- 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 Phase III confirmatory studies are indicated.

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, however, and “promising activity” is harder to define.

- For these studies, the use of conventional criteria for ORR and tumour progression is mandatory and independent review is recommended. It is recognised, however, that, e.g. tumour swelling 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 of late exploratory trials. 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.

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, also 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.
Also in this phase of drug development, 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)

This class of compounds is mentioned under a separate heading, not because they raise more complex problems in early drug development, rather the opposite. Including fields outside oncology, the experience gained with these compounds is rather extensive and this experience might be used to guide the development of non-related so-called targeted compounds.

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 specificity is frequently not to be expected, but “unwanted” targets are possible to screen for also in vitro, facilitating the safety assessment. Understanding the PK provides some guidance for dose-finding as clearance may be related to target saturation. Tumour cells should be screened for (over-) expression of the target and the relationship between target expression and activity should be investigated. Thus there is at least a conceptual simplicity related to the “understanding” of MoAbs, which might be helpful in the design of development programmes for non-related products.

If, e.g., a growth factor receptor is targeted, it is of relevance 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 repeat histological examination 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 Tumour vaccines and similar approaches

Immune modulating compounds, such as so-called tumour vaccines, constitute a special problem with respect to “proof of anti-tumour activity” studies. Nevertheless, such data are 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. If no other way forward is identified, tumour biopsy data showing signs of immune activation after “vaccination” could serve as an early marker for possible anti-tumour activity.

II.3 Combination therapies

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

The selection of patients with available alternative therapies should take into account the documented activity of the individual components of the combination regimen.

The exploratory phase encompasses also here the determination of MTD 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, most dose-finding studies are initiated at doses rather close to the recommended monotherapy dose for each compound (50-80%, pending on toxicity profiles). 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.
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 benchmark study comparing the monotherapy regimen with the combination might be informative prior to the initiation of confirmatory studies.

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.

Given the current status with respect to predictability of add-on activity, randomised benchmark 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.

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, are normally defined by disease, stage and prior lines of therapy.

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 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 existing and future patients.

The investigators should be encouraged to include patients representative of those likely to be treated in clinical practice. For a non-inferiority trial, it is essential to define in the protocol a subgroup of patients based on performance status, comorbidity, etc. where the likelihood of anti-tumour activity is
not decreased. Reasonable consistency in study outcome is expected between the full study population and this subgroup. Similarly, it is essential to define a per protocol analysis set based on violations and compliance where the likelihood of anti-tumour activity of the reference treatment is not decreased. Reasonable consistency in study outcome is expected between the full analysis set and the per protocol set. It might be advisable to direct sample size calculations towards the per protocol analysis set.

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 should be considered in case strongly prognostic covariates have been identified (CPMP/EWP/2863/99).

If exploratory studies provide a firm basis for including/excluding certain patients based on tumour phenotype/genotype, this is considered acceptable from a regulatory perspective and will be reflected in the labelling.

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

### III.1.2 Randomisation and blinding

Randomisation and, if appropriate, 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, nevertheless, expected. If the study has to be conducted as an open label study, this has implications, e.g. with respect to choice of study endpoints and conduct of sensitivity analyses.

### III.1.3 Study endpoints

While it is generally acknowledged that the aim of treatment is to improve quality of life and duration, restraints on the conduct of clinical trials frequently 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.

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. 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 also if crossover is foreseen according to protocol.

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 baseline, symptom control, if related to anti-tumour effects, is a valid measure of therapeutic activity. In certain cases, time to symptomatic tumour progression may also be an adequate 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. However, analyses of location- or cause-specific events should in general be avoided. A problem of competing risks may arise if patients may experience a number of events and the occurrence of some events precludes the occurrence of others. Analyses of location- or cause-specific events may draw the focus away from the main objective, namely the overall success of the treatment strategy in question. They may also be misleading because differences in treatment strategies can lead to a change in the distribution of failures without affecting the overall risk of an event.

Without further qualifications ORR is not an acceptable primary endpoint for confirmatory trials.

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.

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. Treatments administered after tumour progression on study drugs should be documented and their putative effects on later events discussed in the study report.

**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, symptom control and QoL (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. Wherever possible regimens with similar cycle lengths should be compared as it facilitates the identical scheduling of tumour assessments.

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 a documented 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.

In many cases, the absence of evidence-based therapies refers to patients who have failed several lines of therapy. In this situation, it is recommended to base a submission for marketing authorisation on properly conducted studies in less advanced patients, i.e. where there are available reference therapies, supported by studies conducted in the “salvage” situation.

Placebo, as add-on to BSC, is increasingly used in pivotal trials. To be meaningful, unblinding due to adverse reactions should not be a frequent event. If, however, BSC is otherwise an acceptable comparator and if placebo can be used meaningfully and is ethically acceptable, placebo 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).

**Single agent and combination therapies**

Irrespective of 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 it is preferable that doses and schedules are selected so that AB is reasonably equitoxic to B, especially if PFS is the selected primary endpoint.

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, than the contribution of C to the activity of BC has to be well defined (CPMP/EWP/2158/99).
III.1.5 Drug resistance modifiers, radiosensitisers and chemoprotective agents

In principle, the design of confirmatory studies for experimental drug resistance modifying agents and radiosensitisers (A) is straightforward; 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.

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 organ preservation and/or improved overall outcome. If organ preservation is the main objective, non-inferior or superior DFS/PFS should be documented. As for adjuvant therapy, a defined number of cycles is frequently administered, but 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, mature OS data showing at least non-inferiority should be reported. In some cases and due to toxicity concerns favourable effects also 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 patients 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 should be borne in mind not only in the sample size calculations, but also in the interpretation of interim results.

Interim analyses are frequently undertaken in Phase III trials, but early stopping whether for futility or difference is a very sensitive issue. In this context, study maturity has to be considered. Due to heterogeneity in the study population and possible differential anti-tumour activity related to subgroups of patients, it is important to avoid conclusions based on formal statistically convincing, but biologically immature results where events related to a certain patient population may be over represented.

A majority of the total number of the expected events in the long term should have been observed for an analysis to be considered reasonably mature. To exemplify, if in a study population tumour progression is expected in all patients if followed for a sufficiently long time, a majority of the patients
should have reported progression at the time of analysis. In cases where the recruitment period is short when put in relation to time to progression, however, more events may be needed to reflect effects also on late events. In the adjuvant setting and for similar reasons, the number of late events should be sufficiently large to form a basis for conclusions. This is especially true for long-term adjuvant therapy such as hormonal therapy. In cases where the treatment effect has been underestimated in the planning of the study, this may create a dilemma if statistically convincing effects have been demonstrated too early, but mainly if the difference relates to survival.

In open labelled studies and instead of PFS/DFS as repeatedly assessed, fixed-time point comparison of the proportion of patients that are event-free have some merits as primary measure of efficacy. One or in some cases two time points should be selected taking study maturity into account. Thus if, e.g. >70 % of expected events are predicted to have occurred at, e.g. 12 months, tumour status is to be assessed after 12 months of study in all individuals without previously documented progression. From a statistical perspective, this reduces 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 endpoint, using appropriate survival analysis methods and based on assessment of tumour progression conducted with the same frequency as in clinical practice.

For studies with PFS/DFS as primary endpoint, adherence to protocol-defined schedules for tumour assessments by imaging techniques, etc. is essential and deviations should be reported. Sensitivity analyses are recommended to explore possible effects when events are detected between scheduled tumour assessments.

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

For non-inferiority studies it may be appropriate to present, in addition to PFS, sensitivity analyses investigating effects of censoring or not treatment withdrawal/change of therapy/death.

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 in respect to tumour burden. 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 induce bias 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.2.1 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 analyses.

Response duration comparing groups of patient on different therapies may be regarded as informative, but statistical testing should be avoided as the comparison refers to non-randomised groups.

III.2.2 Studies in small study populations, very rare tumours

For some truly rare tumours or very narrow indications, it is simply not possible to recruit a
sufficiently large number of patients to conduct reasonably powered, randomised studies in order to detect also 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 Draft Guideline on clinical trials in small populations (CPMP/EWP/83561/2005). As there is no general solution to the problem of how to document benefit – risk in these cases, regulatory scientific advice is recommended.

III.2.3 Use of external control

The use of external control (including historical control) is discussed in the note for guidance on 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

Cancer is in many cases a disease of the elderly and this should be reflected in the study database at the time of submission. 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 measures such as dependency scales might become more relevant. In these cases it is advisable to seek regulatory agreement on the development program.

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. For most indications it is therefore expected that it should be possible to conduct meaningful subgroup analyses of the confirmatory trials.

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, as appropriate exploring the relationship between, e.g. enzyme levels, or bilirubin increase and exposure.

For compounds developed to be used also in late line therapies, 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).

III.4 Safety

In addition to standard reporting of adverse events, it is expected that effects of preventive measures, such as antiemetics or use of growth factors are delineated. Safety in special populations, as detailed above, should also 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.

Cumulative toxicity, including secondary tumours should always be investigated.
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”). Licensing based on superior PFS might be possible despite non-mature OS data, in case of non-inferiority, however, mature survival data are normally expected.
REFERENCES


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