Phase I Cancer Clinical Trials: A Practical Guide (2 ed.)

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Reporting and Interpreting Results

Chapter: Reporting and Interpreting Results

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12.1 Background

Phase I trials are the cornerstone of the development of any new cancer therapeutic. While is it imperative that design, conduct, and analysis of phase trials be conducted with appropriate methodology, a critical and sometimes undervalued step is the complete and transparent reporting of the results. Although most of the literature regarding inadequate reporting of clinical trials has focused on later-stage trials, with the creation of registries and mandatory reporting, phase I trials may also either not be reported at all (if development stops), or not be adequately reported [1, 2, 3, 4]. Failure to adequately report the key design, conduct, and results of the phase I trial in a timely manner may negatively affect the further development of that new therapeutic, or other agents in the same class, and result in failure of the agent and increased risk to patients [5, 6, 7, 8, 9].

Almost all early clinical trials conducted or planned in the last decade have included at least one molecularly targeted agent, used either as a single agent, or more commonly, in combination with standard therapies, usually cytotoxic chemotherapy [10]. Increasingly, immunotherapies are entering the clinic in trials that incorporate novel designs and endpoints [11]. Therefore, the need to adequately report the results is now even more critical as, not only are the designs more complex, with multiple arms, adaptive model-based designs, randomization, dose-expansion cohorts, incorporation of multiple correlative studies and biomarkers, but also the recommended dose may be based on feasibility, cost, or a decision that is not toxicity-based (Figure **12.1**).

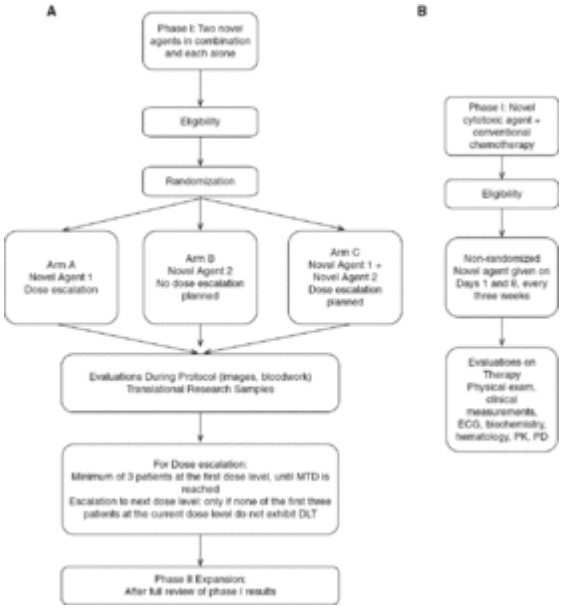

Figure 12.1
Comparison of two possible phase I clinical trials to demonstrate the growth in complexity of trial regimens evolved. DLT: dose-limiting toxicity; MTD: maximum tolerated dose; PK: pharmacokinetics; PD: pharmacodynamics.

Because targeted agents act by different mechanisms and may lead to distinctive toxicities, and are often administered in a chronic oral-dosing schedule, phase I designs, endpoints, and conduct have often been modified. Increasingly, doses for further study (recommended dose [RD]) are not defined based only on traditional dose-limiting toxicity (DLT) and maximal tolerated doses (MTD). It is also important to demonstrate that a novel compound has the target effect for which it was designed [12].

New targeted agents are now being combined with each other, in the hopes of maximizing anticancer effect by using two or more drugs active on the same target or on different targets within an aberrant pathway. The selection of agents to combine, and the design and conduct of early

clinical trials of combinations of molecularly targeted agents, has been largely empirical and based on experience with cytotoxic agents leading to difficulties with trial design, endpoint selection, and combination effects of the agents themselves being novel [13].

Not only are phase I trials now more complex and more likely to combine two or more agents, novel designs are being used. Phase 0 or exploratory trials, are exploratory first-in-human trials, where sub-therapeutic doses of an agent are administered to a small number of participants to obtain preliminary data on drug pharmacokinetics (PK) and pharmacodynamics (PD). Phase 0 studies are conducted prior to traditional phase I dose-escalation safety and tolerance studies and involve very limited human exposure, with no therapeutic or diagnostic intent. The purpose of the phase 0 study is to assist in the go/no-go decision-making process of a drug's fate earlier in the development process, using relevant human models instead of relying on sometimes inconsistent animal data to confirm endpoints such as mechanism of action, pharmacology, bioavailability, PD, and metabolic microdose assessments. A small number of patients are exposed (10 or fewer, usually) to a limited duration (generally seven days or less) and dose of a novel agent. Such studies can be conducted early in the development process to be more of a discovery tool to assist in efficient development and understanding. Information from sub-therapeutic dosing has helped us move more quickly into combination studies, and should be considered [7].

Most modern reports now include such key elements as the rationale for the trial, justification for starting doses and escalation schemes, what occurred during the course of the study, including key safety information, PK, signs of antitumor activity, and, hopefully, recommendations regarding future trials of the agent or drug combination. As described in other chapters and by published recommendations, prior to the implementation of a phase I trial, preclinical data should ideally establish the molecular target of the novel drug, the effect of the drug on malignant (and normal) cells, and the relationship between dose/schedule of the drug and antitumor effects, target effects, PK measures, and toxicology [12].

Unfortunately, even when the results of phase I trials are published, many still do not report fully on preclinical data that may be pertinent; complete adverse event data, including, if any, those from later cycles; dose intensity; and dosing information, as well as results of planned correlative studies and biomarkers. Frequently studies did not report the recommended dose (RD) or the planned dose-escalation scheme, putting the design of the study into question [14, 15, 16, 17, 18]. Parulekar and Eisenhauer also reported that most publications did not indicate how the starting dose was justified or describe the planned dose-escalation scheme [19].

This chapter is intended to outline how phase I results should be represented, and incorporates published recommendations, including the Consolidated Standards of Reporting Trials (CONSORT) statement, which applies to randomized trials but may also be applicable in early-phase trials [20]. The Standards for Reporting of Diagnostic Accuracy (STARD) are particularly relevant to biomarker discovery research [21]. The REporting recommendations for tumour MARKer prognostic studies (REMARK) guidelines, which were a major recommendation of the National Cancer Institute and the European Organization for Research and Treatment of Cancer (NCI-EORTC) presented at the First International Meeting on Cancer Diagnostic (From Discovery to Clinical Practice: Diagnostic Innovation, Implementation and Evaluation) conducted in Nyborg Denmark, July 2000 [22]. REMARK presents recommendations for reporting studies on tumor markers. The goal of all these guidelines is to encourage transparent and complete reporting so that the relevant information will be available to others to help them to judge the usefulness of the data and understand the context in which the conclusion apply. In the phase I context, the data may also inform future studies.

12.2 Contents of Phase I Trial Reports

The following discussion outlines the common sections, including content recommendations, for authors to use when creating a report or manuscript describing the results of a phase I trial. Other guidelines for reporting include: Food and Drug Administration (FDA) mandated reporting: participant flow, baseline characteristics, outcome measures and statistical analysis, and adverse events; and requirements for reporting to clinical trial registries such as clinicaltrials.gov. Further details can be found under “How to Submit Your Results, Scientific Information” (https://clinicaltrials.gov/ct2/manage-recs/how-report). An example flow diagram representing the enrollment of patients and their loss to a study based on the CONSORT guidelines is shown in Figure **12.2**.

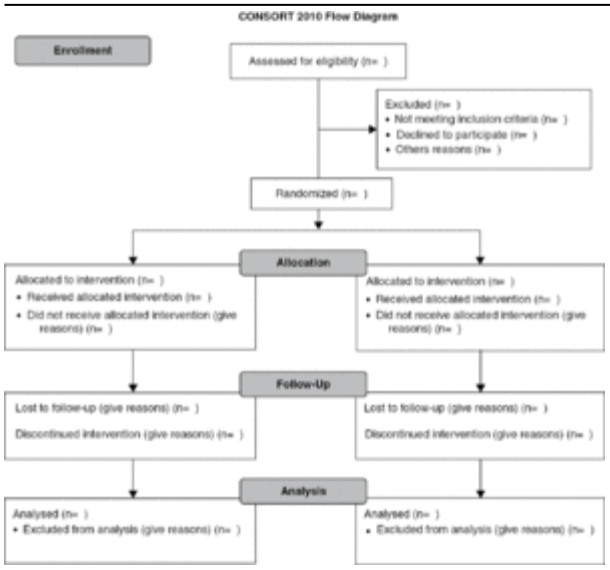

Figure 12.2
CONSORT Statement 2010: Diagram for patient tracking in early-phase clinical trials.

Reprinted with permission from CONSORT: Flow Diagram 2010. Available at http://www.consort-statement.org/consort-statement/flow-diagram0/. Published 2010. Accessibility verified October 30, 2013.

12.2.1 Introduction; disease and drug information

The introductory section of a report should provide a succinct summary describing the background of the drug and disease, as well as the hypothesis to be tested. An important focus should be the justification of why the target is relevant, and why the agent was selected for testing in humans, and it should include relevant supporting preclinical data as well as references. A description of the hypothesized target, describing what steps were taken to confirm proof-of-target and proof-of-principle, should be summarized. In addition, biomarkers that have been tested and undergone preliminary validation and are to be included in the clinical trial should be briefly described and their inclusion justified. The patient population must be justified, including a brief description of standard treatments and what setting is to be tested. If the patient selection is planned (e.g., based on a biomarker), then a brief summary and justification should be provided. The structure of the agent must be included or referenced. Safety data pertinent to expected toxicities and the dose should be summarized, as well as preclinical efficacy data that support the design of the study. Reference should be made to any available data on the schedule and route of administration, along with details of the planned schedule in the trial. Comparative data available

for other agents of similar structure or target already in clinical use or development should also be included.

For phase I trials of combination agents, begin with describing the disease(s) for which the combination is intended and the justification for improving on currently available therapy. Each drug used in the combination should be summarized, including the safety and activity of each drug alone in the disease being tested. The hypothesis for using the combination should be clearly described, with available preclinical data provided or referenced. A robust justifiable hypothesis is required, one that is tested and proven in validated non-clinical models that demonstrate clear synergy or synthetic lethality and also demonstrate effects in multiple different models. Ideally, clear pharmacodynamic markers should be present and tested on clinical models and be benchmarked to “active” and “inactive” levels to help with go/no-go decision-making in the clinic [13]. A summary of combination toxicology should be included, or if not available, an estimation of what additive or synergistic toxicities might be expected. For combination studies, future plans for the combination should be described to ensure that there is a clear development plan and resources are used wisely [7]. Finally, a brief justification of the design should be included, and whether it is to be rule- or model-based.

The introduction should conclude with a statement to indicate the primary and secondary goals of the study and to justify those objectives. There should be clear objectives that will prove or disprove the hypothesis being tested. The goals of a typical phase I clinical trial of single agent and combination agents are to determine the RD for further testing. For cytotoxic agents, this optimal dose is typically based upon the highest dose level that can be achieved without encountering unacceptable toxicity in a prescribed number of patients. For molecularly targeted agents, the dose that results in a relevant level of target modulation and clinical activity may differ greatly from the MTD, complicating the design of studies with regard to determination of the optimal dose for future clinical trials [7, 24]. The go/no-go criteria in these objectives must be met before researchers test the agents or combinations in later phase studies [13].

12.2.2 Methods

The methods section is usually divided into subsections for clarity.

12.2.2.1 Patient Entry Criteria

This section should include relevant requirements for ethical review (e.g., by the research ethics board/committee) as well as for informed consent. Relevant inclusion and exclusion criteria should be clearly summarized so that the reader clearly understands the patient population that was tested. If patients were selected based on the presence of a biomarker, then that should be clearly described, including the method used to test

the biomarker, and the cutoff used for entry. For phase I studies, it is generally recommended that patients not be selected based on biomarkers unless there is a reasonable hypothesis that would suggest that only a subset of patients would benefit [13]. If an expansion cohort is planned in patients with specific biomarkers or tumor types, these must be described here.

12.2.2.2 Starting Dose and Schedule

Detail the starting dose and justify why this dose was chosen, using preclinical animal toxicology data for first-in-human studies or clinical data for later phase I trials or combination studies. The schedule should always be justified (e.g., daily or weekly dosing), as well as any planned changes in the event of toxicity, or lack thereof; or unexpected pharmacokinetics.

For combination-agent trials, the optimal dose for each drug in a combination may not always be the same for all tumor types, patients, or molecular phenotypes [13, 25]. The schedule of the agents used in combination should be justified, including sequences used for ease of PK assays.

12.2.2.3 Design

The method of dose escalation, the number of patients per dose level, and the planned dose-escalation steps/levels should all be included in this section. It is important that the original plans be described, rather than what was actually done during the trial, as that will be reported in the Results section. A description of the rules for expansion, escalation, or reduction of dose levels and the basis of the decision (toxic effects or other observations) are also part of this section. Indicate the rules for terminating escalation and declaring the RD, along with definitions of terms used such as MTD, maximum administered dose (MAD), and DLT. The Task Force for the Methodology for the Development of Innovative Cancer Therapies (MDICT) noted that MTD generally refers to “recommended dose” in the United States, while in Europe and other jurisdictions it often refers to the dose level *above* the RD; thus, it is imperative to be clear about this definition in the report [12]. It is critical that the DLT criteria are clearly described, including any exceptions (such as alopecia, or inadequately managed nausea), and what period of time was used to assess them (e.g., cycle one only? Were DLTs in cycle 2 onwards further used to inform decisions or evaluate RD?). Any intra-patient dose escalation must be clearly defined, if planned, and it must also be defined whether or not data from patients undergoing intra-patient escalation will be used to guide decisions about further dose-level escalation or the selection of a recommended phase II dose [7].

For combinations of agents, an early clinical study is an appropriate setting to explore dose and schedule by including a randomized component in the study or by considering a Bayesian adaptive design, which allows learning from emerging data so that toxic or ineffective

doses or schedules can be closed to further accrual. If the trial design is flexible rather than being based on a strict progression from phase I to II to III, then this should be described in this section [13].

If an expansion at the RD, or phase II component, is planned, this should be described in this section, justifying the number of patients, as well as describing any additional selection criteria that might be considered, such as selecting patients with tumor types where clinical activity was seen in earlier patients. If all patients treated at the RD are to be included in that expansion (rather than only patients included after the decision has been taken), that should also be described.

If there is a change in the design, dose levels, or escalation approach at any time in the study, this should be briefly detailed here along with the new design. Plans for replacing patients who were not evaluable should be prospectively included in the protocol and described in this section of the report.

12.2.2.4 Treatment

The drug administration plan is described in this section. This includes the recommended or required pre-medication and supportive post-medication, drug route, and schedule of administration, as well as the dose-adjustment criteria for adverse effects. Also include the planned maximum treatment duration and indications for therapy discontinuation, which should include: intercurrent illness of the patient affecting clinical status to a significant degree, unacceptable toxicity (specific to agents/combinations involved), objective tumor progression or disease recurrence, or a request by the patient.

12.2.2.5 Follow-up and Investigations

The timing/intervals and type of standard investigations to be done before, during, and after therapy completion should be outlined in this section. This typically includes laboratory and imaging investigations as well as correlative studies. Efforts should be made to maintain the investigation schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or are no longer attend the participating institution, and this should be documented here.

12.2.2.6 Criteria for Assessing the Study Endpoint

Description of and reference to the criteria used for assessment of toxic effects, objective tumor response, and any other study endpoints should be included here. Laboratory, imaging, or PD studies are described in subsequent sections.

Traditional phase I trial design assumes toxicity and clinical benefit will increase as the dose of an agent increases, so toxicity has long been the usual primary endpoint, used to inform RD, of phase I trials. For cytotoxic therapeutic agents, this assumption usually holds true, and it may hold

true even with targeted agents. However, if toxicity is not mechanism-based, it may not be as useful to guide dose selection to find the most biologically active dose level [12], although toxicity is often used, together with PK, to establish the dosing range. Targeted agents may show a plateau on the dose-efficacy curve, meaning higher doses will not improve clinical benefit. Because of this, alternate endpoints have been used in many phase I trials, including measuring inhibition of a target; plasma drug levels that are estimated to be likely to be biologically relevant (PK); surrogate markers of biological activity in non-tumoral tissues [26]; and novel or functional imaging. If PD and PK are used as the primary means of selecting the RD, then ideally there should be a clear relationship with antitumor efficacy. Whatever the primary endpoint selected, PKs and toxicity evaluation are standard and/or mandatory endpoints for first-in-human studies [7].

Whatever endpoints are selected and justified, this section should define clearly what reference criteria were planned and used for the assessment of toxic effects, objective tumor response, and all other study endpoints.

The National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) [27] were initially developed for use in adverse drug experience reporting, study adverse event summaries, and investigational new drug (IND) reports to the FDA and publications. The CTCAE (now in version 4.0) has been used for collecting treatment-related adverse event data when studying new cancer therapies, treatment modalities, and supportive measures. The CTCAE can be mapped back to the Medical Dictionary for Regulatory Activities (MedDRA) [28], which is a dictionary of highly standardized medical terminology that facilitates sharing of regulatory information internationally for medical products used by humans. It can also be appropriate to develop trial-specific criteria for agents with unusual toxicity, such as BKM120, a small-molecule inhibitor of PI3 kinase, which results in mood alterations, including depression [29].

All serious adverse events (SAE) reported in the trial should also be briefly summarized. The total number of patients with such events should be reported, along with description of their disease, where they were in the treatment cycle of the agent, and a description of the event itself. This should include the grade of the event as per the reporting guidelines being used (e.g., CTCAE), the believed relationship to the agent (possible, unlikely, probable, related, unrelated), outcome of this event for the patient, and outcome for the therapy of the event: discontinuation, continuation, or alterations to the therapeutic regimen for the patient.

Although efficacy has usually been an exploratory endpoint of phase I trial, for targeted agents and highly selected patient populations, it may be critical to establish proof-of-principle and inform development decisions. For solid tumors, the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria are typically used to describing response to treatment [30], although in the phase I setting other criteria may be

incorporated. RECIST 1.1 may underestimate evidence of clinical activity that may be of interest in an early-phase study, as it is categorical—as tumor shrinkage is actually a continuous variable [31]. Further tumor necrosis may also occur without a marked decrease in tumor size: the receptor tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib, sorafenib, and axitinib are known to cause early and extensive necrosis [31]. Functional imaging, while exploratory and not yet validated, may provide additional useful information that may guide decisions regarding selection of dose and schedule. In gastrointestinal stromal cell tumors (GISTs) [32], investigators have developed new response criteria to evaluate imatinib treatment in patients with GIST. These criteria include change in tumor attenuation on computed tomography (CT), which reflects tumor density. The Choi criteria appear to correlate better with disease-specific survival in imatinib-treated GIST patients than RECIST does [32].

When evaluating the response of immune therapy activity in solid tumors, recent guidelines published by Wolchok et al. describe the immune-related response criteria (irHC) [11]. Because immunotherapeutic agents produce antitumor effects through the induction of cancer-specific immune responses or through modification of native immune processes, the outcomes are beyond those of cytotoxic agents, leading to the need for specific encompassing assessment criteria. The irHC was developed through phase II data with ipilimumab, an antibody that blocks cytotoxic T-lymphocyte-associated (CTL) antigen-4, and was evaluated in the treatment of advanced melanoma. These response definitions are listed in Table 12.1. Similarly, assessment of response for leukemia and lymphomas or so-called liquid tumors also differs from RECIST 1.1 criteria. The International Workshop on Chronic Lymphocytic Leukemia (CLL) of the NCI—Working Group, updated their guidelines for the diagnosis and treatment of CLL in 2008. Specific responses to treatment guidelines were included in this meeting discussion and have been published [33] and include multiple criteria that are needed for response definitions (Table 12.2).

Table 12.1. Immune-related Response Criteria: Response Categories

By irRC	Description of response	Confirmation by
irCR	Complete disappearance of all lesions (whether measurable or not), and no new lesions	Repeat, consecutive assessment no less than 4 weeks from the date first documented

irPR	Decrease in tumor burden >50% relative to baseline	Consecutive assessment at least 4 weeks after first documentation
irSD	Not meeting criteria for irCR or irPR, in absence of irPD	
irPD	Increase in tumor burden >25% relative to nadir (minimum recorded tumor burden)	Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
New measureable lesions (i.e., >5 × 5 mm)	Incorporated into tumor burden	
New, non-measurable lesions (i.e., <5 × 5 mm)	Do not define progression (but preclude irCR)	
Non-index lesions	Contribute to defining irCR	

ABBREVIATIONS: irCR: immune-related complete remission; irPR: immune-related partial remission; irSD: immune-related stable disease; irPD: immune-related progressive disease.

Reprinted from Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res.*2009;15(23):7412–7420, with permission from AACR Publications.

Table 12.2. Response Definition After Treatment for Patients with Chronic Lymphocytic Leukemia

Parameter	**CR***	**PR***	**PD***
Group A			
Lymphadenopathy†	None > 1.5 cm	Decrease >50%	Increase >50%

Hepatomegaly	None	Decrease >50%	Increase >50%
Splenomegaly	None	Decrease >50%	Increase >50%
Blood lymphocytes	< 4000/μL	Decrease >50% from baseline	Increase >50% over baseline
Marrow	Normocellular, <30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines Cri (5.1.6)	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	>100 000/μL	> 100 000/μL or increase >50% over baseline	Decrease >50% from baseline secondary to CLL
Hemoglobin	>11.0 g/dL	> 11g/dL or increase >50% over baseline	Decrease of >2 g/dL from baseline secondary to CLL
Neutrophils‡	>1500/μL	> 1500/μL or >50% improvement over baseline	

ABBREVIATIONS: CR: complete remission; PR: partial remission; PD: progressive disease, SD: stable disease, CLL: chronic lymphocytic leukemia.

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).

*CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR: at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group G has to be met.

† Sum of products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡ These parameters are irrelevant for some response categories.

Reprinted from Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute—Working Group 1996 Guidelines. *Blood*. 2008;111(12):5446–5456, with permission from the American Society of Hematology.

For malignant pleural mesothelioma, the growth pattern makes use of RECIST response criteria difficult. RECIST specifies that partial response (PR) is defined as a 30% decrease in the sum of the longest diameter for all target lesions; however, it is difficult to select measurement sites in mesothelioma with potential for inter-investigator variation. Bryne and Nowak reported on the development and validation of modified RECIST [34] criteria adapted to the growth pattern of malignant pleural mesotheliomas where tumor thickness perpendicular to the chest wall or mediastinum was measured in two positions at three separate levels on thoracic CT scans. The sum of the six measurements defined a pleural unidimensional measure. “Partial response” was defined as a reduction of at least 30% on two occasions four weeks apart; progressive disease was an increase of 20% over the nadir measurement. Response according to these criteria predicted a superior survival (15.1 versus 8.9 months; $P = 0.03$), and these modified RECIST criteria are now used in subsequent clinical trials [34].

The Prostate-Specific Antigen (PSA) Working Group has proposed a hybrid-type model for measurement of response to therapy in patients with prostate cancer. RECIST 1.1 works for the solid lesions identified on imaging, but PSA levels are not taken into account with RECIST [35]. Thus, in the latest NCIC-CTG trials for prostate cancer for example, response sections are used to define objective response as well as PSA response criteria. It is important to clearly define the response criteria chosen in this section.

12.2.2.7 Pharmacokinetics

This section should include the blood sampling plan, as well as justification for the timing of the sampling, methods for measurement,

and analysis for PK. Often an appendix is useful in this section to detail analytic methods, if there are no previously published references.

Although PK evaluation is mandatory for early phase I studies, it is not always required for combination studies. In combination studies, PK evaluation should always be performed when interactions are anticipated or where overlapping toxicity is likely to guide the optimal dose of the two agents. In other situations, limited or no PK evaluations may be appropriate. The FDA published “Guidance for Industry, Population Pharmacokinetics” [36] in 1999 to aid with reporting PK, and the European Medicines Agency published its “Guidelines on Reporting the Results of Population Pharmacokinetic Analyses” [37] in 2007.

12.2.2.8 Biomarkers

The three main types of biomarkers are type 0 biomarkers, which correlate with the emergence or development of a disease; type 1 biomarkers, which reflect the action of a therapeutic intervention; and type 2 biomarkers, which may be used as surrogate clinical endpoints. The last aims to predict the outcome (e.g., complications and clinical response) of a patient exhibiting disease symptoms [21]. PD biomarkers are of particular interest, as these markers have the potential to give proof of drug-target inhibition and support further studies of the agent with the goal of providing evidence that the agent reaches or modulates the putative target [21]. While PD evaluation to confirm the hypothesis should always be formally considered, researchers might consider performing these only in a subset of patients closest to the RD, rather than during dose escalation [13].

Biomarkers include qualitative and semi-quantitative assays of tumors (indirect assays such as apoptosis or reduction in blood flow) or surrogate tissues such as peripheral-blood mononuclear cells (PBMCs). Assays may be based on various methods, including imaging, immunohistochemistry or fluorescence in situ hybridization (FISH), circulating tumor cells (CTC), or circulating DNA (cDNA) [38, 39].

The development of an appropriate, accurate, and standardized assays is critical [40]. Predictive biomarkers/classifiers should preferably be explored in phase I studies, rather than used to select patients [13], unless there is a strong hypothesis.

The degree of scientific and analytical validation of a biomarker and assay depends on whether the biomarkers are exploratory or are to be used to make decisions within the trial. If a biomarker has an integral role to guide the dose-escalation decisions for subsequent patients in a phase I trial, key challenges are determining the magnitude of biomarker effect related to drug; detecting the effect within patients or samples independently of the variability due to specimen or assay performance; and establishing the methodology for completing the assay within a short turnaround time. In addition, Clinical Laboratory Improvement

Amendment (CLIA) [41] regulations imply that if the test results are used for medical decisions for the patient who has the test, the test should be done in a CLIA facility. The rule for deciding whether to dose escalate, expand, or de-escalate the trial design will reflect the specifics of the agent tested, the biomarker characteristics, and whether toxicity or other parameters will also be used to guide the decisions. When the biomarker levels are approximately normally distributed, the number of patients will determine the precision with which the true standard deviation can be estimated [42].

Biomarkers have the potential to benefit clinical development assisting both in dose determination as well as identification of patients likely to benefit or be at greater risk of toxicity. However, practically speaking, their success remains limited in early clinical drug development. In 2010, the Biomarker Task Force of the NCI Investigational Drug Steering Committee (IDSC) published guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents [42]. These recommendations provide a useful checklist, not only for the trial designs, but also for the reporting of biomarkers included in phase I trials. Recommendations to the investigator include ensuring a hypothesis and rationale for the biomarker are clearly stated as well as a description of the impact of the biomarker on the therapeutic agent development. In addition, a description of the assay’s method of validation, the investigators’ experience with the proposed assays, and data supporting the fit of a biomarker for the particular study should be included, along with justification for the number of patients and specimens, with references to studies that show feasibility and interpretable, meaningful results. Given that biomarker studies often require fresh sampling from the patient, with varying degrees of risk to the patient, consideration of feasibility, patient eligibility in the population in question, the amount of specimen needed, central and laboratory processing, and confidentiality for patients must also be described [42].

Good reporting practice should provide enough information to allow the reproduction of experimental findings and the reconstruction of quantitative prediction models [21].

12.2.2.9 Statistical analysis

Because phase I trials are non-randomized, generally no direct comparisons between cohorts are performed. In certain instances, more formal comparisons of measurements at different dose levels may be required. These comparisons and the tests used for them are often best summarized in a subsection of the Methods section. All tests should be described upfront in the protocol. It is not recommended to perform post-hoc statistical testing. Clearly, if a model-based design has been used [43, 44] or the trial is randomized, then complete details are required, including the statistical methodology.

All patients should be accounted for in the report, and if certain patients are to be excluded (e.g., patients who did not receive a pre-specified number of doses of drug for reasons other than toxicity), this should be appropriately justified and prospectively described.

12.2.2.10 Quality assurance

The key monitoring and auditing plans should be briefly described, as well as whether any external review was planned, such as an external imaging review.

12.2.3 Results

Key trial results are described, using text, tables, figures, and diagrams to display data. All tables, figures, and diagrams should be clearly described. The following are standard Results subsections.

12.2.3.1 Patient Entry

Patient characteristics can be easily represented in a table: see example Table 12.3. Descriptions should include the dates when the trial opened and closed, the number of centers that participated, and the total number of patients enrolled. All patients should be accounted for. Patients who were ineligible should also be indicated, along with their reasons for ineligibility and whether they received any study therapy. The number of patients who were evaluable for toxicity and response or other secondary endpoints should also be included. In general, at a minimum, all treated patients should be included in the reporting of phase I trials, especially for safety reports.

Table 12.3. Patient Characteristics: *Sample*

		No. Patients
Number of Patients	Entered	
	Eligible	
	Evaluable for toxicity	
	Evaluable for response	
	Evaluable for PD	
	Endpoint	
	Etc.	
Median age (range)		(years)
Performance status (ECOG)	0	
	1	
	2	
Prior chemotherapy regimens	0	
	1	
	2	
	3	
	Etc.	
Prior therapy	(specific agent as appropriate)	
Prior radiation		
Primary tumor site	Lung	
	Colon	

	Etc.	
Sites of disease	Liver	
	Lung	
	Etc.	
Measurable disease	Yes	
	No	

ABBREVIATION: ECOG, Eastern Cooperative Oncology Group.

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12.2.3.2 Drug Administration and Dose Levels

Drug administration by dose level is best described by a table that details the total number of patients treated, the total number of cycles given for each dose level, and the number of incomplete cycles (Table 12.4). Also in this section, a brief description of what happened in dose escalation should be included; e.g., if DLT was seen, at which dose level, and details on the creation of intermediate dose levels.

Table 12.4. Dose Levels and Drug Administration: *Sample*

Dose Level	Actual dose (mg/ m^2) Days 1, 8, 15	No. patients started at that dose	No. cycles started	No. cycles completed	No. patients escalated to that dose	No. cycles at escalated dose
1	100	1	3	2	–	–
2	200	3	8	8	1	2
3	300	8	18	15	1	1
4	400	6	15	13	2	2
Total		18	44	38	4	5

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Dose holds, reductions, and delays, and permanent discontinuation of drug should be summarized, with reasons for each. In addition, some estimation of dose intensity should be summarized; for example, how many patients were able to receive the planned dose intensity (Table 12.5).

Table 12.5. NCIC-CTG IND.181: Phase I study of AT9283 Given as a Weekly 24-hour Infusion in Advanced Malignancies. Dose Levels and Dose-limiting Toxicities in Cycle 1.

Dose level (mg/m^2/ day)	**No. of cycles**	**No. of patients with DLT/Total no. of patients**	**DLT**
1.5	5	0/3	–
3.0	8	0/3	–
4.5	7	0/3	–
9.0	5	0/3	–
18	5	0/3	–
24	9	0/4	–
36	22	0/3	–
40	14	0/7	–
47	14	2/6	1 (febrile neutropenia), 1 (grade 3 wound infection)

ABBREVIATIONS: no.: number; DLT: dose-limiting toxicity; NCIC-CTG IND. 181, NCIC Clinical Trials Group IND.181.

Reprinted from Dent SF, Glemon KA, Chi KN, et al. NCIC-CTG IND. 181: Phase I study of AT9283 given as a weekly 24-hour infusion in advanced malignancies [published on-line ahead of print]. *Invest New Drugs*. 2013, with permission from Springer.

12.2.3.3 Adverse Effects

The estimation of whether adverse events (AEs) are causally related to a drug is often difficult to ascertain, especially for symptoms such as fatigue, and also because the toxicity profile of a drug is not known for an agent entering clinical testing. While some toxicities are easy to assign causality to (such as rash or diarrhea that resolve on de-challenge or dose reduction), others may be unusual, such as thromboembolism or psychiatric disorders. Because of this, all AEs are usually reported rather than only those considered potentially drug-related. It is also important to present the AE data in two ways—including the data/cycles upon which decisions were made, so that the decisions are easily understood and justified, but also including all available AE data [24].

Simple tables of AEs display the worst grade by dose level, which allows the reader to understand whether a dose relationship was seen. Some variations in the table include columns for each grade, while some only include a column for “any grade” and separate columns for grades 3 and 4. Most often, hematological and non-hematological effects are reported in separate tables (see Tables 12.6–12.9 for examples). Tables may also report effects by cycle, which may aid interpretation if intra-patient dose escalation was common. To explore evidence of cumulative toxicity, the worst cycle toxicity may be compared with the first cycle. In some instances, figures may be useful to demonstrate specific information (Figure **12.3**). In the text, this section should describe the main findings shown in the tables, including the most common and the most serious effects, especially DLTs. If toxicity-modifying therapies were used, they should be discussed here with a description of their impact. Serious and severe events that are life-threatening deserve special attention.

Table 12.6. Non-hematological Adverse Effects: Worst by Patient by Assigned Dose Level.* *Sample*

	Dose level	**100**			**200**			**300**			**400**		
	No. Patients	**1**			**3**			**8**			**6**		
Category	*Adverse event term*	*Any*	*Grade 3*	*Grade 4*	*Any*	*Grade 3*	*Grade 4*	*Any*	*Grade 3*	*Grade 4*	*Any*	*Grade 3*	*Grade 4*
Gastrointestinal	Nausea	1			2			5			5	2	
	Vomiting				1			3	1		4	1	1
	Diarrhea	1			1			3	1		5	2	
Constitutional	Fatigue	1			2			5			6	2	
Neurology	Neuropathy—sensory										2		

Etc.													

*Indicate here if any of the grade 3/4 events were seen in patient when they were receiving an escalated dose: i.e., at one level higher than assigned and found in the table. As a way of avoiding this confusion, sometimes patients at escalated levels do not have the events “counted” if seen at the escalated level.

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Table 12.7. Non-hematological Adverse Effects: Worst by Cycle. *Sample*

	Dose level	**100**			**200**			**300**			**400**		
	No. Cycles *	**3**			**10**			**19**			**17**		
Category	*Adverse event term*	*Any*	*Grade 3*	*Grade 4*	*Any*	*Grade 3*	*Grade 4*	*Any*	*Grade 3*	*Grade 4*	*Any*	*Grade 3*	*Grade 4*
Gastrointestinal	Nausea	1			5			12			14	4	
	Vomiting				2			4	1		7	1	1
	Diarrhea	1			1			4	1		8	2	
Constitutional	Fatigue	2			4			9			10	3	
Neurology	Neuropathy—sensory										2		

Etc.													

*This includes cycles for patients escalated to this level.

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Table 12.8. Hematological Adverse Effects: Worst by Patient by Dose Level (Described by Grade) *Sample*

Dose Level		No. Patients Evaluable*	Grade	0	1	2	3	4
100	Granulocytes	1			1			
	Platelets	1		1				
	Hemoglobin	1			1			
200	Granulocytes	3		1	2			
	Platelets	3		3				
	Hemoglobin	3		1	1	1		
300	Granulocytes	8		1	2	3	3	
	Platelets	8		4	2	2		
	Hemoglobin	8		1	2	3	1	
400	Granulocytes	6			1	1	3	1
	Platelets	6		1	2	3		
	Hemoglobin	6			1	4	1	

*To be counted as “evaluable,” a patient must have had a baseline value and at least one follow-up determination while on study.

Reprinted from Eisenhauer EA. Reporting and interpreting results. In: *Phase I Cancer Clinical Trials: A Practical Guide.* 1st ed. Oxford, England: Oxford University Press; 2006:261–275, with permission from Oxford University Press.

Table 12.9. Hematological Adverse Effects: Worst by Cycle by Dose Level (Described by Grade). *Sample*

Dose Level		No. Cycles Evaluable*	Grade	0	1	2	3	4
100	Granulocytes	3		1	2			
	Platelets	3		3				
	Hemoglobin	3		1	2			
200	Granulocytes	9		6	3			
	Platelets	9		9				
	Hemoglobin	9		4	4	1		
300	Granulocytes	18		6	4	5	3	
	Platelets	18		8	6	4		
	Hemoglobin	18		2	6	8	2	
400	Granulocytes	17		2	2	5	7	1
	Platelets	17		5	8	4		
	Hemoglobin	17		2	5	8	2	

*To be counted as “evaluable,” a cycle must have had at least one follow-up determination between days 8 and 22.

Reprinted from Eisenhauer EA. Reporting and interpreting results. In: *Phase I Cancer Clinical Trials: A Practical Guide.* 1st ed. Oxford, England: Oxford University Press; 2006:261–275, with permission from Oxford University Press.

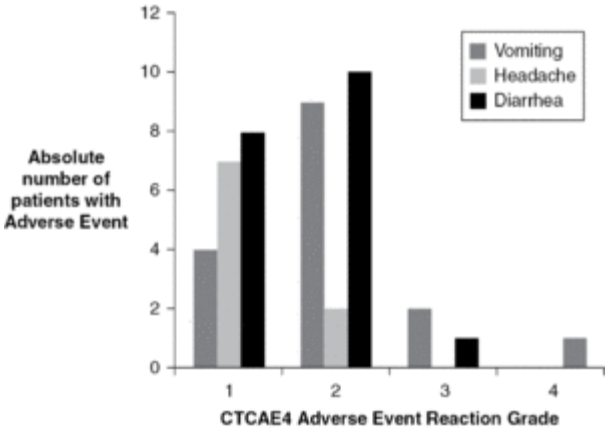

Figure 12.3
Example of bar-style graph to represent AEs in one cycle of therapy.

The full reporting of all adverse event data is critical for the interpretation of the results and informing the design of later studies with the same, or similar, agents. Traditional DLT classification is not always appropriate for non-cytotoxic chemotherapy because of prolonged administration with more chronic toxicities, which do not wax and wane. The DLT and Toxicity Assessment Recommendation Group for Early Trials of Targeted therapies (DLT-TARGETT) presented data from 27 centrally reviewed phase I trials evaluating non-cytotoxic agents as monotherapy in 1,126 patients. The overall conclusions recommend that selected lower-grade toxicities need to be taken into account to lead to a significant decrease in recommended dose intensity (RDI). Also, the RD for further studies should take into account toxicities observed after the first cycle and preferably be based on achieving >75% RDI [24].

12.2.3.4 Pharmacokinetics

Tables that show mean (+/– standard deviation [SD]) PK parameters by dose level and overall are ideal for facilitating the reader's understanding. General trends can be demonstrated with a representative patient plasma × time curve. If the PK observations have high variability between patients who were treated at the same dose level, a plot of several patients can be helpful. Figure **12.4** demonstrates substantial inter-patient variability in C_{max} and the area under the curve (AUC) from a liposomal encapsulated topoisomerase 1 inhibitor. This figure also indicates the patients who had dose-limiting effects, thus demonstrating no obvious predictable level for this. Other elements to include are information on whether the PK follows a linear or non-linear pattern related to dose and factors that seem to impact on PK observations (e.g., patients with low creatinine having lower AUC). These observations are not conclusive, but they help with directing future studies and should be further elaborated upon in the discussion section.

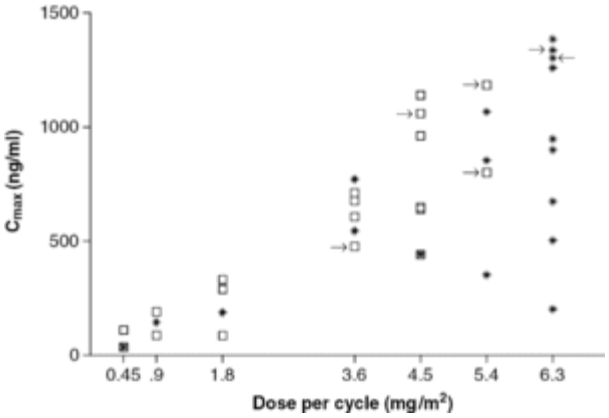

Figure 12.4
Phase I trial of OSI-211. C_{max} vs dose (dose 1 from cycle 1). □, heavily pretreated; *, minimally pretreated; → patient with DLT.

Reprinted from Gelmon K, Hirte H, Fisher B, et al. A phase 1 study of OSI-211 given as an intravenous infusion days 1, 2, and 3 every three weeks in patients with solid cancers. *Invest New Drugs.* 2004;22(3):263–275.

All correlations between PK measures and PD effects, including adverse events or other correlative studies, are best mentioned in this section, and are often best represented by a figure. This includes more examples of the relationship between C_{max}, AUC, or steady-state levels in individual patients, and the occurrence of DLT, grades 3 or 4 events, changes in surrogate markers, or tumor tissue effects. Figure **12.5** demonstrates how both dose-PD and PK-PD effects can be effectively represented in a phase I study report of farnesyltransferase inhibitor BMS-214662 [48]. The relationship between farnesyltransferase expression over time to dose in PBMCs in two schedules (panels A and B) and the relationship in each of those schedules between plasma levels in selected patients (Panels C and D) is demonstrated.

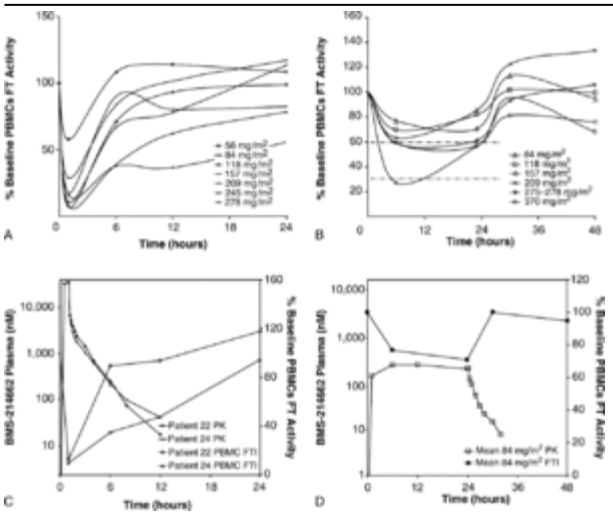

Figure 12.5
(A) Mean inhibition of PBMCs farnesyltransferase (FT) activity in the 1-hour infusion schedule; (B) mean inhibition of PBMCs FT activity in the 24-hour infusion schedule; (C) correlation between BMS-214662 PKs and PBMCs FT inhibition (FTI) in two patients at 245 mg/m^2 1-hour infusion schedule dose level; (D) correlation between BMS-214662 PKs and PBMCs FTI in patients at 84 mg/m^2 24-hour infusion schedule dose level.

Reprinted with permission from Tabernero J, Rojo F, Marimon I, et al. Phase I pharmacokinetic and pharmaco- dynamic study of weekly 1-hour and 24-hour infusion BMS-214662, a farnesyltransferase inhibitor, in patients with advanced solid tumors. *J Clin Oncol.* 2005;23(11):2521–2533.

Other considerations with PK reporting include indicating whether the trial showed that the drug achieved minimum blood levels or some other critical measure derived from preclinical data, and at what dose level did this occur. Protein-binding information should also be included to explain any important variance between species. Also include the presence and degree of any inter- or intra-patient variability seen in PK.

12.2.3.5 Biomarkers

Key results of biomarker assays by dose level are easier to follow when you include the number of evaluable patients per dose level, any meaningful changes in dose level, and the relationship between dose levels, toxicity, PK measures, or type of tissue. Figures can clearly illustrate these points, especially for immunohistochemical or other semi-quantitative measures, if used. Most figures compare PD measure with dose, rather than with PK parameters. Figures **12.5** and **12.6** demonstrate options from phase I trials of how to report such data. Figure **12.6** is from a report of a phase I trial of the small molecular angiogenesis inhibitor PTK87, which targets vascular endothelial growth factor (VEGF) receptor tyrosine kinases, including VEGFR-1/Flt-1,

VEGFR-2/KDR, VEGFR-3/Flt-4, the platelet-derived growth factor receptor tyrosine kinase, and the c-kit protein tyrosine kinase. In the phase I study, dynamic-contrast enhanced magnetic resonance imaging (MRI) was used as a technique for studying the effect of the drug on permeability and vascularity of tumor masses measured by the bidirectional transfer constant (Ki). The results were presented in several different ways: Figure **12.6a** shows the mean change from baseline in Ki, expressed as a percentage of baseline values, in two dose groups. The results suggest that there was a greater reduction in Ki at higher doses (1000 mg/day) compared with lower doses (<1000 mg/day). Figure **12.6b** shows the relationship between the effect of Ki and the plasma AUC of PTK787 in patients with liver metastases. Again, results suggest that greater effects on Ki were seen at higher levels of exposure [49].

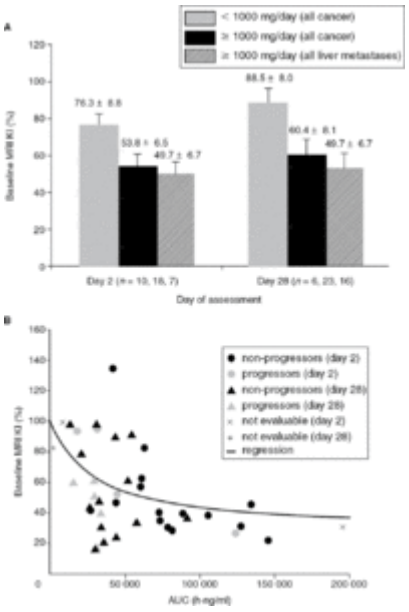

Figure 12.6
(A) Mean (=/– SE) percentage of baseline MRI bidirectional transfer constant (Ki) for patients receiving <1000 mg/day and >1000 mg/day on days 2 and 28 of PTK787/ZK 222584 treatment. (B) Inhibitory maximum effect (E_{max}) model fitting for percentage of baseline MRI bidirectional transfer constant (Ki) versus area under the plasma concentration curve (AUC) for patients with liver metastases.

Reprinted with permission from Thomas AL, Morgan B, Horsfield MA, et al. Phase I study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of PTK787/ZK 222584 administered twice daily in patients with advanced cancer. *J Clin Oncol.* 2005;23(18):4162–4171.

12.2.3.6 Antitumor effects

There is often a subset of patients who can be evaluated for antitumor effects using standard criteria in phase I trials. In some trials where activity is expected to be high, the protocol may require all patients to have response-evaluable disease. This section should outline the number of patients who are evaluable for antitumor assessment. Radiological images can be used to demonstrate effects in selected patients. It may be appropriate to summarize evidence of anticancer effects that did not meet the protocol definition of response, such as other biological effects. This may help with determining in which tumor types the agent or regimen should be evaluated in subsequent trials. Figure **12.7** shows a waterfall-style plot, which can be used to demonstrate the change in tumor size of each patient.

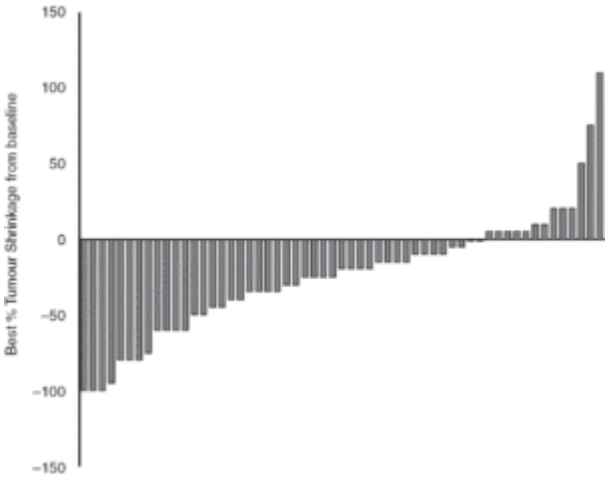

Figure 12.7
Simulated examples of a waterfall plot to represent tumor response with a particular agent.

In interpreting the results of phase I trials, there should be a clear distinction between the observation of the desired molecular effect of a drug (i.e., proof of concept) and the impact of the drug treatment on clinical measures such as tumor shrinkage or delay in progression (i.e., clinical benefit). Although tumor response is not normally a primary endpoint in phase I trials, evidence of molecular target effects in subsets of phase I patients may assist in defining which predictive biomarkers and assays are worth investigating further in phase II studies [12]. For vismodegib, for example, a first-in-class, small-molecule inhibitor of smoothened homologue, a phase II study was performed to more fully evaluate its efficacy and safety in patients with locally advanced or metastatic basal-cell carcinoma (BCC). RECIST 1.1 was used for evaluation of metastatic BCC; however, a standard endpoint for locally advanced basal-cell carcinoma did not exist at the time of the study design. Response was then defined as a decrease of 30% or more in the

externally visible or radiographic dimension (if applicable), or complete resolution of ulceration (if present at baseline). Progressive disease was defined as an increase of 20% or more in the externally visible or radiographic dimension, a new ulceration, or a new lesion. These endpoints were assessed by both independent reviewers (with photographs and radiological images) and the investigators themselves [50]. It is always important to provide a full and accurate description.

12.2.3.7 Recommended phase II dose

Arguably, this is the most critical section of the report. Establishing a clinical dose range with the upper limit defined by toxic effects is the key goal in this section (if feasible), as it is generally agreed that toxicity remains a useful measurement to establish dose range where feasible. This is particularly true if toxic effects are mechanism-based. In the absence of a clear biological rationale to suggest otherwise, it should generally be concluded that the RD will be the highest safe dose. However, before a final decision on the RD is made, it is necessary to review all data from the trial. The PK data should be reviewed to ensure that the minimum or target concentrations are achieved in plasma and/or tissue (taking account of protein-binding). Evidence of antitumor activity and its relationship to the dose should be considered. Evidence of proof-of-concept data of the drug's having the intended molecular effect, in the relevant and expected tissue(s), relationship to dose, and whether the minimum target effect level was achieved must also be factored into the decision.

This section must indicate whether a dose is recommended for further study (and if not, why not) and the basis for the recommended phase II dose. It is useful to outline the number of patients actually treated at this dose level and their toxicities, as well as the dose intensity delivered. This will inform later trials, including combination trials, since it may affect future consent forms, safety information, and estimating starting doses in combination studies. If multiple phase I studies have been performed testing different doses and schedules, but only one feasible schedule and dose will be taken forward, that should also be stated.

If the RD decision is not made based on the pre-specified criteria in the protocol for the degree of toxicity permissible, level of target or clinical activity, PD effect or PK, then a robust justification should be provided.

12.2.4 Discussion

The discussion section brings all the observations of the trial together. Details here should include what was observed, any interpretations that have been made, and the investigator's opinion on the significance of the results. Information on data that became available during the conduct or analysis of the study on the agent or regimen should also be added. The final dose recommendation and evidence for its selection, along with any caveats about the agent's use in subpopulations, should be reiterated. In

conclusion, the author should give suggestions for subsequent plans for the agent, such as planned phase II trials, or whether subsequent trials will define the dose–effect relationships in phase Ib trials, or in randomized or combination phase I trials.

12.3 After Phase I

Increasingly, more importance is given to the results of phase I studies, and the need to make development decisions as early as possible, including a decision not to proceed further, for reasons such as safety concerns, poor PK, inadequate evidence of target effect, or inability to deliver a dose likely to be active. Decisions on further development of an agent may require the evaluation of more than one phase I trial, or may require the conduct of additional studies, either pharmacodynamic studies, or in specific patient or molecular subsets. In other instances, reformulation of a drug or the selection of another candidate with a superior PK profile may be appropriate, and require additional phase I studies. Drug development continues to move toward a more tumor- and/or target-specific focus, and it is increasingly recognized that the incorporation of endpoints relative to patient selection and eligibility in the design of phase I trials is needed to more effectively and efficiently develop therapies [7]. Although there may be a reluctance to delay further development to optimize the dose, schedule, or patient population, phase III studies are not cost-effective ways to demonstrate inadequacies in dose or design. Adequate phase I and II testing is critical. The Clinical Trial Design Task Force (CTD-TF) of the NCI IDSC has published a series of discussion papers on phase II trial design in *Clinical Cancer Research* [50] which discuss these topics in greater detail.

Critical evaluation of drug-development methodology is critical. Complete reporting of clinical trials assists in the review and evaluation of methodology, but is limited. The collection of individual patient data, such as is done for RECIST and DLT-TARGETT initiatives is important to further inform future clinical trials. Collaborations will allow the acquisition of data that will better inform future development of effective combination therapy for cancer [13].

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