

Chapter 28. Neoplastic Diseases

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I. INTRODUCTORY REMARKS

Cancer is a global health problem. While there have been some major advances in the treatment of solid tumours over the past 30 years, most therapeutic successes have been relatively modest, leading to survival gains of a few percentage points at best. Thus there is an urgent need for continued clinical research involving new drugs or drug combinations. In acknowledgement of the intense resource and ethical implications of exposing patients with life threatening illnesses to experimental and potentially ineffective therapies, there exists an equally compelling need for well designed and conducted studies.

Chemotherapy is the mainstay of drug therapy for most solid tumours. These agents generally target DNA or the mitotic apparatus. In general, the principles behind chemotherapy dosing are based on preclinical data demonstrating that there is a direct relationship between dose and tumour cell kill as well as dose and toxicity. Thus selection of the appropriate dose for treatment represents a balance between antitumour effect and side effects.

The initial evaluation of new agents in human subjects occurs within the context of phase I and II studies. Phase I or dose finding studies seek to determine the appropriate dose for further study (recommended phase II dose or RPTD). This typically involves exposure of successive cohorts of 3 to 6 patients with various tumour types to increasing doses of drug. Careful evaluation of the toxicity and pharmacokinetic profiles of the new agent(s) occurs at each dose level. The RPTD is defined as that dose which produces serious but reversible side effects in a predefined proportion of patients. Subjects with advanced, heavily pretreated, disease are usually included in phase I trials provided that they have adequate organ and functional status as defined within the protocol.

Phase II studies screen for activity of a new drug or drug combination using the RPTD determined in the phase I study. Previously untreated or minimally treated patients with susceptible tumour types based on pre clinical and early clinical evidence are included. The primary endpoint is estimation of the objective response rate, which is usually defined as the proportion of patients who have partial or complete shrinkage of tumour after drug exposure according to predefined standard criteria (1). In addition to characterization of the toxicity profile of the new therapy, these studies may also include pharmacokinetic or other pharmacodynamic endpoints. Many approaches exist for the conduct of phase II studies in cancer medicine including those that incorporate progression (2) and toxicity (3) information as part of the criteria for early termination of a trial. A common approach is that of the two stage design (4): if a minimum predetermined number of responses are seen with the first cohort of patients then the accrual is continued to the second stage to provide a more reliable estimation of activity. Sample size calculation is performed by specifying a response rate of interest as well as a lower response rate level below which the drug will be declared inactive. Traditional phase II design is non-comparative although randomization may be used to improve the efficiency of this type of study as a screening tool (5).

Phase III studies serve as the definitive tests of efficacy of new therapies. Using a randomized design to minimize bias, patients are allocated to the new agent(s) of interest or the standard therapy. In the field of oncology, these studies are powered to detect clinically meaningful differences in relevant endpoints such as overall or disease free survival. Quality of life or palliation of disease related symptoms may be the primary objective of symptom control studies. Phase III trials are generally resource intense due to the large sample sizes and duration of follow up generally required. Careful consideration must therefore be given to the primary study question and design since it is unethical to involve patients and investigators in trials addressing clinically irrelevant issues or involving poor methodology.

II. PHASE II STUDIES FOR REGISTRATION OF NEW THERAPIES

II.1. Outline of a typical development plan

Patients with advanced tumours of a single specific histological type are enrolled in a single arm, non-comparative study of a new drug/drug combination. The study may be conducted in a single or multi-institutional fashion although the latter is preferred to better estimate general feasibility of delivery of the new drug regimen.

II.2. Study plan

II. 2.A. Study Objectives

Primary objectives:

- a. To estimate the activity of drug X given in schedule Y (mg/route/frequency) in patients with previously untreated advanced tumours of a particular histology.

Secondary objectives:

- a. To assess the toxic effects (or “adverse effects”) of drug X in patients with previously untreated advanced tumours of a particular histology.
- b. In some studies consider also: To describe the relationship between molecular tumour characteristics and objective response.

II.2.B. Primary Endpoints

- a. Objective tumour response for solid tumours is assessed using the RECIST criteria.¹ In phase II studies of new agents in hematological malignancies, response may be measured using peripheral blood indices (hemoglobin, white blood cell count, platelets, presence of malignant cells), bone marrow (cellularity and % of malignant cells) and cytogenetics.

II.2.C. Secondary Endpoints

- a. Duration of response.
- b. Adverse effects (toxic effects) in patients receiving drug X given in schedule Y as categorized and graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3 (6).

II.2.D. Exploratory Endpoints

- a. Molecular measure of drug effect in tumour or surrogate tissue.

II.2.E. Study Design

Patients will be entered on this multi institutional, open label, single arm cohort study provided that all eligibility criteria are met and informed consent has been obtained.

Treatment must begin within 2 days of study entry. All patients will begin treatment at the protocol mandated dose and dose adjustments will be made on the basis of adverse (toxic) effects as required. Response and adverse event evaluation will be measured according to standard criteria as noted above.

All concomitant therapy, including alternative therapies, must be recorded on the case report forms. Other cytotoxic chemotherapy or investigational anti-cancer agents are not permitted.

II.2.F. Planned Sample Size

A typical sample size calculation will employ the Simon Two Stage Phase II Design method. Utilizing a response probability of interest (H_a) of 30%, a minimal response probability of 10% (H_o), error probabilities of 5% for accepting the drug with the minimal response probability and 20% for rejecting the drug with the response probability of interest:

Stage I of accrual: 10 response evaluable patients will be entered in the first stage. Using $H_0 \leq 10\%$ and $H_a \geq 30\%$, the drug will be declared inactive at the end of the first stage if there are fewer than 2 objective responses.

Stage II of accrual: If the above criterion is not met then 19 additional patients will be accrued onto the study for a final sample size of 29. The drug will be declared active if there are greater than 5 objective responses in the total sample.

II.2.G. Study Population

Previously untreated or minimally treated patients with susceptible tumour types based on pre clinical and early clinical evidence are included.

II.2.H. Specific inclusion criteria

Patients will be considered eligible for study entry provided that the following criteria are met:

- a. Histologically documented advanced/recurrent solid tumour of the specific histological type under evaluation.
- b. Presence of clinically or radiologically documented disease. At least one site of disease must be unidimensionally measurable defined as follows:
 - X – ray, physical exam $\geq 20\text{mm}$
 - Spiral CT scan $\geq 10\text{ mm}$
 - Non-spiral CT $\geq 20\text{ mm}$
- c. Patients must have a life expectancy of at least 12 weeks.
- d. Age ≥ 18 years.
- e. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (See Appendix 1).
- f. Previous therapy: Prior adjuvant therapy is permitted but patients must not have had systemic therapy for advanced/recurrent disease.
 - Patients must be at least ≥ 6 months since the last dose of adjuvant chemotherapy, if applicable.
 - Patients may have received prior radiation provided that all of the following conditions are met:
 - i. There is measurable disease outside the previously irradiated area. Patients whose sole site of disease is in a previously irradiated area are ineligible unless there is evidence of progression or new lesions in the irradiated field.
 - ii. At least 4 weeks must have lapsed since the last treatment with radiation.
 - iii. Surgery is permissible provided that at least 4 weeks have lapsed since any major surgery.
- g. Laboratory Requirements: (must be within 7 days prior to study entry)
 - Hematology:
 - i. Absolute granulocyte count (AGC) $\geq 1.5 \times 10^9/\text{L}$
 - ii. Platelets $\geq 100 \times 10^9/\text{L}$
 - Chemistry:
 - i. Serum creatinine \leq Upper Normal Limit
 - ii. Bilirubin \leq Upper Normal Limit
 - iii. AST $\leq 2.5 \times$ Upper Normal Limit
- h. Patient consent must be obtained according to local institutional policy of University Human Experimentation Committee requirements.
- i. Patients must be accessible for treatment and follow-up.

II.2.I. Specific Exclusion Criteria

- a. Prior history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.

- b. Prior chemotherapy for advanced/recurrent disease.
- c. Non- measurable disease only.
- d. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmias or psychiatric illness/ social situation that would limit study compliance.
- e. Concurrent treatment with anticancer or investigational agents including hormonal therapy.
- f. Symptomatic brain metastases.
- g. History of allergic reactions attributed to compounds of similar chemical or biologic composition to the study drug.
- h. Pregnant or lactating women. All patients of child bearing potential must use adequate contraception while on study.

II.2.J. Tools for Assessment of Endpoints

Objective Response Criteria

Response and progression will be evaluated in this study using the RECIST criteria. Changes in only the largest diameter (unidimensional measurement) of the tumour lesions are used in the RECIST criteria.

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (physical examination, CT, x-ray, MRI) or as ≥ 10 mm with spiral CT scan. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres).

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumour response of the measurable dimension of the disease. If there are > 10 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target Lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 10 listed as *target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All patients who receive at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response. All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): disappearance of all clinical and radiological evidence of tumour (both *target* and *non-target*).

Partial Response (PR): at least a 30% decrease in the sum of LD of target lesions, taking as reference the baseline sum LD.

Stable Disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD): at least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute progressive disease. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	≥ 4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥ 4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration*”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Quality of life is measured using validated instruments such as the EORTC QLQ C30 (7). Patient diaries are appropriate for symptom control studies.

Specific Criteria for Early Withdrawal and Discontinuation: See Phase II Section.

Tools for Assessment of Primary Endpoints:

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT, MRI. CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound. When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centres. Therefore, the utilization of such techniques for objective tumour response should be restricted to validation purposes in reference centres. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

Tumour Markers. Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of PSA and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Tools for Assessment of Secondary Endpoints:

Response Duration. Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

Stable Disease Duration. Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Adverse Events. All patients will be evaluable for assessment of adverse events from the time of their first dose of study drug.

Adverse events will be monitored on an ongoing basis by the study principal investigator and, if applicable, the study coordinating office. Adverse events will be categorized using the CTCAE Version 3.0. The worst event for each patient in each category or subcategory will be described. Events related and unrelated to treatment will be captured.

II.2.K. Specific Criteria for Early Withdrawal and Discontinuation

Patients may stop protocol treatment in the following instances:

- a. Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree and require discontinuation of protocol therapy.
- b. Unacceptable toxicity: Patients with intolerable or limiting toxicity despite dose reductions as defined in the protocol may be removed from study as well as those patients with Grade 3 or 4 toxicities which do not improve to \leq Grade 1 despite drug hold for 2 weeks.

- c. Tumour progression as defined by RECIST criteria.
- d. Patient request.

II.2.L. Data Analysis Method

Enrollment will occur using a 2-stage design described above. Using the null hypothesis that the response rate is 10% and the alternate hypothesis that the response rate is 30%, the sample size will yield a significance level of 5% and a power of 80%.

Primary Endpoints:

Using the primary endpoint of overall survival in study of patients with advanced disease as an example, the data analysis will involve the generation of survival curves for each treatment arm. All randomized patients will be included in the primary analysis. Survival will be defined as the time from randomization to death from any cause. Patients who are alive at the time of final analysis will be censored at the time of last contact. A Kaplan-Meier curve for proportions of survival in each treatment arm will be displayed and 95% confidence intervals for median survival computed using the method of Brookmeyer and Crowley (8). The two treatment arms will be compared using the log-rank test adjusted for the stratification variables. In addition, the effect of study centre and other potential prognostic factors on overall survival will be assessed using Cox regression. The Schoenfeld residual plots will be used to check the model assumption for the Cox regression (9).

Secondary Endpoints:

Progression free survival (PFS):

This is defined as the time from randomization to the first observation of disease progression according to the RECIST criteria or death due to any cause. A patient who stops treatment with study drug and receives alternative therapy prior to documentation of disease progression will be censored on the date that the alternative therapy begins. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All analyses for overall survival will be similarly performed for PFS.

Response Rate:

Patients will be evaluable for objective tumour response if they have at least one measurable lesion at baseline and at least one disease assessment after baseline. In addition, patients who develop PD prior to this time will also be considered evaluable for response. The response rate will be estimated as the proportion of patients evaluable for response who meet the criteria for complete or partial response. A Cochran-Mantel-Haenszel test will be used to compare tumour response rate between arms adjusting for stratification factors.

The duration of response will be calculated for all patients achieving a PR or CR. Duration of PR/CR is defined as the time from first objective status assessment of CR/PR to the first time disease progression or death is documented. A patient who stops treatment with all study drugs and receives alternative therapy prior to documentation of disease progression, will be censored on the date alternative therapy begins. The date of progression will be considered as the event date for the duration of response. If a patient has not progressed or died, the duration of response will be censored on the date of the last known alive date. The duration of response will be analyzed using similar methods described for overall survival.

Quality of Life:

The quality life of patients will be assessed using EORTC QLQ-C30. The EORTC QLQ-C30 is a validated and reliable self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functioning domains, a global quality of life domain, three symptom domains and six single items. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100.

Since quality of life will be assessed longitudinally, the method of analysis of variance for repeated measures will be used for domains represented by aggregate scores.

Toxicity:

All patients who receive at least one dose of protocol therapy will be included in the safety analysis. Descriptive summary tables will be presented on safety parameters by treatment arm.

Toxicity rates will be compared between treatment arms using the Fisher's Exact Test, as needed.

Oversight of the study by an independent data safety monitoring committee (DSMC) will occur. Included in the mandate of this committee will be ongoing review of the toxicity experience on trial and any interim analysis results as specified in the protocol (10).

III. PHASE III STUDIES FOR REGISTRATION OF NEW THERAPIES

III.1. Outline of a typical development plan

A promising drug/drug combination is selected for further study based on pre clinical and early clinical evidence. Using an active and tolerable dose of therapy as defined in phase I and II studies, the relevant patient population (histological subtype, disease stage) and study question are chosen for the phase III trial.

III.2. Study plan

III.2.A. Study Objectives

As for Phase II studies.

III.2.B. Primary endpoints

Overall survival

III.2.C. Secondary endpoints

- a. Disease free survival (adjuvant trials).
- b. Progression free survival (advanced disease trials).
- c. Toxicity.
- d. Response rate and duration of response (advanced disease setting).
- e. Quality of life.

III.2.D. Exploratory endpoints

- a. Relationship between molecular characteristics of tumour and prognosis.
- b. Relationship between molecular characteristics of tumour and probability of response to therapy.

III.2.E. Study Design

A randomized parallel group design is used. Blinding of treatment assignments may be appropriate, particularly in studies involving quality of life or symptom control endpoints.

Prior therapy may be allowed depending on the disease under evaluation but, in general, previously untreated or minimally treated patients with good functional status are assigned to the experimental or control arm as defined by the protocol.

Treatment: For advanced disease studies, therapy is generally continued until progression or occurrence of dose limiting toxicity. In early disease or adjuvant studies, protocol therapy is given for a fixed number of cycles or duration.

Treatment must begin within 2 days of study entry. All patients will begin treatment at the protocol mandated dose and dose adjustments will be made on the basis of adverse (toxic) effects as required. Response and adverse event evaluation will be measured according to standard criteria as noted above.

All concomitant therapy, including alternative therapies, must be recorded on the case report forms. Other cytotoxic chemotherapy or investigational anti-cancer agents are not permitted.

III.2.F. Planned Sample Size

Sample size calculations for clinical trials require specification of the type I and II errors as well as the magnitude of difference in outcome that the trial is designed to detect. The latter specification is a clinical one and depends on what difference in efficacy is likely to be present between the treatments and what difference would change current practice if detected.

As an example, a study in the advanced disease setting is designed to compare overall survival between patients randomized to ARM 1 (control) and patients randomized to ARM 2 (experimental). Based on other clinical data, the median survival of patients randomized to ARM 1 is estimated to be 0.55 years. In order to have 80% power to detect a 33% improvement in median survival in the experimental arm (hazard ratio of 1.33) using a two-sided 5% significance test, 381 deaths must be observed before the final analysis. In anticipation of accrual of 450 patients in 9 months, the required number of deaths (381) would be observed after following all patients for another 18 months.

Some studies employ interim analyses with adjusted p values to detect early and potentially clinically significant differences in outcome between arms before the final analysis. If interim analyses are planned, this should be clearly indicated in the body of the protocol.

Balance between the treatment arms for known prognostic factors is achieved by use of stratification factors at the time of randomization. Examples of typical stratification factors in oncology include disease stage, sex and performance status.

III.2.G. Study Population

Using a randomized design to minimize bias, patients are allocated to the new agent(s) of interest or the standard therapy.

III.2.H. Specific inclusion criteria

Inclusion Criteria: See Phase II section for typical eligibility criteria.

For advanced studies, prior systemic therapy may be allowed as long as an appropriate time lapse has occurred at the time of randomization. For adjuvant studies, no prior systemic therapy is generally allowed.

Patients with measurable or unmeasurable disease may be appropriate for advanced disease studies in which survival is the primary endpoint. Adjuvant study protocols for patients with early disease mandate the absence of tumour (clinically and radiologically) at the time of randomization.

III.2.I. Specific Exclusion Criteria

See Phase II section for typical ineligibility criteria

III.2.J. Tools for Assessment of Endpoints

Tools for Assessing Primary Endpoints:

For overall survival, the date of death is determined from hospital records or the death certificate whenever possible.

Tools for Assessing Secondary Endpoints:

In early disease studies measuring disease free survival, the date of relapse is the first date of clinical or radiological relapse.

Recurrence will be categorized as local, regional or distant, based on the histology and location of the primary tumour. The date of first recurrence should always be based on the onset of a sign of recurrence rather than the onset of a symptom.

The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumour involvement is subsequently established.

The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first positive record, even if this is determined in retrospect.

For toxicity and response assessment, see Phase II Section regarding use of appropriate tools.

Quality of life is measured using validated instruments such as the EORTC QLQ C30 (7). Patient diaries are appropriate for symptom control studies.

III.2.K. Specific Criteria for Early Withdrawal and Discontinuation

See Phase II Section

III.2.L. Methods of Measurement

See Phase II Section

IV. EXAMPLES OF LANDMARK WELL DESIGNED TRIALS

IV.1. Phase II studies

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V. SUGGESTED READINGS

V.1. Phase II studies

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APPENDIX I - PERFORMANCE STATUS (ECOG)

Grade

- 0 Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100).
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) (Karnofsky 70-80).
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
- 2 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40).
- 3 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).