EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN

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Additional Notes	**This note for guidance is intended to assist applicants for a marketing authorisation in the interpretation of Directive 75/318/EEC as amended with respect to the clinical investigation of anticancer agents and in particular of cytotoxic/cytostatic agents. This version replaces the 1990 guideline: *Evaluation of Anti-Cancer Medicinal Products in Man.***

CONTENTS

EVALUATION OF ANTICANCER MEDICINAL PRODUCTS IN MAN

This note provides guidance for the clinical investigation of anticancer agents and in particular of cytotoxic/cytostatic agents. However, the sections dealing with requirements for authorisation and Phase II/III studies are generally applicable for other classes of anticancer agents. It should be read in conjunction with Directive 75/318/EEC, as amended and is intended to assist applicants with its implementation. Applicants should also refer to the EU guidelines for conducting clinical trials, especially those on *Good Clinical Practice*; *Biostatistical Methodology in Clinical Trials*; and *Structure and Content of Clinical Study Reports*; and the EU guideline on the *Preclinical Evaluation of Anticancer Medicinal Products* (due to be adopted in 1997).

Although the main emphasis of this guideline is on trials with conventional cytotoxic/cytostatic agents, much of the guidance given for Phase II and Phase III trials and on the requirements for authorisation is relevant to other anticancer agents. It is recommended that for all non-cytotoxic/cytostatic agents the guidance given herein should be carefully considered and that where it is felt to be inappropriate for a particular agent justification for the chosen alternative should be given.

1 DEFINITIONS

Antineoplastic agents used in humans belong to different chemical families and have different modes of action.

Most of the widely used anticancer agents exert their activity through destruction of neoplastic cells. This group of agents includes (among others):

- Inhibitors of DNA replication/translation;
- Antimetabolic agents;
- Tubulo-binding agents;
- Membrane active agents;
- Inhibitors of reparases.

Other agents may exert their anticancer effect also by means other than direct destruction of the neoplastic cells.

This group of agents includes (among others):

- Cytokines;
- Monoclonal antibodies;
- Vaccines;
- Gene therapy.

Since other medicinal products such as chemoprotector agents and medicinal product resistance modifiers are used as part of chemotherapeutic regimens, guidance on

requirements for clinical trials for these agents will be given in the appropriate sections of this guideline.

2. PHASE I TRIALS: INITIAL HUMAN STUDIES

Phase I trials are the first studies in man. They screen mainly for toxicity as the dose is gradually escalated.

The methodology used relies on the assumption that active and toxic dosage will be close (i.e. low therapeutic index). When such an agent is to be used only for the care of cancer patients, studies in normal volunteers are not required nor recommended. Phase I trials are undertaken in cancer patients but should not be conducted in patients who have a reasonable chance of prolonged symptom free survival or alternative options for generally accepted therapy.

One of the main objectives of phase I trials is to define dose-limiting toxicity and maximum tolerated dose (MTD) to take forward into phase II trials.

The definitive optimum antitumour dose and schedule are not normally established in Phase I trials.

2.1 Objectives and background

Primary:

- the determination of the maximum tolerated dose (MTD) of a medicinal product for a specified mode of administration, taking into account all side effects; hence a safe dose for Phase II trials will be defined. This dose should take into account (a) any corrective measure which may be used as part of the treatment and which may have a beneficial effect on the risk/benefit assessment and (b) whether or not the patients were previously treated with cytotoxic chemotherapy and/or radiotherapy;
- characterisation of frequent side effects of the agent under study and of their dose relationship. Identification of dose-limiting toxicity by determining the qualitative (target organ) toxicity as well as the quantitative (predictability extent, duration and reversibility) toxicity of the medicinal product;
- determination of the relevant main pharmacokinetic parameters, using appropriate studies (when no other approach exists, studies may be conducted with a radiolabelled molecule).

  (These investigations may also take place during Phase II studies).

Secondary:

- tumour measurement and response evaluation should be carried out whenever possible and reported. However, the absence of evaluable disease should not be a contra-indication to participation in Phase I studies;
- symptomatic therapy or other measures may be determined as well as any specific toxicity study.

2.2 Eligibility of patients

All patients must have histologically/cytologically confirmed diagnosis of cancer, and preferably with evaluable disease, 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 preclinical data (whenever available). It is acknowledged that the probability of meaningful clinical response in Phase I studies is low. Main eligibility criteria are summarised in the Table I in Annex.

2.3 Treatment

The medicinal product must not be administered concomitantly with other anticancer agents unless it is being specifically developed for combination therapy.

2.3.1 Route of administration

Route of administration and duration must be specified as well as special instructions.

The intravenous route should be used whenever possible since it would eliminate variations in bioavailability. The oral route may be used if predictable bioavailability has been demonstrated.

2.3.2 Schedules: dosing frequency and type of i.v. administration

Although toxicity and pharmacokinetic animal data are useful in choosing the starting dose, these preclinical data may not permit identification of an optimal schedule in man. Therefore it is usual to start the trial with a single intravenous dose repeated every 3-4 weeks.

Should the preclinical pharmacology, the pharmacokinetics or similarity with other known agents suggest it, different schedule(s) (e.g. 5 days administration, weekly administration or continuous infusion) may be studied concomitantly.

2.3.3 Doses

a) Starting dose

When no prior experience exists in humans, the starting dose will be based on the dose devoid of severe toxicity expressed as mg/m^2 as defined from animal studies.

b) Dose escalation

During the Phase I trial(s), the smallest 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. Fibonacci scheme with modifications or pharmacokinetically-guided dose escalation by comparison of AUC values in man and mouse). 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, within-patient dose escalation may be appropriate.

Lowest increments will be studied:

– when manifestations of toxicity have occurred;

– in heavily pre-treated patients.

c) Number of cycles

Each patient preferably should receive at least 2 cycles at the same dose level. If acceptable side effects occur the patient may be retreated upon recovery at the same dose level.

Treatment shall be discontinued:

– if there is evidence of disease progression after two cycles;

– if a non-acceptable side-effect has occurred;

– upon request of the patient.

Those patients who show evidence of tumour response should be kept on treatment up to further disease progression, subject to satisfactory toxicity profile.

2.3.4 Number of patients at each dose level

Three or more fully evaluable patients are normally studied at each dose level if no severe side-effect has occurred. Inclusion of fewer than 3 patients per dose level may be acceptable if there is no/minimal toxicity at that dose.

In the case of overt toxicity:

- the number of patients will be increased to six at that dose level to further evaluate toxicity;
- enough time should have elapsed before including further patients at a higher dose level to assess dose modification.

2.4 Evaluation of toxicity

The minimal requirements of evaluation of side-effects include assessment of symptoms, physical examination, blood and urine laboratory analyses and radiological assessment as appropriate. Any other assessments predicted by preclinical evaluation should be included. Such data will be obtained prior to study and thereafter at intervals in order to quantify a given toxicity, its duration and reversibility. Any local toxicity at the site of administration will be specifically recorded. The toxicity must be graded according to a validated system (e.g. WHO toxicity criteria, Common Toxicity Criteria).

Reported data will allow not only for evaluation of the medicinal product under study but also for factors influencing toxicity (organ dysfunction, concomitant therapy). These factors will require Phase II trials to be fully elucidated.

If death occurs during the study, the precise cause of death and of its relationship to the medicinal product under study, including autopsy when possible, should be assessed.

2.5 Termination of the study

The Phase I study should be terminated when the MTD and side-effects that have lead to its determination are assessed.

The report should describe all the encountered toxicities, their severity and reversibility, dose-relationship and symptomatic measures if available. All the observed responses should be reported. If applicable, the immunological findings should additionally be reported.

2.6 Conclusions of the study

Conclusions should be included for each schedule and/or route of administration, where appropriate:

- maximum tolerated dose (MTD);
- 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 should be recommended with the intervals when these tests should be applied;
- recommendations for specific toxicity studies in experimental models;
- recommendations for preventive measures to be used in future studies.

3. PHASE II TRIALS THERAPEUTIC EXPLORATORY STUDIES

These trials involve investigation of antitumour activity in patients with specific tumour type(s).

3.1 Objectives and design

Phase II trials are generally non-controlled studies, intended to:

- determine if significant responses can be achieved with the agent under study in a series of target tumours at doses and schedules defined by Phase I studies, and to reject ineffective medicinal products;
- to assess the probability of response in target tumours and state the need for further therapeutic studies (e.g. Phase III studies);
- further characterise the pharmacokinetic profile;
- further characterise dose and schedule dependency, with respect to safety;
- further characterise the best route of administration;
- further characterise the side-effects of the medicinal product:
  - detection of rarer manifestations of toxicity;
  - assessment of cumulative/subacute toxicity;
  - assess the possible measures to manage the toxicity.

3.2 Selection of patients

3.2.1 Eligibility criteria

The eligibility criteria are summarised in Table 2 in Annex. Normally only patients with advanced disease for whom no established standard form of therapy is available for that stage of disease may be considered for Phase II Study of anticancer agents. In disease-orientated studies, exact definition of the target disease, previous therapy (if any) and disease extension should be given.

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

3.2.2 Prior treatment

Prior treatment tends to reduce the response to any further treatment. This must be taken into account in the design of the study.

3.2.3 Patient homogeneity

In order to ensure validity of conclusions, the sample of patients should be as homogeneous as possible with respect to both the extent of disease, the prognostic factors and prior treatment.

3.2.4 Statistical considerations

The number of patients should be sufficient to meet the study objectives. Recruitment should be conducted according to a predefined plan that allows the objectives to be achieved with the smallest number of patients. In evaluating response, data for all patients entered into the trial should be considered.

3.3 Measurable/evaluable target indicators

The validated method(s) used to measure target indicators should be stated in the protocol and used later to assess tumour response. Whenever possible, cytological/pathological characteristics of the target lesion should be obtained. Lesions in previously irradiated fields will not be considered as evaluable, except if clear documentation of progression exists.

Lesions which are measurable (measurements taken in 2 or 3 transtumoural diameters) or evaluable (unidimensional only) are included for the definition of objective response rates.

3.4 Treatment

The medicinal product must not be administered concomitantly with other anticancer agents unless it is being specifically developed for combination therapy.

3.4.1 Medicinal product dosage and schedule

The dosage and schedule should be clearly indicated for each medicinal product under investigation. Details on the administration of the medicinal product with special precautions (e.g. hydration of patients, protection against light and temperature denaturation of the medicinal product) will be given as well as other agents **not** to be used during the study period.

3.4.2 Dosage /schedule modification

- A table should be supplied outlining dose modifications related to the severity of the observed toxicity.
- Consideration should be given to examining high risk patients (i.e. high risk with respect to target organ toxicity or compromised metabolic or excretory mechanisms for the investigational medicinal product) separately.

3.4.3 Other treatment

All chemoprotector/medicinal product 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 flow sheets.

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 as a parameter for response assessment.

3.5 Evaluation of toxicity

This should be conducted (as during Phase I studies) at predetermined intervals.

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

3.6 Evaluation of response

3.6.1 Objective responses

An objective response is defined as a measurable reduction in the tumour burden, (assessed by reduction of the target lesion/other indicator). When multiple lesions are present, representative lesions may be selected for the assessment of medicinal product activity but no progression of other/new lesions should occur during the study period.

The objective response rate will have to be documented according to international standards (e.g. WHO Criteria)

The volume of the tumour can be measured using validated imaging procedure(s). When only unidimensional measurements are available, the lack of sensitivity of the measure precludes evaluation of volume modification (partial response).

Whenever a tumour marker (e.g. biochemical, molecular biology) is a valid measure of the therapeutic effects on tumour burden, it can be used to define efficacy of the medicinal product on the neoplastic disease. In this case both the use of this marker and the validation of the measures should be fully justified by the applicant.

External independent review of the responses should be undertaken, according to the objectives of the trial.

3.6.2 Other criteria

In addition to the above:

- survival of all patients (dated from the beginning of treatment) should be assessed. Cause of death should be stated whenever possible;
- time to treatment failure or to disease progression, time to response will be recorded;
- assessment of symptom control and quality of life may be performed.

3.7 Termination of the study

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

Early termination may occur:

- when a non acceptable medicinal product related side-effect not observed during Phase I study has occurred;
- when evidence for cumulative toxicity preventing further use of the agent has emerged.

3.8 Conclusions of the study

Each Phase II study should allow for clear-cut conclusions with respect to the number of cycles/patients evaluable for efficacy and toxicity:

- significant (i.e. not inferior to expected) activity or inactivity on a target tumour;
- adequacy of the studies dose/schedule;
- acute and subacute observed toxicity, including cumulative toxicity;
- reasons for early termination if it has occurred.

4. PHASE III TRIALS: THERAPEUTIC CONFIRMATORY STUDIES

Phase III trials are disease-orientated which seek to confirm the efficacy of the product seen in the Phase II studies in the claimed indication, using the chosen dose schedule and to determine its relative efficacy/toxicity. They are comparative in nature and should allow for the full evaluation (including establishment of a treatment regimen) of the active agent selected at the end of the Phase II study.

4.1 Objectives and background

4.1.1 To confirm the antineoplastic activity that has been previously identified in Phase II studies.

- To assess the therapeutic value of the new agent or combination.

4.1.2 To study the effects of a new agent. Appropriate endpoints of assessment, in order of importance, are:

- progression-free survival;
- overall survival;
- response rate.

The results reported must be shown to be unequivocally due to the new agent.

The primary endpoint used for assessment should be justified and the study designed accordingly.

To assess the symptomatic effect of the compound, an additional efficacy endpoint is

- symptom control supported by quality of life data.

4.1.3 To study the side effects profile of a new agent:

- acute toxicities where some rare event (allergic reactions) may not have been observed in early clinical trials;
- subacute and chronic toxicities, including cumulative toxicities;
- medicinal product interactions.

4.2 Types of treatment investigated

4.2.1 Single agent treatment

If the medicinal product under investigation is to be administered as a single agent, use will be compared to:

- existing standard treatment regimens (including surgery/radiotherapy) for the tumour type being treated;
- treatment regimen/strategies (including best supportive care + radiotherapy) which have been used previously for the tumour type being treated;
- a “no treatment” arm when ethically accepted.

4.2.2 Combination treatment

When a new medicinal product (A) is entered as an add-on to an established therapy (B), clinical efficacy should be demonstrated in randomised comparative trials (AB vs. B) with recognised clinical endpoints. Depending on previously demonstrated single medicinal product activity of A, a three armed design should be considered (AB vs. B vs. A).

In many cases, a new medicinal product is added to an established combination regimen as a substitute for a medicinal product belonging to the same pharmacological category, e.g. anthracyclines. If the aim is not to improve efficacy compared with the established regimen, the problems associated with equivalence studies must be considered.

A completely new combination therapy may sometimes be explored for clinical efficacy. In this case the need for all components of the regimen should be justified based on solid preclinical and clinical Phase I/II data. The main therapeutic Phase III trials should be carried out with recognised comparator regimens. The choice of the comparator regimen and study design should be justified by the applicant.

4.2.3 New use for established agent

This includes changes from use in previously treated patients to first line treatment, use in a new indication and change from use in patients with advanced disease to an adjuvant treatment setting.

Requirements depend on the type of new indication/new use. Furthermore, the applicant must ensure that the Part III data and clinical pharmacokinetics/pharmacodynamics, already available from the original dossier, are relevant to the new indication. If not the case, these data must be generated to support the new application.

4.2.4 Chemoprotector agents/drug resistance modifiers

The requirements for combination therapy apply also to these agents. The use of multi medicinal product resistance modifying agents is complex, as the pharmacokinetics of cytostatics are also influenced by interaction with the clearance of the chemotherapeutic agents in the liver. Pharmacokinetic studies including determination of AUC of chemotherapeutic agents (plus and minus the modifier) should be included.

4.3 Design of Phase III trials

As the goals of Phase III trials are the exact assessment of the therapeutic value brought by new agents or strategies, a comparison with established therapeutic procedure is required. Randomised trials, comparing the studied approach with a reference therapeutic modality is the optimal way to carry out such comparisons. They allow for clear demonstration and quantification of the expected therapeutic benefit.

Factorial designs are a useful tool to investigate simultaneously two or more treatments.

4.4 Eligibility criteria

These criteria are defined according to the parameters that should be studied. Adequate definition of the disease (characterisation, extension, prior/associated therapeutic modalities) and of the population of patients (age, status, coexisting diseases, renal, liver, cardiac, respiratory functions) is required.

4.5 Evaluation of efficacy

4.5.1 Overall survival

Overall survival: the type and efficacy of other treatments used after failure of the study medicinal product should be reported.

4.5.2 Disease-free survival

It should be defined as well as the periodicity of the investigations used.

4.5.3 Objective responses

An objective response is defined as a measurable reduction in the tumour burden, (assessed by reduction of the target lesion/other indicator).

The objective response rate will have to be documented according to international standards (e.g. WHO Criteria) (see 3.6.1).

4.5.4 Symptom control & Quality of life

The choice of the scales should be justified and the validity of the scale for the specific study population and its reliability should be documented. Cultural aspects should be taken into account, especially in the case of multinational studies.

4.6 Termination of the study

The study should end when the experimental plan (including early termination rule) has been fulfilled.

In addition early termination may occur:

- when a non-acceptable side-effect not observed during Phase I and II studies has occurred;
- when evidence for cumulative toxicity precluding further use of the agent has emerged.

4.7 Conclusions of the study

Any Phase III study should allow for clear-cut conclusions with respect to:

- The efficacy of the new agent in the study population, as defined by the primary endpoint;
- The safety of the new agent, taking into account the cumulative and unexpected toxicity;
- The relative efficacy/toxicity of the new agent to the comparator.

The following points should be taken into account, when analysing the data (see guidelines indicated in the Introduction section):

- Compliance with protocol;
- Number of patients treated;
- Reasons for early termination.

5. REQUIREMENTS FOR AUTHORISATION

In general, Phase III randomised, comparative studies are required for authorisation. However, Directive 75/318/EEC, provides for granting a marketing authorisation, in exceptional circumstances, in cases where full comprehensive data are not available. Where an applicant considers that the Phase II studies have unequivocally established the benefits of the new agent for the target patients this position must be fully justified by the applicant before an authorisation can be granted. Furthermore, in such circumstances, a further trials programme must be agreed as well as any other experimental study judged necessary by observed adverse drug reactions.

5.1. Assessment of efficacy

The primary endpoint used for assessment should be justified by the applicant and evaluated in conjunction with the other endpoints (see 4.1.2).

5.2 Design of Main Therapeutic Studies aimed at showing efficacy

In general the requirements for proof of efficacy and safety are similar irrespective of whether the indication is for use in previously untreated or previously treated patients.

Normally, the following requirements should be fulfilled:

5.2.1 Use in previously untreated patients – existing standard treatment regimen

Randomised clinical trials, using as comparator, standard treatment regimen(s) for the tumour type being treated, are required to prove efficacy and safety. The comparator regimen used must be justified by the applicant.

5.2.2 Use in previously untreated patients – no existing standard treatment regimen

Randomised clinical trials, which show superiority when compared with treatment regimens/strategies (including best supportive care +/- radiotherapy) which have been used previously for the tumour type being treated, are required to prove efficacy and safety. The comparator regimen used must be justified by the applicant.

5.2.3 Use in previously treated patients – existing standard treatment regimen

Randomised clinical trials, using as comparator, standard treatment regimen(s) for the tumour type being treated, are required to prove efficacy and safety. The comparator regimen used must be justified by the applicant.

5.2.4 Use in previously treated patients – no existing standard regimen

Randomised clinical trials, which show superiority when compared with treatment regimens/strategies (including best supportive care +/- radiotherapy) which have been used previously for the tumour type being treated, are required to prove efficacy and safety. The comparator regimen used must be justified by the applicant.

Non-comparator studies may be acceptable in this subgroup **only** in the following circumstances:

a) proven outstanding anticancer activity (based on response rate and duration of response) in patients strictly defined as resistant to relevant first-line therapies and

b) the new agent has an acceptable and extensively documented toxicity profile and

c) tumour response is a justified surrogate marker for clinical benefit and

d) the results indicate a positive risk/benefit assessment for this treatment in this clinically identifiable group of patients.

5.3 Problem areas in design of clinical trials

5.3.1 Studies to determine symptom control

Studies to assess symptom control should be randomised and use established scales/methods. Baseline objective criteria must be established to evaluate symptom control. Where many symptoms are involved, “core” symptoms should be predefined for the disease being treated and evaluated during treatment and follow-up.

The possibility of assessing symptomatic progression (e.g. as time to symptomatic progression), or other modalities of symptom control should be considered.

To reduce bias, the following should be undertaken:

- independent investigators (blinded to objective tumour response) should be used in the collection and evaluation of symptom control data;
- wherever possible and appropriate, patients should be blinded to treatment (and to objective response). The effect of possible patient bias should be discussed.

5.3.2 Quality of life studies

Quality of life studies may be used to support symptom control data provided that established quality of life questionnaires (including for example level of hospitalisation etc.) are used, which are relevant to the study population being treated.

5.3.3 Studies of chemoprotective agents/medicinal product resistance modifying agents

The design should take into account both the effects on normal tissue (safety) and effects on tumour tissue (efficacy). Tissue selectivity should be demonstrated, taking into account the dose/response curves, both with respect to safety and efficacy (see also 4.2.4).

Based on current knowledge, it is not possible to extrapolate the effects of these agents on specific tissues/tumours to other tissues/tumours.

TABLE 1

Eligibility Criteria for Phase I Trials with Cytotoxic Agents

	Phase I
diagnosis	histologically or cytologically demonstrated
age	adults only
disease status	disease not amenable to established form(s) of treatment
prior radiotherapy	not within 4 weeks
prior chemotherapy	not within 4-6 weeks
status	< 3 (WHO grading)
life expectancy	> 8 - 12 weeks
marrow function	normal*
renal function	no major impairment*
liver function	no major impairment*
heart function	no major impairment*
other function	no major dysfunction in a site of known or assumed toxic effects
lesions	at least one evaluable/measurable desirable
informed consent	according to national/institutional rule

* Special dosage requirements will be studied in heavily pretreated patients.

TABLE 2

Eligibility Criteria for Phase II Trials with Cytotoxic Agents

	Phase II
diagnosis	histologically or cytologically demonstrated
age	the specific studies in children and elderly possible
disease status	patients with advanced disease for whom no established form of therapy is available for that stage of disease
prior Disease	no prior history of other cancer except for lesions with no/minimal potential for mestatases
prior radiotherapy	not within 4 weeks
prior chemotherapy	not within 4-6 weeks
status	< 3 (WHO grading)
life expectancy	> 8 - 12 weeks
marrow function	specific studies in disease with bone marrow involvement are possible
renal function	no major impairment*
liver function	no major impairment*
heart function	no major impairment*
other function	no major dysfunction in a site of known or assumed toxic effects
lesions	at least one evaluable/measurable
informed consent	according to national/institutional rule

* Phase II studies in specific high risk patients may be undertaken to aid pharmacokinetic assessment.