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Clin Cancer Res 2014;20:4210-4217.

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Review

Clinical Cancer Research

Design of Phase I Combination Trials: Recommendations of the Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee

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Abstract

Anticancer drugs are combined in an effort to treat a heterogeneous tumor or to maximize the pharmacodynamic effect. The development of combination regimens, while desirable, poses unique challenges. These include the selection of agents for combination therapy that may lead to improved efficacy while maintaining acceptable toxicity, the design of clinical trials that provide informative results for individual agents and combinations, and logistic and regulatory challenges. The phase I trial is often the initial step in the clinical evaluation of a combination regimen. In view of the importance of combination regimens and the challenges associated with developing them, the Clinical Trial Design (CTD) Task Force of the National Cancer Institute Investigational Drug Steering Committee developed a set of recommendations for the phase I development of a combination regimen. The first two recommendations focus on the scientific rationale and development plans for the combination regimen; subsequent recommendations encompass clinical design aspects. The CTD Task Force recommends that selection of the proposed regimens be based on a biologic or pharmacologic rationale supported by clinical and/or robust and validated preclinical evidence, and accompanied by a plan for subsequent development of the combination. The design of the phase I clinical trial should take into consideration the potential pharmacokinetic and pharmacodynamic interactions as well as overlapping toxicity. Depending on the specific hypothesized interaction, the primary endpoint may be dose optimization, pharmacokinetics, and/or pharmacodynamics (i.e., biomarker). *Clin Cancer Res; 20(16); 4210–7. ©2014 AACR.*

Disclosure of Potential Conflicts of Interest

L. Baker is a consultant/advisory board member for Cytrx, Immune Design, and Morphotek. L.M. Ellis is a consultant/advisory board member for Amgen, Genentech/Roche, and ImClone Systems/Eli Lilly. G. Rosner reports receiving speakers bureau honoraria from Novartis. M.J. Ratain reports receiving a commercial research grant from Bristol-Myers Squibb and is a consultant/advisory board member for AbbVie, Daiichi Sankyo, and Genentech. No potential conflicts of interest were disclosed by the other authors.

CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should be able to describe what is required to justify phase I evaluation of a combination of drugs. In addition, the participant should be able to determine whether a combination of drugs needs a formal phase I evaluation or a formal drug–drug interaction study, or no formal phase I study is needed.

Acknowledgment of Financial or Other Support

This activity does not receive commercial support.

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doi: 10.1158/1078-0432.CCR-14-0521

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Introduction

In most tumors, no single pathway has been identified that uniquely drives the malignant process. A more favorable therapeutic response may be obtained by combining drugs that target multiple pathways and/or inhibit resistance mechanisms (e.g., pharmacodynamic modulation). The past decade has seen the development of a vast array of new drugs focusing predominantly on specific molecular targets or pathways of interest. Perhaps the greatest clinical benefit from this approach has been demonstrated in malignancies driven predominantly by an identifiable molecular aberration (1–5). However, resistance usually develops (6–10). Conversely, in tumors that are genetically diverse (multiple "driver" mutations/alterations), focusing on a single target in an unselected population has had modest results (11–16). Combining molecularly targeted and/or cytotoxic drugs may be one strategy to overcome these limitations and improve efficacy (17).

The design and conduct of the phase I combination trial present specific challenges, such as the optimum selection of agents to combine among the range of possible combinations; the selection of the appropriate dose and schedule (including which drug or drugs to dose escalate); drug–drug interactions; overlapping toxicities; and logistic and regulatory challenges. To address these challenges, the Investigational Drug Steering Committee (IDSC) of the National Cancer Institute (NCI) appointed a Clinical Trial Design (CTD) Task Force composed of academics, pharmaceutical industry representatives, and patient advocates, to develop recommendations (Table 1) similar to those developed previously for phase I and II clinical trials (18, 19). The CTD Task Force focused on development of combinations of systemic agents (marketed or investigational), with consideration of the proposed mechanism of action, pharmacokinetics, and expected toxicities. The recommendations provide pragmatic clinical guidelines rather than a rigid set of rules and do not encompass in-depth details of study designs or regulatory or logistic challenges of combination regimens. The consensus recommendations were reviewed and approved by the IDSC on March 13, 2012 (Fig. 1; ref. 20).

Consensus Recommendations

Recommendation 1

All phase I combination trials should state an explicit or implicit hypothesis justifying the combination, including a pharmacologic or biologic rationale that includes at least one of the following: ***in vitro*** *data,* ***in vivo*** *data, or clinical data. The rationale may extrapolate from results with similar drugs and may be based on* ***in silico*** *analyses. The hypothesis supporting the combination should be clearly stated in the protocol.*

Given the vast number of combinations of anticancer drugs that could be evaluated (21), priority should be given to those combinations that are based on the strongest rationale and are most likely to result in clinically significant therapeutic advances. The phase I study should, therefore, have a clearly referenced rationale justifying evaluation of the combination. The overarching hypothesis to combine anticancer drugs is to enhance antitumor effects (Table 2). The underlying hypothesis should include a pharmacologic and biologic rationale supported by at least one of the following: *in vitro* data, *in vivo* data, or clinical data.

The level of preclinical data required to predict a benefit in clinical trials is currently unknown, because preclinical studies do not generally predict success of clinical trials (22–24). Preclinical data may help in the prioritization of combinations to advance to clinical trials and in the design of the subsequent clinical trial (see recommendations 3 and 4; ref. 25). Poor therapeutic indices may be associated with the high attrition rates found in oncology drug development, yet seem to be infrequently evaluated (26). Preclinical models have been shown to predict some non hematologic toxicities in humans, including skin toxicity and gastrointestinal toxicities associated with EGFR inhibitors (27). Toxicities such as myalgias, arthralgias, and headaches are not detectable in preclinical studies.

The additive or synergistic effects of a drug combination can be evaluated in cell line assays; however,

Table 1. Past and present members of the of the IDSC Clinical Trial Design Task Force

Position	Name
Co-chairs	Mark J. Ratain, Michael L. LeBlanc
Members	Laurence H. Baker, Penelope A. Bradbury, Lee M. Ellis, Elizabeth Garrett-Mayer, Richard Gaynor, Gary Gordon, Susan Groshen, Robert Iannone, Patricia Keegan, Patricia M. LoRusso, Stuart Lutzker, Channing J. Paller, Gary L. Rosner, Larry Rubinstein, Daniel J. Sargent, Lalitha K. Shankar, Manish Sharma, Anthony Shields, David R. Spriggs
NCI liaison	S. Percy Ivy
Past chair and co-chair	Lesley Seymour, Donald Berry
Nonvoting members	Rajeev Agarwal, Lori Minasian, Peter Ujhazy
IDSC patient advocate	Deborah Collyar
Past members	John Crowley, Afshin Dowlati, Jeffrey Humphrey, Mario Sznol, Miguel Villalona-Calero, Siu-Long Yao

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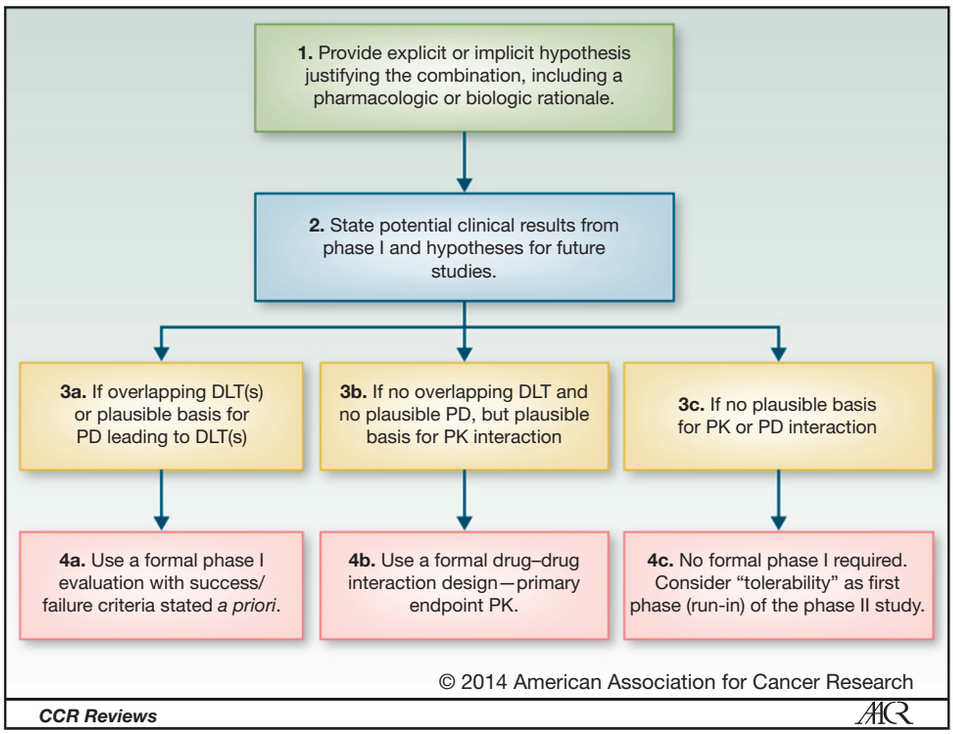

Figure 1. Process for determination of the phase I combination trial design. PD, pharmacodynamic; PK, pharmacokinetic.

determining synergy *in vivo* is complex, standard definitions of synergy *in vivo* do not exist, and such standard definitions are used exclusively with *in vitro* models (28). Another consideration is the potential for antagonistic effects of agents when combined and the effect of sequence, rarely tested preclinically. The addition of gefitinib or erlotinib to chemotherapy has not conferred a demonstrable clinical benefit. Subsequent preclinical studies demonstrated that concurrent administration of an EGFR TKI with standard chemotherapy in non–small cell lung cancer may be antagonistic, whereas sequential administration may have improved activity (29–31). This potential can be explored using preclinical models and may inform the design of schedules in the clinical trials. The IDSC has outlined some considerations about the selection of agents to take forward into clinical trials (18). However, negative preclinical results may not be reported because of publication bias, limiting relevant evidence, and possibly contributing to high failure rates in oncology drug development. Publication of negative results through journals such as the *Journal of Negative Results in BioMedicine* (32, 33)

Table 2. Hypotheses justifying combination trials

Target	Tumor type	Examples
Target multiple mechanisms of action	Gastric, colorectal, and NSCLC	Addition of HER-2 (22), EGFR (23), or VEGF (46–48, 60) pathway inhibitors broadened anticancer activity of standard chemotherapy while minimizing cross-resistance
Optimize the inhibition of a specific target or pathway	Melanoma	Combination of CTLA-4 and PD-1 receptor inhibitors resulted in tumor regression beyond that expected from monotherapy (61)
Target a potential resistance mechanism (bypass pathway)	Breast, melanoma, and NSCLC	Addition of an mTOR inhibitor to antiestrogens (62), a MEK inhibitor to a BRAF kinase inhibitor (34), or an EGFR inhibitor to a MET inhibitor (49, 63) results in restoration of sensitivity and decreased proliferation in cell lines and, for patients with NSCLC, to increased progression-free survival

Abbreviations: CTLA-4, cytotoxic T lymphocyte–associated antigen 4; NSCLC, non–small cell lung cancer; PD-1, programmed death 1.

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may provide important information for the combination trial design.

Recommendation 2

The potential results and next steps of the development plan of the combination should be clearly described. The description should include two parts: the rationale for why the biologic or pharmacologic interactions should translate into clinical effects, and one or more examples of phase II studies to test the hypothesis. The phase II example(s) should follow the guidelines of the Phase II Consensus Recommendations of the NCI's IDSC CTD Task Force.

In addition to a robust underlying hypothesis outlining why specific agents should be combined (recommendation 1), a clearly defined plan of how the combination will be evaluated in phase I and II clinical studies (recommendations 3 and 4), and the anticipated outcome of those trials, should be outlined. The trial design may aim to optimize a toxicity endpoint, pharmacodynamic biomarker or be descriptive and exploratory. As there are an infinite number of maximally tolerated doses for a drug combination, which may also be the case when optimizing a pharmacodynamic biomarker, the recommendation is not intended to be restrictive in nature. However, the rationale for the design should consider future trials. For example, a three-part phase I/II trial explored the potential for an MEK inhibitor to delay the resistance to BRAF inhibition and the safety of the combination: (part A) determined potential pharmacokinetic interactions; (part B) evaluated toxicity, safety, and pharmacokinetics of escalating doses of both agents; and (part C) proof-of-principle in the randomized phase II study evaluating progression-free survival (PFS; ref. 34). If the development plan for a combination is unclear or not feasible, it calls into question the rationale for undertaking the phase I trial in the first place. Furthermore, specific criteria, including decision rules for success (e.g., a regimen that can be moved forward in development) and failure (e.g., a regimen that is too toxic for further evaluation), should be defined and fully developed in the clinical protocol (Table 3). Trametinib and dabrafenib were successfully combined with no significant incremental toxicity and fewer squamous cell carcinomas than for patients receiving monotherapy, and proof-of-principle was demonstrated with an improvement in PFS with the combination (34). In contrast, when low-dose sorafenib and bevacizumab were combined, the tolerated doses of both agents were a quarter to half the single-agent dose used in other solid tumor studies because of unexpectedly severe toxicities, including hand–foot syndrome, hypertension, proteinuria, and thrombocytopenia (35).

Recommendation 3

The design of combination phase I studies should address the following three factors: overlapping dose-limiting toxicities (DLT); a plausible mechanistic basis for a pharmacodynamic interaction leading to DLTs; and a plausible mechanistic basis for a pharmacokinetic interaction.

Because of the differences in pharmacology, mechanism of action, and toxicity of individual agents, the design of the phase I combination study should be tailored to the specific drugs to be combined. This may involve a formal phase I dose escalation trial (36), a pharmacokinetic endpoint (37), or a safety run-in to a phase II study. Three important considerations are (i) the potential for overlapping DLTs, (ii) pharmacodynamic interactions, and (iii) pharmacokinetic interactions.

Overlapping DLTs may limit escalation of doses to levels required for optimal activity or may affect dose intensity due to dose reductions when a regimen is administered chronically. Even when overlapping DLTs do not exist, pharmacodynamic interactions may result in toxicity and affect dose. Combining bevacizumab and sorafenib (35, 38) or sunitinib (39) resulted in proteinuria and thrombocytopenia, requiring modification of dosing and scheduling. The

Table 3. Selected pharmacokinetic interactions

Drug–drug or drug–food combination	PK interaction	Mechanism
Gefitinib with bexarotene	Plasma levels of gefitinib significantly reduced (64, 65)	Gefitinib is metabolized by multiple cytochrome P450 enzymes, including bexarotene
Temsirolimus with lenalidomide	Administration of temsirolimus increased maximum concentration and area under the concentration-time curve of lenalidomide (43)	Lenalidomide is P-glycoprotein substrate
Imatinib, dasatinib, and nilotinib with high-fat meals	AUC increased by 82% when nilotinib was given 30 minutes after a high-fat meal (66)	Oral TKIs have a high risk of PK interactions when administered in conjunction with high-fat meals
Imatinib, dasatinib, and nilotinib with ketoconazole, levothyroxine, and verapamil	Imatinib exposure increased following ketoconazole coadministration (67)	Oral TKIs such as have a high risk of drug interactions when administered with drugs affecting CYP3A4

Abbreviations: AUC, area under the curve; CYP3A4, cytochrome P450 3A4; PK, pharmacokinetic; TKI, tyrosine kinase inhibitors.

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additive effects of mild overlapping adverse events may impair tolerance, particularly for drugs that are intended to be administered chronically (28).

Pharmacokinetic interactions may alter the absorption, distribution, metabolism, and excretion of one or both drugs (Table 3). However, pharmacokinetic assessments of drug–drug interaction should be routinely included in the phase I trial design only when scientific justification for such interactions, at pharmacologically achievable drug concentrations, has been identified (40). We recommend completing an initial pharmacokinetic analysis of the individual drug before initiating the next drug to increase the reliability of evidence for or against an interaction (37, 41, 42), rather than performing pharmacokinetic studies of all drugs in the combination and comparing the results to historical controls (43).

Combining agents with conflicting requirements with respect to the timing of meals adds challenges. Understanding these potential interactions will help generate hypotheses to be addressed in the phase I clinical trial, which will then influence the subsequent clinical trial design. Explicit instructions to trial participants are critical to ensure careful treatment selection for future trials.

Drug scheduling of combinations may affect additive or synergistic effects on efficacy, toxicity, or both. Combining drugs with on-off scheduling, such as sunitinib (4 weeks on, 2 weeks off is standard) and capecitabine (2 weeks on, 1 week off), will require the evaluation of sequences different from those used when the drugs are administered as single agents. If drug–drug interactions affect exposure to either drug or their metabolites, then applying common single-agent, on-off schedules may result in variable drug exposure (21). Preclinical studies could identify alternate schedules that result in more consistent drug exposures. Similar scheduling and sequencing issues may arise when intravenously administered drugs are combined with oral agents. Drug sequencing may also be a design issue when combining drugs with pharmacokinetic or pharmacodynamic interactions and short half-lives. Scheduling and dosing decisions also affect toxicities, and novel schedules such as alternating administration of the drugs may allow extended administration when concurrent administration is too toxic (44).

Recommendation 4

Selection of the clinical trial design should be based on the scientific rationale, underlying data and hypothesis for the combination, and the intended development plan for the combination (recommendations 1–3). Recommendation 4 is not intended to be prescriptive, but to provide pragmatic guidelines on the selection of the phase I trial design for a drug combination.

No single standard exists for the phase I trial design for combinations, but the design should address the specific hypothesis (recommendation 1) and subsequent development plans for the combination (recommendation 2). The classic DLT-driven cohort expansion design (3+3) has most commonly been used (45). To date, most combinations have added one or more investigational agents to a standard backbone already in clinical practice (34, 46–49). One challenge is the need to distinguish the incremental toxicity of the combination. Hamberg and colleagues propose some solutions, including a 3+3+3 design, which may reduce the chance of falsely declaring that the maximum tolerated dose (MTD) has been reached (when in fact observed DLTs might be due to the standard therapy alone; ref. 21). Another alternative is to include controls in phase I trials, either an intrapatient control (e.g., by introducing the novel agent after the standard backbone has been started) or the randomization of patients to commence the combination up front or in a staggered approach (21). Mathematical modeling can also be used to refine dose escalation based on data that emerge during the trial. A Bayesian approach has been proposed to address background toxicity that arises when a new agent is added to standard treatment (21). In addition, if the combination is intended to be developed in several disease settings with different backbones, multiarm studies may also be more efficient than a series of separate single-agent trials (50–52). Furthermore, a phase I trial may fail to reflect optimal dose relationships. Thus, investigators may need to compare alternate doses and schedules in subsequent trials (21). Although there may be multiple appropriate phase I design options, the proposed design should be fully specified in the protocol as an algorithm, including any stage-wise decision rules, so that the statistical properties of the proposed phase I design can be evaluated under hypothesized outcome probability models.

Recommendation 4A

Combination therapies with overlapping DLTs or a plausible basis for a pharmacodynamic interaction leading to DLTs require formal phase I evaluation. The selected doses to be studied should be justified on the basis of the specific phase II plans.

Where overlapping DLTs exist or where pharmacodynamic interaction may be anticipated, a formal phase I design is required to evaluate toxicity, and to explore the recommended phase II doses and possibly the optimal schedule of the combination. The selection of doses to be evaluated should be justified on the basis of the preclinical data, nature of interaction of the study drugs, and dependence of the target for DLTs versus efficacy. In addition, the criteria for success and failure of a combination should be defined. An inability to escalate one or more drugs such that the combined dose would be expected to have greater efficacy than the single-agent counterparts may mean the combination is not suitable for progressing to a phase II study. In addition, DLTs occurring after the first cycle can prevent administration of subsequent cycles and should be factored into determination of recommended phase II dosing. Finally, toxicity may be unacceptable in the population for which the combination is planned to be developed.

When considering dose escalation for both agents, a model-based approach can be very helpful, particularly when it considers both toxicity and efficacy (53–55). When

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one of the agents has markedly less single-agent activity or is being added primarily as a modulator, the agent with greater single-agent activity should, in general, be maintained at or near its single-agent dose (MTD), while gradually titrating the second agent.

Recommendation 4B

Combinations without overlapping DLTs and without a plausible basis for pharmacodynamic interaction, but with a plausible pharmacokinetic interaction, should be studied using a formal drug–drug interaction design. The primary endpoint is pharmacokinetics. The crossover design is often optimal.

In phase I trials in which pharmacokinetic interactions are anticipated (e.g., drugs metabolized by the same pathway; ref. 56), a drug–drug interaction design should be considered. This would facilitate pharmacokinetic analyses for both single agents and the combination. A common method of assessing pharmacokinetic interaction uses crossover study designs that limit the number of patients required and allow testing for different effects based upon different sequential ordering of the agents. Statistical analysis using repeated measures over the same patient can account for interpatient variability for some of the endpoints and thereby increases statistical power. Combinations involving drugs with long half-lives, such as vismodegib, require phase I designs with pharmacokinetic washout periods (57). Crossover studies may use randomized designs in which drug 1 is followed by drug 1 and drug 2, or drug 1 and drug 2 are followed by drug 1, with a washout period, with extensive pharmacokinetic sampling during both the single-agent and combination phases. An alternative is the single sequence crossover design in which drug 1 plus drug 2 always follows drug 1, or the reverse (58). In both of these designs, both interpatient and intrapatient variability may need to be considered.

Where pharmacokinetic interactions could lead to drug accumulation, washout periods and/or low initial doses should be considered. The decision to escalate to the next dose would be based on interim pharmacokinetic results in which the predefined dose-escalation rule might be "If the drug A level at steady-state increases less than x% over the previous level, and no DLT is present, then use dose B, otherwise use dose C." In situations in which CYP3A4 interactions are expected, for example, this pharmacokinetic-informed dose escalation method is appropriate. The hypothesis-driven development plan performed in recommendation 2, in case of clinically significant pharmacokinetic interactions, must be based upon a reasonable assurance that any dose reductions in individual agents, necessitated by the need to maintain acceptable toxicity, preserves the expectation of superior efficacy for the combination (59).

Recommendation 4C

Combinations without overlapping toxicities, without a plausible basis for a pharmacodynamic interaction leading to a DLT, and without a plausible basis for a pharmacokinetic interaction do not require a formal phase I study. A pilot or safety run-in for tolerability can be conducted as an initial step of a phase II study.

If a combination regimen is not anticipated to have overlapping toxicity, pharmacodynamic or pharmacokinetic interaction, a formal phase I trial may not be required. Instead, a short pilot or safety run-in period may be undertaken as the initial part of a phase II trial to explore a limited number of dose levels (for example, clinicaltrials.gov identifier NCT01839487 or NCT01708993), or to evaluate an anticipated recommended phase II dose directly before enrolling patients in the phase II portion of the trial. If this approach is chosen, the phase II design could include an early safety interim analysis to ensure the regimen is tolerable (21). However, before determining that a formal phase I trial is not required, consideration should be given to involving pharmacokinetics, pharmacodynamics, and data safety experts.

Summary

The CTD Task Force formulated recommendations for the design of early-phase combination trials of anticancer agents based on consensus developed with members of the IDSC, the Task Force, and external experts. The selection of the proposed regimens is based on a biologic or pharmacologic rationale supported by clinical and preclinical data, accompanied by a plan for subsequent development of the combination trials. The potential pharmacokinetic and pharmacodynamic interactions, as well as overlapping toxicities, should be considered. Depending on the specific hypothesized interaction, the primary endpoint may be dose optimization, pharmacokinetics, and/or pharmacodynamics. The rationale and design of combination clinical trials should be carefully evaluated. Additional guidance may be obtained by consulting with regulatory authorities (e.g., the FDA and/or the European Medicines Agency) before trial initiation. These recommendations complement consensus guidelines on the design of phase I and II clinical trials testing cancer therapeutics (18, 19), and were reviewed and formally approved by the IDSC.

Acknowledgments

The authors thank Amy Gravell.

Grant Support

P.A. Bradbury was supported by a Cancer Care Ontario Research Chair in Experimental Therapeutics.

Received March 5, 2014; revised May 4, 2014; accepted May 9, 2014; published online August 14, 2014.

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