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# The Effects of Novel Design Strategies on the Risks and Benefits of Phase I Oncology Trials

Shlomo Koyfman

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THE EFFECTS OF NOVEL DESIGN STRATEGIES ON  
THE RISKS AND BENEFITS OF PHASE I  
ONCOLOGY TRIALS

A Thesis Submitted to the  
Yale University School of Medicine  
In Partial Fulfillment of the Requirements for the  
Degree of Doctor of Medicine

Shlomo Asher Koyfman

Class of 2006

# THE EFFECTS OF NOVEL DESIGN STRATEGIES ON THE RISKS AND BENEFITS OF PHASE I ONCOLOGY TRIALS

Shlomo A. Koyfman, Cary P. Gross

Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT.

Considerable ethical debate surrounding the risks and benefits of Phase I oncology trials is based on older response and toxicity data that does not account for recent changes in the types of agents and trial design. This study aims to not only update these data, but to investigate the impact of novel trial designs on various clinical outcomes.

We performed a review of the literature using the Medline database. *Part I* included nearly all phase I trials published in 2002. *Part II* identified phase I studies of cytotoxic agents alone, published from 2002 through 2004.

221 Phase I oncology studies, consisting of 6,008 patients, were studied in *Part I*, while 149 studies, comprising 4,532 patients, were analyzed in *Part II*. Overall, the response rate for Phase I oncology trials in 2002 was 19%, the mortality rate was 1.1%, and the rates of severe hematologic and non-hematologic toxicities were 19% and 22%, respectively. “Classic” phase I trials of single agent cytotoxic drugs accounted for only 18% of trials, while more than half (55%) included at least one FDA approved therapy. The response and toxicity rates varied with the class of agent (e.g. cytotoxic, biologic, vaccine), and the combinations of agents (e.g. approved, investigational) studied. Only 34% of studies utilized aggressive dose escalation schemes, 22% permitted intra-patient dose escalation, and only 28% enrolled fewer than 3 patients to any dose level

before proceeding to the next higher dose level. Studies that allowed intra-patient dose escalation or used fewer than three patients per dose were not associated with rates of response or toxicity that differed from trials using a more “traditional” design, nor did they increase the percentage of patients who received the recommended phase II dose. However, aggressive dose escalations were associated with increased rates of both hematologic (17% vs.10%) and non-hematologic (17% vs. 13%) toxicity for participating patients without increasing response rates. None of these novel design strategies were associated with a smaller patient requirement.

Phase I oncology trials represent a spectrum of different classes of agents and design strategies that are often associated with distinct clinical outcomes. Accounting for this variety is critical when evaluating their risk-benefit profiles and ethics. While some innovations in trial design do not appear to be any more helpful or harmful than standard methods in phase I trials of single agent cytotoxic drugs, using aggressive dose escalations may, in fact, be more hazardous for patients. These findings highlight the need for continued effort towards improving trial design and its impact on our patients.

## ACKNOWLEDGMENTS

This thesis is the culmination of work that spanned nearly my entire medical school career. I began researching phase I oncology trials during the summer of 2003 after completing my first year of medical school. Since then, I have gone through a crash course in clinical research. From collaborations and conference calls to submissions, rejections and resubmissions, writing my thesis has taught me as much about what it means to do clinical research as it has about the risks and benefits of phase I oncology trials.

This project was the result of collaboration and I am indebted to all those who helped me along the way: First and foremost, to my beloved medical school, for encouraging us to pursue original research and for providing all of the financial and administrative support we needed; to Benjamin Krohmel and Elizabeth Wolf, for helping me with the arduous task of data abstraction; to Elizabeth Garrett-Mayer for her statistical expertise; to Manish Agrawal for conceiving and guiding the first part of this project; and to Ezekiel Emanuel for his overwhelming expertise and invaluable mentorship.

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Finally, I want to thank my wife, Aliza, for her selfless devotion to our family and her undying support of my professional ambitions.

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## INTRODUCTION

Cancer remains the second leading cause of death in the United States, claiming the lives of more than 550,000 annually. Despite the many advances made over the past several decades, there is still a continual need to develop new anti-cancer therapies. In fact, as cancer research has become a national priority, the number of new anti-cancer therapies in development each year exceeds all other classes of therapeutics.<sup>1</sup>

For an investigational anti-cancer drug to be approved for use in the U.S., it must endure three phases of clinical trials. After a compound has shown promise in preclinical testing, an agent is administered to humans for the first time in a phase I oncology trial. This is primarily a dose finding study in which the highest dose that has an acceptable safety profile is identified and recommended for further testing. The drug then proceeds to a phase II trial in which it is tested for both safety and efficacy, or how well the tumor responds to the therapy. If the trial reveals at least a moderate response rate, the drug will proceed to a phase III trial, which requires the participation of greater numbers of patients in multiple centers and is conducted as a prospective randomized controlled trial comparing the new therapy to the current standard of care. If the results demonstrate a substantial benefit in overall survival, or reduced cancer suffering, with an acceptable risk of toxicity, the drug will likely receive final approval.<sup>2</sup>

As first in human trials, phase I clinical oncology trials play a vital role in translating laboratory science into therapies that may reduce cancer morbidity and mortality. Traditionally, phase I oncology trials begin by administering a small dose of the experimental agent, typically 10% of the dose that would be lethal to 50% of exposed rats or dogs, to a group of 3-6 patients. Subsequently, cohorts of patients receive

increasing dosages, first by 100%, then 66%, 50%, 40%, 33% based on a “modified Fibonacci” protocol. In addition, patients are usually restricted to their designated dose levels and may not receive higher doses of the investigational agent even if they experienced no significant toxicity. The trial ends when severe, or life threatening toxicities (i.e., dose limiting toxicities, or DLTs) are experienced by a large fraction of patients at a given dosage level. The dose just below this maximum tolerated dose (MTD) is generally recommended for phase II efficacy studies. These studies often gather pharmacokinetic information as well, to help guide future dosing schedules.<sup>3,4</sup> It is important to recognize that phase I trials are also used to evaluate established therapies in new areas of clinical application (ie. a new cancer type) and are not restricted to agents that have never before been used in humans.

Ethical concerns have been raised regarding the nature and design of phase I oncology trials. In order to better appreciate these viewpoints, it is important to first review some of the basic ethical issues involved in clinical trials in general.

### **Ethics of Clinical Trials**

The primary objective of clinical research is to further our understanding of science and/or improve the health of a population. To accomplish this, clinical trials enroll research participants who, at least in some sense, serve as a means towards obtaining results that can be applied towards society at large. Because trials often times include a risk of harm to patients, clinical trials leave room for exploitation.<sup>5-7</sup> As such, sets of criteria have been formulated against which the ethicality of a research trial can be gauged. For example, Emanuel and colleagues identified seven elements that need to



exist in order for a trial to be ethically justified. These include value, scientific validation, fair subject selection, informed consent, favorable risk benefit ratio, independent review and respect. Consequently, a trial would have to demonstrate its potential benefit to the scientific community and/or society at large according to rigorous scientific methodologies; offer participating patients potential for benefit that is commensurate, or greater than, the risk of harm; recruit patients equitably only after they understand the details of, and have freely agreed to participate in, a given trial; provide them with continued care and monitoring and allow for their withdrawal at any time, for any reason.<sup>6</sup>

### **Ethics of Phase I Oncology Trials**

Phase I oncology trials present a unique challenge. Patients have usually failed conventional therapies and are dying of a disease that is incurable with standard methods. Agents used in phase I trials, however, are often tested for the first time in humans without extensive knowledge experience with their potential toxicities. Also, a narrow therapeutic window often characterizes cancer therapies; doses most likely to produce responses are also likely to produce toxicity.

Two primary ethical challenges have been charged against these trials. The first is based on the assumption that patients do not fully understand the nature of phase I studies and that they are primarily motivated by a misplaced hope of deriving clinical benefit from the investigational agent.<sup>8</sup> Several surveys have confirmed this phenomenon.<sup>9, 10</sup> Also, while dedicated to the best interests of their patients, physician-

scientists may have competing interests in conducting trials expeditiously that will yield scientifically meaningful results. Consequently, even assuming the utmost integrity on the part of the physician, the interests of the clinician and the patient may diverge.<sup>11</sup>

Physicians may also be able to capitalize on patients' desperation and place undue emphasis on the potential benefits of participation, thereby perpetuating, albeit perhaps inadvertently and/or subconsciously, the "therapeutic misconception." This term characterizes the belief that the primary objective of a given trial is to directly benefit the research participant when this is, in fact, not the case. This concern is not only limited to physician communication, but informed consent forms themselves have been implicated in this misrepresentation.<sup>12-16</sup>

The accuracy of these critiques have been questioned. Horng and colleagues found that consent forms do a fairly good job of conveying the dose finding nature of phase I trials, their associated risks and the unlikely prospects of deriving significant benefit.<sup>17</sup> Whether this translates into better patient understanding remains a question. A recent review found that the most effective means of ensuring adequate patient understanding before enrolling on a trial was having more time to discuss the details of the trials with the physician and/or researcher and that doing so was a more effective intervention than improving informed consent forms.<sup>18</sup>

The second fundamental ethical problem stems from the supposition that these trials have an inherently unfavorable risk-benefit ratio for patients on account of the substantial risk of harm they present to patients with little chance of deriving any clinical benefit.<sup>3, 4, 19-21</sup> Our study focuses on this concern. Because these trials include dose escalations that often start at a relatively low dose, slowly increase, and prohibit

individual patients from receiving higher doses, regardless of how he/she is tolerating the agent, investigators have claimed that too many patients are treated at “sub-therapeutic” dose levels.<sup>8</sup> That is, because investigational agents have been shown to most often be biologically active (ie. produce tumor responses) between 80%-120% of the eventual recommended phase II dose, patients who receive lower doses of the drug are unlikely to be exposed to even potentially therapeutic doses.<sup>22</sup> In fact, an older study by Estey and colleagues found that only 40% of participants received biologically active doses.<sup>23</sup>

### **Response and Toxicity Data in Early Meta Analyses**

Several meta-analyses examined objective response rates experienced by patients who participated in phase I oncology trials. These earlier studies looked at trials published in the 1970s and 1980s and found objective response rates around 4%, most of which were partial or minor responses.<sup>22-25</sup> While clinical benefit was rare, the potential risks associated with participating in these trials was significant. These studies found a toxic death rate of 0.5%, that is 5 out of every 1,000 patients participating in phase I studies experienced an early death due to the toxic effects of the investigational agent.<sup>24</sup> Although not recorded in these studies, the rate of serious, or life threatening toxicity could be presumed to be substantially higher. This increased risk of serious toxicity, or death, coupled with the presumed inconveniences and costs of frequent blood draws, medical appointments, radiologic evaluations and biopsies in exchange for a small chance of benefit all bolster the position that these trials are not in the best interests of patients, and therefore, unethical.<sup>26</sup>

In 2003, Agrawal and Emanuel presented a contemporary review of the ethics of these trials and challenged this perspective.<sup>19</sup> They identified several limitations to the available aforementioned data. First, the data was outdated, as the trials included in the meta-analyses were completed in the 1970s and 1980s. Second, phase I studies of agents already approved by the Food and Drug Administration (FDA), or studies using more than one agent were not included in these analyses. Third, neither newer compounds being evaluated, such as antibodies, vaccines, immunotoxins, and anti-angiogenesis factors, nor improved supportive care measures, were reflected in the commonly cited response rate of 5% and mortality rate of 0.5%. These old data did not seem to reflect the increasing complexity and heterogeneity that characterize current phase I clinical trials. This review also highlighted the potential psychological benefits to participating in a trial either because of the frequent physician contact, or as an act of defiance and battle against one's illness. George Zimmer, a professor of English who participated in several phase I oncology trials, explained his motivation as follows:

Letting a patient choose the poisons (under professional guidance) adds something to the will to struggle. We who are struggling to escape cancer do not, obviously, want to die of it. We do prefer death in the struggle to life under cancer's untender rule. The enemy is not pain or even death, which will come for us in any eventuality. The enemy is cancer, and we want it defeated and destroyed...Just before assaults on fortified positions, U.S. Civil War soldiers would pin their names and addresses to their uniforms to make it easier for the body-sorters to do their work after the battle. Patients going into these modified protocols could likewise place their names on specific protocol adjustments. Survivors could then proclaim: This is how I wanted to die-not a suicide and not passively accepting, but eagerly in the struggle.<sup>27</sup>

Two meta analyses subsequently sought to update and expand upon the data derived from the older studies. The first was published in *JAMA* in 2004 by Roberts and

colleagues.<sup>1</sup> They identified 213 single agent trials of non-FDA approved drugs the results of which were originally submitted to annual meetings of the American Society of Clinical Oncology (ASCO) from 1991 through 2002. They reported an overall toxic death rate of 0.54%, which had decreased from 1.1% in 1991-1994, to 0.06% between 1999-2002. They also were the first to report the overall rate of serious (grade 3-4) toxicity experienced by patients at 10.3%. To their surprise, they reported an overall objective response rate of only 3.8%, though they surmised that by excluding trials that tested approved agents, or a combination of agents, they had likely “biased downward” their response rate estimates. They did, however, include non-cytotoxic agents and found that they accounted for almost half of all of the trials. In addition, multivariate analysis showed that the odds of a patient dying from a biologic/targeted agent were one fourth those of a patient dying from a cytotoxic agent (OR, 0.25; 95% CI 0.10-0.65; p=.005), though they did not differ in predicting response.

The second meta-analysis was published in the *NEJM* in 2005 by Horstmann and colleagues.<sup>28</sup> They analyzed 460 trials sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) between 1991 and 2002. Their study offered the first published analysis that included FDA approved therapies, as well as trials which used a combinations of agents. They found an overall objective response rate (complete and partial response, or CR+PR) of 10.6%, with a CR of 3.1% and a PR of 7.5%. When patients who experienced disease stabilization were included, the response rate climbed to 34.1%. And while studies that tested single investigational agents were associated with an overall response rate of 4.2%, this percentage improved to 7.1% for

studies that used multiple investigational agents, and to 27.4% for studies testing FDA approved therapies.

The rates of toxicity also varied according to the types of agents that were used. Overall toxic deaths occurred in 0.49% of all patients, similar to all previous published reports, and overall 14.3% of patients experienced a grade 4, or life threatening, toxic event. The rates were highest in trials using cytotoxic agents at 17.4%, while vaccine trials had no grade 4 toxic events. And the rate varied even within the cytotoxic class, with 15% of patients on trials testing single agents experiencing a severe toxicity as compared to 34% of patients who received FDA approved therapies while on trial.

After enhancing our understanding of the objective risks and benefits of phase I oncology trials, especially through an appreciation for the heterogeneity of these trials, we decided to reexamine the ethical arguments presented above. Indeed, Agrawal and Emanuel were correct in their speculation that modern response and toxicity rates would likely be different than those found in the 1970s and 1980s. The rate of serious toxicities is considerable, estimated between 10-14%, and the death rate appears to be stable between 0.5-1%. However, overall objective response rates have increased from about 4% to between 10-20%, with almost half of all patients deriving some clinical benefit (CR+PR+SD), largely due to the increasing use of FDA approved agents and/or combinations of agents. One could certainly argue that based on the updated data, the risk-benefit ratio of phase I oncology trials may be more favorable than was originally thought.

A careful review of the data, however, reveals that trials that tested single investigational agents reported response rates around 4%, similar to the data from older

studies. Cytotoxic agents were also associated with higher toxicity than targeted therapies or vaccines. It would therefore seem that while overall, the risks and benefits of phase I oncology trials appeared to have changed for the better in recent years, this may not apply to trials involving single cytotoxic agents, especially investigational ones.

Perhaps more fundamentally, these updated data do not address some of the most compelling ethical charges against phase I oncology trials. Largely due to constraints imposed by study design, many patients receive “sub-therapeutic” doses of an agent, yet are still exposed to the risks of participating. Several components of the classic phase I trial design may contribute to this phenomenon. Firstly, intra-patient dose escalation, or the ability of a patient who is tolerating an agent well to receive a higher dose, is usually prohibited, which confines patients enrolled earlier in the trial to the lowest, and probably inactive, doses. There appears to be an inherent injustice in this design, insofar as patients with few, if any, alternative therapies who are tolerating the agent well do not get the chance to benefit from the drug. A recent survey showed that most patients, in fact, desire to retain control of their destiny and are willing to endure higher risks for the possibility of clinical benefit.<sup>29</sup> These trials also classically require 3-6 patients in each dose level, even the initial ones which are often several dose levels below the recommended phase II dose. Both of these design limitations almost guarantee the need for a significant number of patients to fill the lower dose levels in which they are less likely to experience serious toxicity, but also less likely to experience a significant response. Lastly, the ““modified Fibonacci”” escalation scheme is often times too conservative for agents that prove to be relatively benign during early dose levels.

## **Aggressive Design Strategies: Current Data**

Based on these observations, there has been a concerted effort over the past decade or so to devise more innovative dosing strategies that will decrease the number of patients receiving lower doses of drugs on trial. In 1997, Simon and colleagues at the NCI suggested a variety of accelerated titration designs, including allowing for inpatient dose escalation, using fewer patients in earlier dosage levels and repeatedly increasing drug dose levels by 100%. The trial would revert back to traditional designs when some patients experienced toxicity. The goals of these newer designs were twofold: to increase the number of patients who received doses presumed to be biologically active, usually the recommended phase II dose, and to reduce the number of patients needed to complete a phase I trial. They fit a stochastic model to data collected from 20 completed phase I trials and found that these methods increased the percentage of patients receiving higher doses and decreased the total number of patients required for a trial. Objective response outcomes were not considered.<sup>30</sup>

Other novel designs include sophisticated statistically based models, such as the continual reassessment method (CRM) and its variants, which employ certain predictions in designing a dose escalation which is then continually modified throughout the trial based on encountered toxicities.<sup>31, 32</sup> Using pharmacokinetic, biologic and radiographic endpoints has also been suggested for newer targeted biological therapies, rather than the traditional toxicity endpoints of classic cytotoxic chemotherapeutic drugs.<sup>33-36</sup>

While the use of these latter design strategies have been studied fairly extensively, surprisingly very little research has been published examining the prevalence of the three



novel design strategies suggested by the NCI group and their impact on response and toxicity rates, the percentage of patients who receive recommended phase II doses and the overall number of patients needed to complete a trial.

Dent and Eisenhauer reviewed 46 single agent trials of cytotoxic compounds that were published between 1993 and 1995.<sup>37</sup> They found that the majority of trials still used a “modified Fibonacci” escalation, while only 3/46 doubled the dose until toxicity was seen. Furthermore, they found that only 39% of patients received the recommended phase II dose in trials that tested agents being administered for the first time in human as compared to 57% of patients who received drugs that had previously undergone phase I study. They did not examine the usage of intra-patient dose escalation or fewer patients per dosage level. In 1998, a workshop of phase I investigators was convened to review their experiences with novel phase I designs. They describe two phase I trials of the same investigational agent that were being conducted simultaneously at two different institutions. One used a traditional design while the other allowed a single patient per dose and intra-patient dose escalation until toxicity was reached. The latter design was able to accomplish 8 dose escalations with only 15 patients, compared to just 3 dose levels that required 12 patients in the study which used a traditional design.<sup>38</sup>

Unfortunately, the two large meta-analyses published recently placed little emphasis on this issue. The only data that was gleaned was that only 29% of the studies included in the Roberts paper allowed intra-patient dose escalation, and doing so was associated with greater odds of experiencing response in multivariate analysis (OR 1.7). There were no differences between these types of studies in predicting toxicity, and they

did not evaluate the endpoints of patients receiving the recommended phase II dose, or the average number of patients needed to complete a trial.<sup>1</sup>

Appropriately, the editorial that accompanied that paper included the subtitle, “A Case for More Innovation,” in which the authors argued that single agent trials of cytotoxics in particular are in need of new design strategies that can improve the opportunity for patient benefit, especially in light of their consistently minimal response rates. They specified the design strategies introduced in the NCI study as hopeful possibilities.<sup>39</sup>

### **Rationale for Current Study**

In trying to modernize and update the response and toxicity data of phase I oncology studies, we designed a project with Agrawal and Emanuel in which we would perform a meta analysis on phase I oncology studies published in 2002. Our points of interest included cataloging the various types of agents used in phase I trials, including FDA approved agents and the use of multiple drugs, documenting response and toxicity rates, and investigating the impact that geography and study sponsorship had on these data. Our hypothesis was that, in fact, the types of agents used in phase I oncology studies had changed over the past decade and that the variety of different categories of therapeutic options would yield a spectrum of response and toxicity results rather than a uniform picture. This study would also be able to add to the two previous meta-analyses by providing a comprehensive data set, including the variety of agents and trial types looked at by Horstmann *et al*, as well as geography and sponsorship data looked at by

Roberts *et al*, in a more recent cohort of studies. The results of this study are included in *PART I* of the original research component of this thesis.

Because ethical questions would remain even after we accumulate data from *Part I*, we proceeded towards an analysis of novel dosing strategies. Their prevalence, as well as their utility in improving the risk-benefit profile of these trials remains largely unknown. We therefore set out to answer these questions and decided to focus on single agent trials of cytotoxic agents, as they represent the ideal arena for the implementation of these novel designs. However, as our data set from *Part I* of this thesis was insufficient, we decided to expand our body of studies to include those published in 2003 and 2004 with the hopes of increasing our sample size and the power of our analysis. This comprises *Part II* of this project.

## METHODS

This section will detail the methods of two distinct components of our study, entitled *part I* and *part II*. The first part of this study focused on identifying the various categories of agents (e.g. cytotoxic, biologic, vaccine) and types of agents (e.g. investigational, FDA approved) used in phase I oncology trials along with their associated rates of response and toxicity. The second component aimed to identify the prevalence of several novel dose escalation design strategies and their impact on a variety of clinical endpoints, in a more uniform sample of single agent trials of cytotoxic drugs.

## Search Strategy

We performed a review of the literature using the Medline database. *Part I* included nearly all phase I trials published in 2002. *Part II* identified phase I studies of cytotoxic agents, published from 2002 through 2004. Their respective search criteria are included as an appendix (appendix 1). Overall, the search criteria were purposely designed to be broad so as to include the vast majority of published phase I oncology trials.

The primary reason for exclusion was that studies were not standard phase I chemotherapy trials. This included trials for which: (1) the primary trial objective was not to determine safety; (2) the experimental treatment was not intended to have independent or synergistic anti-cancer effects; (3) there was not sufficient differentiation between data from a Phase I and Phase II portion of the study; (4) the trial was not performed on human subjects; (5) the experimental protocol included radiation or photodynamic therapy; (6) the paper did not directly report the results of a clinical trial; (7) the paper was not a complete report; and (8) the trial was testing a supportive care rather than an anti-cancer intervention. For *Part II*, studies were also excluded if more than one agent was used in the study and/or if the investigational agent was not cytotoxic (ie. immunotherapy, signal transduction inhibitor, angiogenesis inhibitor, gene therapy, vaccine). Our search for *Part I* yielded 301 studies, of which 221 met all inclusion criteria. Of the 955 studies originally identified in *Part II*, 149 were included (Figure 1).

## Data Extraction

Two investigators independently extracted the pertinent information using a formal abstraction instrument that included number of patients, patient gender, patient age ranges, prior therapy history, toxicity and response data, dose escalation strategy, the allowance of intra-patient dose escalation, minimum patients per dose, class and approval status of agent and the number of patients who received the agent at or above the recommended phase II dose at least once. For *Part I*, all results were compared and all discrepancies were resolved by consensus. For *Part II*, in a comparison of the abstracted data from 15% of the studies, the discrepancy rate between data points was found to be less than 5% overall. Discrepancies were reviewed and resolved by the two investigators.

For *Part I*, trials were grouped into six different categories according to mechanism of action of the investigational agent(s): 1) chemotherapy/cytotoxic agents, 2) immunomodulators, 3) receptor or signal transduction inhibitors 4) anti-angiogenesis agents, 5) gene-therapies, and 6) vaccines. Treatments were categorized into three groups: (1) non-chemotherapy agents, (2) FDA-approved chemotherapies, and (3) investigational chemotherapies. Dosing strategies comprised three distinct categories: 1) traditional, according to a “modified Fibonacci” protocol; 2) conservative, in which the initial dose increase was less than 100%; and 3) aggressive in which at least the first two dose increases were by 100%. Study design was obtained from the methods section of each published trial. Intra-patient dose escalation was only recorded as allowed if the study explicitly indicated as such in the methods section.

Study sponsorship was assessed in the trials conducted in the U.S. because information on study sponsorship was reported in only 30% of the studies conducted in Europe and the other countries. Among U.S. studies, study sponsorship was coded into three categories: 1) industry, (this does not include instances in which only a drug was provided with no other financial support), 2) government, foundation or other non-profit, and 3) study support was not indicated.

The location of the first author's employing institute or corporation was coded into three categories: 1) U.S., 2) Europe, or 3) other.

### **Outcome Definitions**

Response data included the number of patients who experienced a complete response (CR), partial response (PR) and stable disease (SD) according to standard definitions. For solid tumors, CR was defined as complete radiographic disappearance of the lesion at 4 weeks, a PR was 50% or greater decrease in the sum of the products of the perpendicular diameters of all measured lesions at 4 weeks, progressive disease was defined as an increase of these tumor dimensions by more than 25%, any new lesion, or any definitive increase in tumor size and SD included anything that did not qualify as progressive disease or a PR, including "minor responses."<sup>40</sup>

Toxicity data included possible or probable toxic deaths, non-hematologic toxicity, and hematologic toxicity. Deaths explicitly reported as toxic deaths or other deaths in the study not expressly reported to be unrelated to the intervention (ie. possible, probable) were counted in the toxic death rate. All toxicity grades follow the standard

definitions outlined in the Common Toxicity Criteria v2.0 (1999) and/or the Common Terminology Criteria for Adverse Events v3.0 (2003) as part of the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute. Grade 3/4 non-hematologic and grade 4 hematologic toxicity were recorded because these determine toxicity rules for dosing modification in Phase I oncology studies. For this reason, grade 3 febrile neutropenia was included as a hematologic toxicity. Alopecia was not included as toxicity.

### **Statistical Analysis**

For each study, response rates, mortality rate, and toxicity rates were calculated based on the published data and exact confidence limits estimated. For some rates, data were not available and so the rates for these studies were treated as missing at random. For grade 3-4 non-hematologic and grade 4 hematologic toxicities, some of the studies only provided information such that the minimum and maximum number of patients incurring the toxicity could be ascribed (i.e. these studies reported the number of toxicity events rather than number of patients with toxicity events). In these cases, we used a weighted approach for estimating the true number of patients who had experienced a toxicity, where the estimated number of toxicities ( $t_i$ ) is defined as:

$$t_i = 0.75 \times \min_i + 0.25 \times \max_i$$

For example, in one study it could be assumed that at least six, but no more than 10 patients, had grade 4 hematologic toxicities. The imputed number of grade 4 hematologic toxicities for this study was 7 patients. This estimate is more conservative

and also more appropriate than simply taking the average of the minimum and maximum. The distribution of toxicities across studies tends to be skewed: the bulk of the toxicity rates are lower values, while higher values tend to be outliers, indicating that an estimate of the number of toxicities within any given study should tend to favor smaller values.

Meta-analysis techniques were used for data analysis. A beta-binomial model was used for estimating rates (i.e., proportions) across studies. This model allows for extra-binomial variability, as would be expected in a meta-analytic setting. For the multiple regression models, a random effects grouped logit model was used. The model is essentially a generalized linear model from the binomial family with logit link where studies are ‘groups’ (i.e., the unit of analysis is study) and a random effect is included for each study. Associations were considered significant if the null value was outside of the 95% credible interval of a parameter. For multiple regression models, we considered covariates that showed significance in simple regression models. Multiple regression models were explored by including main effects and pairwise interactions, and then removing insignificant effects and interactions one by one. These models were not fit for CR and for mortality because the event rates were very low and results were unstable.

For *Part I*, the WinBugs, version 1.4, software was used, which implements a Bayesian estimation approach, for model estimation with diffuse priors in all meta-analyses.<sup>41</sup> Reported point estimates are the means of the posterior distributions of the parameters, and the 95% credible interval for a parameter is the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles of its posterior distribution. For *Part II* a Markov chain Monte Carlo approach was implemented for estimating parameters. Each of the coefficients in the regression model was assumed to have a Gaussian diffuse prior, and random effects were



assumed to have a normal distribution with variance  $\tau^2$ , where the hyperprior for  $1/\tau^2$  is a diffuse Gamma distribution. WinBugs within OpenBugs 2.01 was used for model estimation. For each analysis, a burn-in period of 5000 iterations was performed. Then an additional 20000 iterations were run where every 5<sup>th</sup> iteration was saved for inference. Multiple chains were run for each analysis and traceplots were explored to ensure convergence. No convergence problems were encountered. Point estimates were defined as the posterior mean, 95% credible intervals as the 2.5<sup>th</sup> and the 97.5<sup>th</sup> percentiles of the posterior distribution, and tail probabilities as the (two-sided) proportion of area under the posterior distribution that is more extreme than the observed data. The tail probabilities and 95% credible intervals can be interpreted similarly to p-values and 95% confidence intervals.

## RESULTS

### **PART I: Response Rates and Toxicities in Phase I Oncology Studies in 2002**

The final study sample consisted of 221 Phase I oncology studies published in 2002, which included 6,008 research participants assessable for toxicity and 5,362 assessable for response (Table 1). Almost all of the enrolled participants had an ECOG performance status of 0 or 1, that is they had normal physical activity or only need extra rest less than 50% of the day.<sup>42</sup> Half of the participants were male, the mean age was 60.5, 55% had prior chemotherapy, and 20% had prior radiotherapy.

The majority of the studies were chemotherapy trials (173 trials, 78%) involving 4,268 patients assessable for response. Vaccines were the second largest group (13 trials, 6%), and gene therapy the smallest group (3 trials, 1%) of trials. Overall, 40 (18%) of the studies were “classic” Phase I studies in that they tested a single, non-approved cytotoxic agent. A majority of the published Phase I studies (121, 55%) used only commercially available (ie. FDA approved) agents (Table 2).

### **Response Rates**

Considering all 221 studies, the mean overall response rate (CR + PR) was 19% (95% CI: 17, 22). The complete response rate (CR), in which the tumor disappeared, was estimated to be 3.8%. When adding “minor responses” and stable disease to partial and complete responses, the total rate of clinical benefit was estimated to be 48% (Table 1).

The response rates differed considerably according to the type of Phase I agent(s) assessed (Table 1 and Figure 2a). The estimated overall CR + PR rate was 21% for chemotherapy trials; while for vaccine trials it was just 2.9% (Table 1). The response rates also varied considerably according to the type of trial (Table 2). For non-chemotherapy agents, trials with a single investigational agent alone had an estimated CR + PR rate of 7.7%, while this figure was 4.8% for chemotherapy agents. Studies using only FDA approved agents had an estimated response rate of 29%, and those with a combination of investigational and commercially available agents had an estimated response rate of 14%.

After adjusting for other factors, including sponsorship, solid vs. non-solid tumor, and percentage of patients treated with prior therapies (Table 3), multiple regression

analysis showed that chemotherapy studies using FDA approved agents had significantly higher response rates than non-chemotherapy studies (OR= 5.16, 95% CI 2.72-9.58). Chemotherapy studies using investigational agents, on the other hand, had lower response rates than non-chemotherapy studies (OR = 0.77, 95% CI 0.36-1.55), though statistical significance was not achieved.

### **Death and Toxicities**

The overall mortality rate across all 221 Phase I studies was 1.1% (95% CI 0.8-1.6) (Table 4). Studies of cytotoxic agents had a mortality rate of 1.3%, whereas trials involving vaccine and anti-angiogenesis agents had no observed deaths (Figure 2b). The estimated mortality rate was highest in studies that included FDA approved agents (1.6%), and lowest in studies of single, non-cytotoxic investigational agents (0.4%) (Table 4). Phase I studies with a combination of commercial and investigational agents had an estimated mortality rate of 0.9%. “Classic” phase I studies had a mortality rate of 1.0% (95% CI 0.6%- 1.6%).

The overall grade 3/4 non-hematologic toxicity rate was estimated to be 22% and the grade 4 hematologic toxicity rate was 19% (Table 2). Bivariate analysis showed that grade 3/4 non-hematologic toxicity was very similar for chemotherapy trials (19%) and trials testing non-cytotoxics (18%), with the exception of vaccine trials (0.9%) (Figure 2c). Rates of serious non-hematologic toxicity were also similar across trials regardless of whether trials used commercial agents alone, investigational agents alone, or a combination of agents. By contrast, grade 4 hematologic toxicity rate was higher for both

investigational chemotherapy trials relative to investigational non-chemotherapy trials (2.8% vs. 10%), as well as trials with commercial agents (29%) (Table 2).

Multiple regression analysis confirmed these associations. While both investigational (OR = 5.26, 95% CI 1.99- 14.0) and FDA approved (OR = 18.9, 95% CI 7.92- 48.4) chemotherapy agents were associated with dramatically higher rates of hematologic toxicity than non-chemotherapy agents, the risks of non-hematologic toxicity were similar for non-chemotherapy agents and investigational chemotherapy agents (OR = 1.09, 95%CI 0.64-1.88). However, the multivariate model also found that FDA-approved chemotherapy agents appeared to be associated with a slightly higher rate of grade 3/4 toxicities (OR = 1.62, 95% CI 1.04-2.64) relative to non-chemo investigational agents (Table 3).

### **Sponsorship**

Trials sponsored by for-profit and non-profit organizations had similar response rates, 17% and 16% respectively (Table 5 and Figure 3a). However, the mortality rates did vary across sponsorship. In crude bivariate analysis, for-profit sponsored studies had a mortality rate of 1.4%, as compared to 0.7% for those sponsored by non-profits. Grade 3/4 non-hematologic toxicity did not vary between for-profit and non-profit sponsored studies (Table 5b-d). However, multiple regression analysis showed relatively little differences in response and toxicity rates in for-profit and non-profit trials after adjusting for other factors.

## Geography

There were variations in response rates according to the country in which the study was conducted (Table 6). Studies in the U.S. had response rates of 14%, whereas studies from Europe had response rates of 24%, and the remaining nations had a response rate of 25%. The toxic death rate was 1.3% in the U.S., 1.1% in Europe, and 0.8% in the remaining countries. Grade 3/4 non-hematological toxicity was 20% in the U.S., 25% in Europe, and 18% in the remaining countries. Grade 4 hematological toxicity was 13% in the U.S., 25% in Europe and 26% in the other countries. Multiple regression analyses showed the higher response rate for studies from Europe as compared to those done in the U.S. to be statistically insignificant after adjusting for other factors.

## **PART II: The prevalence and impact of novel design strategies in 2002-2004**

Despite an updated knowledge of the rates of response and toxicity in Phase I trials overall, aspects of the traditional design of these trials have been implicated as a cause for many patients receiving “sub-therapeutic” doses, especially in single agent trials of cytotoxic drugs. Novel design strategies have been introduced with the hopes of improving the ethically questionable risk-benefit ratios of these trials, but little research has been done to determine their prevalence and efficacy. We therefore set out to investigate these questions in the second part of this study.

In 149 phase I studies published between 2002 and 2004 which assessed single agent cytotoxic compounds, 4,350 patients were evaluable for toxicity and 4,027 were evaluable for response (Table 7). Predominantly patients had solid tumors (90%), with 9% of studies including only hematological or lymphatic malignancies and 1% of studies accepting patients with either solid or liquid tumors. While the toxic death rate was small at 1%, there was a more significant incidence of serious, or life threatening drug related hematologic (15%) and non-hematologic (17%) toxicity. The overall objective response rate was 3% (CR + PR), which increased to 25% with the addition of stable disease as an endpoint. Also, 60% of patients received a dose of the investigational agent that was at or above the eventual recommended phase II dose.

As opposed to the first part of this study, most agents used in the phase I trials included in this latter component of the study were investigational, while the FDA had already approved only 26% of them. The majority (66%) of these studies used traditional “modified Fibonacci” or even more conservative dose escalation schemes. Only 34% of

studies utilized aggressive dose escalation schemes, 22% permitted intra-patient dose escalation, and only 28% enrolled fewer than 3 patients to any dose level before proceeding to the next higher dose level (Table 8). Interestingly, the prevalence of studies allowing intra-patient dose escalation or using aggressive titration designs declined in 2004 from the rates seen in the previous year, while a greater percentage of studies used fewer than 3 patients per dose in that year (Figure 4).

### **Trials Using Different Escalation Designs**

Bivariate analysis revealed several important findings. Conservative titration designs were associated with significantly higher hematologic (17%vs.10%, tail probability (tp)=.01) and non hematologic (20%vs.13%, tp=.03) toxicity rates, as well as higher response rates (CR+PR 6%vs.2%, tp=.002; CR+PR+SD 32%vs.21%, tp=.03) as compared to the traditional ““modified Fibonacci”” design. Conservative designs also resulted in the highest percentage of patients who received at least one dose of the investigational agent at or above the recommended phase II dose (71%vs.46%, tp<.001) (Table 8).

When comparing the use of aggressive titration designs to studies using traditional designs, the former were associated with an increased risk of both hematologic (17%vs.10%, tp=.01) and non hematologic (17%vs.13%, tp=.20) toxicity for participating patients, although the finding for non hematologic toxicity was not statistically significant. Importantly, response rates (CR+PR 1%vs.2%, tp=.53; CR+PR+SD 23%vs.21%, tp=.79) and the percentage of patients receiving the

recommended phase II dose (55%vs.46%,  $tp=.18$ ) showed no statistically significant differences (Table 8).

### **Trials Allowing for Intra-patient Dose Escalation, Fewer Patients Per Dose**

The two other novel design strategies, allowing intra-patient dose escalation and using fewer than three patients in the initial dosage levels, revealed no statistically significant differences in response rates, toxicities, or the percentage of patients receiving the recommended phase II dose relative to the standards in their categories. The single exception was an increased CR+PR+SD (28%vs.20%,  $tp=.03$ ) in studies that did not allow fewer than three patients in any given dose level, a finding that is of questionable import (Table 8).

### **Trials with FDA-Approved Agents**

We then analyzed studies using FDA approved agents. Our initial expectations were that these agents would produce a better response rate, and that investigators might be more conservative with their dose escalations given the already well-known characteristics of the particular therapy. What we found was that, in fact, studies that tested a drug that had already been approved by the FDA for another indication were associated with increased objective response rates (CR+PR 10%vs.2%,  $tp<.001$ ; CR+PR+SD 40%vs.22%,  $tp<.001$ ) as compared to investigational agents. In multivariate analysis, no interaction was found between FDA approval and conservative dose



escalation design, as these two variables were independently associated with the increased response (Figure 5). However, multiple regression analysis of the CR+PR+SD endpoint revealed that these two trial types were independently associated with an increased clinical response rate only in trials that used fewer than three patients per dose early on. There did seem to be interactions, however, when these studies used the more traditional design of 3 or more patients for every dose level (Figure 6). Interestingly, increased tumor response to FDA approved drugs was not at the expense of a significantly increased risk of hematologic (18%vs.14%) or non hematologic (19%vs.16%) toxicity, although there did seem to be a trend in that direction.

### **Number of Patients Required Per Trials**

Our final endpoint of interest was the average number of patients needed to complete these phase I trials. If any of these novel designs could reduce this number, their use could possibly limit the number of patients having to participate in, and be exposed to the hazards of, phase I trials. What we found was that trials which used conservative dose escalation designs required a lower average number of patients to complete their trials than those that used aggressive dose escalations (26.2 vs. 33.9;  $p=.04$ ). The same was true of studies that tested FDA approved agents (25.2 vs. 32.3;  $p=.02$ ). However, none of the novel design strategies in question had any significant impact on this endpoint as compared to “standard protocols” (Table 9).

## DISCUSSION

Phase I oncology trials simultaneously embody some of the highest ideals of medicine, and some of the most challenging ethical dilemmas faced in clinical research. These trials serve as the bridge between the promises of laboratory research and powerful therapies that help the sick and suffering. Yet, accomplishing this noble task requires the use of patients as research subjects, from whom objective data can be ascertained. Unlike clinical trials in general which often use healthy volunteers, phase I oncology trials enroll patients with refractory cancer who have few therapeutic options and little hope. This combination of patients in desperate circumstances and investigators who have an interest in the scientific validity of their trials in addition to their patients' well-being, presents a scenario in which misplaced hopes and unjustifiable optimism can easily chart a course towards unintentionally violating a basic principle of medical ethics, nonmaleficence – 'do no harm.' Patients ought not be exploited, even for the sake of serving the greater good. Participation in phase I oncology trials must be based on an adequate understanding of the primary aims of the study - assessing the safety of an agent and finding an appropriate dose to test in phase II trials - coupled with realistic expectations regarding toxicity and response potential. Ensuring that this happens, either through consent forms, consultations with physicians, or both, is often easier said than done.

Even when fully informed, phase I trials may present patients with a greater likelihood of harm than benefit. Antitumor agents often present patients with substantial risks of severe, even life threatening toxicity, which can be even more dangerous with unknown, investigational agents. And while these toxicities occur in phase I trials, historically, a majority of patients enrolled were treated at "sub-therapeutic" dose levels.

The risk-benefit ratios of these trials can only be favorable if patients facing toxicity also have a genuine chance to benefit from these agents. An accurate knowledge of the rates of response and toxicities, and the percentage of patients receiving therapeutic doses are indispensable for patients to weigh the risks and benefits they face. Moreover, from the vantage point of investigators, efforts must be made to continually improve the “research system” and to strive to provide each patient with the opportunity to derive maximal potential benefit from a drug on trial.

What are the overall risks of harm to patients participating in phase I oncology trials? Our results show a toxic death rate of 1.1% overall. Despite this low overall risk of toxic death, a significant percentage of patients did experience severe hematologic (19%) and non-hematologic (22%) toxicity. While these rates were consistent between different categories of agents for both toxic deaths and non-hematologic toxicities, multivariate analysis confirmed that both FDA approved (OR = 18.9, 95% CI 7.92- 48.4) and investigational (OR = 5.26, 95% CI 1.99- 14.0) cytotoxic agents were associated with higher rates of hematologic toxicities than non cytotoxic agents. These data are supported by their similarity to previous studies (Table 10) and are easily applicable to contemporary patients insofar as they reflect trials conducted in an era of better supportive care for much toxicity, including nausea, vomiting, pain, low blood counts and infections.

Patients who participated in these trials also experienced significant tumor responses to the agents under investigation. In fact, response rates seem to have increased substantially from the 3-5% reported in earlier studies (Table 10). Objective response rates were higher than previously reported (CR+PR 19%), with nearly half of all

patients experiencing some clinical benefit (CR+PR+SD 48%). These increases appear to be at least partially due to the increasing use of non-cytotoxic agents, as well as FDA approved agents (55% of trials) in these early clinical trials. Multivariate analysis confirmed the response advantage to commercially available cytotoxic agents (OR= 5.16, 95% CI 2.72-9.58). Indeed, classic single agent trials of investigational cytotoxics, which comprised only 18% of all trials, revealed modest response rates that were no higher than those reported in previous studies (CR+PR 2-4%).

How to interpret these response and toxicity data in a way that can help an individual patient considering participating in a phase I trial understand the associated risks and benefits is in no way straightforward. There are several important elements that must be considered.

Firstly, these data are aggregates of the responses and toxicities seen in hundreds of trials, which tested scores of different agents, often in different tumor types. Phase I trials have produced 98% response rates, as in the case of imatinib mesylate (Gleevac) in patients with chronic myelogenous leukemia, while a study of a novel spicamycin analogue resulted in more than 10% of patients suffering toxic deaths and another 50% experiencing severe or life threatening toxicity.<sup>43, 44</sup> Our response and toxicity data do not apply to any individual phase I trial, but rather provides an estimate of the overall prevalence of these endpoints.

Secondly, whether tumor responses actually translate into clinical benefit is unclear.<sup>45, 46</sup> Some contend that response rates are merely surrogate endpoints and do not correspond to different survival outcomes.<sup>47, 48</sup> In their reply to this position, Horstmann and colleagues cite several studies that demonstrate relationships between tumor response

while on trial and survival, symptom improvement and quality of life endpoints.<sup>28, 49-51</sup>

While response rates are certainly an imperfect measure of clinical benefit, they do appear to have clinical meaning.

How to interpret our response data is also complicated by our inclusion of the non-traditional endpoint of disease stabilization. We believe the benefits of doing so are two-fold. Firstly, disease stabilization captures the benefits of the drug in the form of “minor responses” that are excluded due to an arbitrary definition of 50% or greater tumor shrinkage needed to qualify as an objective response.<sup>52</sup> Moreover, the proliferation of biologic agents that function in a cytostatic capacity, along with continually improving supportive care measures, argues for the value in measuring how well a drug can enable a patient to live with a cancer that is not progressing.<sup>28, 53</sup>

In synthesizing our results, some guiding principles about how to assess the risks-benefit ratios of these trials emerge. First and foremost is the recognition that phase I trials are not all the same. They encompass a wide array of agents and trial designs. Therefore, one must consider the particular type of agent (e.g. cytotoxic, biologic, vaccine), whether it is an investigational or approved therapy and whether it is being tested alone or in combination with other agents. Next, in discussing likelihood of response and toxicity, an investigator must convey some of the uncertainty as to their interpretation. One must also incorporate the values and disposition of an individual patient. Is his/her priority to avoid suffering, or is the goal to persist “eagerly in the struggle” and try to overcome his/her disease to whatever extent possible? Of course, the ability to effectively communicate these ideas in a way that empowers each patient to

decide whether or not the risk-benefit profile of a particular trial is favorable to him/her is part of the difficult art of medicine.

Our appreciation for how different types of trials were associated with distinct response and toxicity rates then led us to reexamine the need for improved trial design. We demonstrated that while the overall response rate in phase I oncology trials had significantly improved from previous reports, this was not the case for “classic” single cytotoxic agent trials, which were associated with increased toxicity without the benefit of increasing response rates. We, therefore, decided to study whether single agent cytotoxic trials that used more aggressive dosing strategies were associated with differences in response and toxicity data, as well as other markers of patient benefit. With growing calls for the use of biologic, rather than toxic, endpoints in Phase I trials of targeted biologic agents, limiting our sample to studies of cytotoxics seemed even more valuable.<sup>33, 34, 38</sup>

There has been much optimism about the potential for these novel design strategies to improve the risk benefit profile of phase I oncology trials for patients. The rationale was that having fewer patients in lower dose levels, escalating the dose more quickly and allowing patients to increase their own dose, would reduce the number of patients receiving “sub-therapeutic” doses and enable more patients to have better chances of achieving response.<sup>30, 37-39</sup> Lending partial support to this assumption, a study that looked at single agent trials of both cytotoxic and biologic agents found that studies that allowed intra-patient dose escalation predicted for an increased response rate with no added risk of toxicity.<sup>1</sup>

We found, however, that these methods did not seem to provide any advantage in the setting of single agent trials of cytotoxic drugs. Allowing intra-patient dose escalation, or using fewer patients in earlier, “sub-therapeutic” dose levels, was neither associated with any increased rates of response, nor with an increased proportion of patients receiving the recommended phase II dose. Also, trials employing these strategies required, on average, the same number of patients as their more standard alternatives. Yet, they do not appear to be any more harmful than standard protocols and may still confer psychological benefits to patients enrolled. Patients may be encouraged by the knowledge that all participants have the potential to receive the highest possible dose and that they would be limited in doing so only on the basis of toxicity rather than by study design constraints.

A more concerning result was that aggressive titration designs were associated with larger percentages of patients who experienced severe, or life threatening toxicity as compared to trials that used traditional “modified Fibonacci” dose escalations, and this relationship was confirmed for hematologic toxicity in multivariate analysis. This data suggests that aggressively increasing the dose of a cytotoxic agent in a single agent phase I trial adversely impacts the risk-benefit ratios that enrolled patients face. While more research is needed to confirm this finding, investigators ought to inform their patients of this observation, and give greater consideration to other methods of reducing the number of patients treated at “sub-therapeutic” dose levels.

Our results for conservative dose escalation strategies appeared counter-intuitive at first. We would have expected trials that increased doses more slowly to be associated with more patients being exposed to “less potent” forms of the drug and therefore with

lower rates of response and toxicity and higher numbers of patients receiving “sub-therapeutic” doses. Quite the contrary, these studies were associated with increased toxicity rates, higher response rates and a greater percentage of patients who received the recommended phase II dose. One way to account for this data is to consider the high likelihood that investigators deliberately chose a more conservative design because of some prior indication as to the potency of the particular agent. Of course, prior FDA approval would be a major reason to do so. This is supported by the fact that of the studies that tested agents already approved by the FDA, 65% (24/38) used a conservative titration design, while only 32% of studies which tested novel agents used conservative titration designs. Another outcome that highlights the overlap between trials that used conservative design strategies and those that tested FDA approved agents is that only these two trial categories required significantly fewer patients to complete their trials.

This study has several limitations. First, our study samples were imperfect. *Part I* reported the results of a meta-analysis that was restricted to 2002. It is possible that studies published in 2002 were not representative of all Phase I oncology trials, although the similarities between our results and other recent meta-analyses reduces this concern. Our sample of studies was also heterogeneous with regard to the agents studied as well as cancer types. This consideration provided the impetus to limit our investigation in *Part II* to single agent cytotoxic drugs, in order to minimize the impact that sample heterogeneity would have on our results. In doing so, however, the generalizability of our results is limited and does not extend to the variety of design innovations currently being used and studied in non cytotoxics, most notably biological agents and targeted therapies. Lastly,



although not currently available, patient level data would have been preferable to trial level data.

The lack of uniform reporting standards as well as publication biases may have also led to overestimated or underestimated response and toxicity rates. However, since publication of Phase I studies is not dependent on response rates, and there was no indication of a suppression of adverse mortality data, publication bias may be less likely than in other types of meta-analysis.

Finally, we must always be cautious about establishing causality in a retrospective analysis. Unfortunately, given the nature of phase I oncology trials, prospective studies examining these different design strategies may be very difficult to undertake from both methodological and practical standpoints.

## **CONCLUSION**

Phase I oncology trials reflect the high stakes of investigative medicine. While the potential for discovery and innovation for the betterment of our patients and society at large is high, so is the potential for exploitation, misrepresentation and causing unnecessary harm to our patients. An evaluation of how the interplay between the risks and benefits of these trials impact on their ethics should be informed by the most current and comprehensive data available. The primary objective of this thesis was to provide this information and understand how it may answer some fundamental questions about the risks and benefits of phase I oncology trials. By doing so, we have come to understand two fundamental insights.

Firstly, all phase I oncology trials are not the same. Rather, they represent a spectrum of different classes of agents and designs strategies that are often associated with distinct clinical outcomes. Accounting for this variety is critical in trying to evaluate the risk-benefit ratios that these trials offer participating patients, and in considering the ethical questions involved.

Secondly, while some novel dosing strategies appear to have little impact on clinical endpoints, others may in fact be harmful. The allowance of intra-patient dose escalation and the use of fewer than three patients in initial dosage levels do not appear to impact response or toxicity rates, the percentage of patients who receive the recommended phase II “therapeutic” dose, or decrease the average number of patients needed to complete a trial. Aggressive dose escalation designs expose patients to greater risk of toxicity with no increased likelihood of benefit. These innovations do not seem to deflect some of the most fundamental ethical challenges made against these trials, which highlights the need for continued effort towards improving trial design and its impact on our patients.

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**TABLE 1: Response Rates of Phase I Oncology Trials published in 2002.**

	# of Trials	# Assessable for Response	Complete Response Rate* (CR) (%)	Response Rate* (CR+PR) (%)	Total Response Rate* (CR+PR+SD) (%)
<b>Total</b>	221	5362	3.8 (2.8, 5.0)	19 (17, 22)	48 (44, 52)
<b>Chemotherapy Cytotoxic</b>	173	4268	4.2 (3.1, 5.7)	21 (18, 25)	50 (45, 55)
<b>Immunomodulator</b>	12	216	6.2 (2.5, 11)	14 (6.0, 26)	43 (29, 59)
<b>Receptor/Signal Transduction</b>	11	377	3.5 (1.0, 8.4)	13 (6.1, 24)	37 (24, 53)
<b>Anti-Angiogenesis</b>	9	225	1.0 (0.1, 2.8)	11 (4.1, 22)	38 (24, 55)
<b>Gene Therapy</b>	3	63	1.7 (<0.1, 6.1)	21 (10, 34)	33 (20, 46)
<b>Vaccine</b>	13	213	0.5 (<0.1, 2.0)	2.9 (1.0, 5.6)	44 (30, 59)

\*Numbers in CR, CR+PR, and CR+PR+SD columns are rates with 95% credible intervals in parentheses.

**TABLE 2: Response and Mortality Rates for Combinations of Agents in Phase I Oncology Trials.**

	# of Trials	Complete Response Rate (CR)	Response Rate (CR+PR)	Total Response Rate (CR+PR+SD)	Total Deaths	Toxic Death Rate	Grade 3-4 non-heme toxicity	Grade 4 heme toxicity
<b>Total</b>	221	3.8 (2.8, 5.0)	19 (17, 22)	48 (44, 52)	63	1.1 (0.8, 1.6)	22 (19, 24)	19 (16, 23)
<b>Single Investigational Agent Alone</b>	chemo	0.6 (0.2, 1.1)	4.8 (2.8, 7.8)	26 (21, 31)	11	1.0 (0.5, 1.6)	19 (14, 24)	10 (6.1, 15)
	non-chemo	1.7 (0.6, 3.7)	7.7 (3.8, 14)	38 (28, 49)	3	0.4 (0.1, 1.0)	18 (12, 25)	2.8 (0.1, 6.5)
<b>Combination of Investigational and Commercial agents</b>	23	1.4 (0.5, 2.8)	14 (9.3, 20)	49 (39, 59)	5	0.9 (0.3, 1.8)	24 (18, 31)	16 (9.8, 24)
<b>Commercial (No Investigational) Agents</b>	121	5.9 (4.3, 7.9)	29 (25, 33)	59 (54, 64)	44	1.6 (1.0, 2.4)	24 (20, 27)	29 (24, 35)

\* Numbers are rates with 95% credible intervals in parentheses.

\*\* There were only two studies with multiple investigational agents. These two studies were excluded because the number of studies was too few to make inferences.

**TABLE 3: Multiple regression analysis of Phase I Oncology Trials.**

	<b>Response Rate (CR+PR) OR (95% PI)</b>	<b>Total Response Rate (CR+PR+SD) OR (95% PI)</b>	<b>Grade 3/4 non-hematological toxicity OR (95% PI)</b>	<b>Grade 4 hematological toxicity OR (95% PI)</b>
<b>non-cytotoxic agent</b>	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
<b>investigational cytotoxic agent</b>	0.77 (0.36, 1.55)	0.65 (0.36, 1.16)	1.09 (0.64, 1.88)	5.26 (1.99, 14.0)
<b>Non- Investigational cytotoxic agent</b>	5.16 (2.72, 9.58)	2.23 (1.32, 3.74)	1.62 (1.04, 2.64)	18.9 (7.92, 48.4)
<b>US for-profit</b>	(ref)	(ref)	(ref)	(ref)
<b>US non-profit</b>	1.51 (0.65, 3.39)	0.90 (0.47, 1.63)	0.98 (0.57, 1.79)	0.85 (0.28, 2.45)
<b>US other</b>	0.61 (0.24, 1.43)	0.44 (0.23, 0.87)	1.56 (0.81, 3.06)	0.39 (0.11, 1.39)
<b>Europe</b>	1.68 (0.93, 3.22)	1.57 (0.92, 2.56)	1.39 (0.89, 2.27)	1.77 (0.84, 3.97)
<b>Other nations</b>	1.72 (0.76, 3.90)	2.34 (1.17, 4.76)	0.85 (0.44, 1.62)	2.29 (0.84, 6.75)
<b>Solid Tumor</b>	0.34 (0.16, 0.75)			0.32 (0.10, 1.06)
<b>Prior chemo</b>	0.54 (0.33, 0.87)	0.63 (0.41, 0.95)	2.14 (1.49, 3.19)	



**TABLE 4: Deaths and Toxicities\* in Phase I Oncology Trials published in 2002.**

	<b>Number of Trials</b>	<b>Number of Participants assessable for toxicity</b>	<b>Total Number of Deaths**</b>	<b>Toxic Death Rate (%)*</b>	<b>Grade 3-4 non-hematologic toxicity (%)*</b>	<b>Grade 4 hematologic toxicity (%)*</b>
<b>Total</b>	221	6,008	63	1.1 (0.8, 1.6)	22 (19, 24)	19 (16, 23)
<b>Chemotherapy Cytotoxic</b>	173	4,724	59	1.3 (0.9, 1.9)	23 (20, 25)	25 (21, 29)
<b>Immunomodulator</b>	12	261	1	0.9 (0.1, 2.4)	18 (13, 24)	8.3 (5.2, 12)
<b>Receptor/Signal Transduction</b>	11	404	2	0.8 (0.2, 2.1)	23 (18, 30)	5.6 (1.6, 14)
<b>Anti-Angiogenesis</b>	9	251	0	0.4 (<0.1, 1.4)	22 (13, 33)	2.0 (0.5, 4.1)
<b>Gene Therapy</b>	3	63	1	2.0 (0.2, 7.6)	31 (20, 44)	13 (6.1, 22)
<b>Vaccine</b>	13	305	0	0.4 (<0.1, 1.3)	9.0 (2.0, 21)	0.7 (0.1, 1.9)

\*Numbers in toxic death rate, grade 3-4 non-hem toxicity and grade 4 heme toxicity columns are rates with 95% credible intervals in parentheses.

\*\*Includes possible, probable and definite deaths.

**TABLE 5: Sponsorship of Phase I Oncology Trials published in 2002.**

	<b>Number of Trials</b>	<b>Complete Response Rate (CR) (%)</b>	<b>Response Rate (CR+PR) (%)</b>	<b>Total Response Rate (CR+PR+SD) (%)</b>	<b>Total Deaths</b>	<b>Toxic Death Rate (%)</b>	<b>Grade 3-4 non-hematologic toxicity (%)</b>	<b>Grade 4 hematologic toxicity (%)</b>
<b>Total</b>	114	3.5 (2.3, 5.1)	14 (11, 18)	38 (33, 43)	35	1.3 (0.8, 2.1)	20 (17, 23)	13 (10, 18)
<b>Profit</b>	54	5.0 (2.9, 8.0)	17 (12, 23)	44 (36, 52)	20	1.4 (0.8, 2.4)	19 (15, 24)	16 (11, 24)
<b>Non-profit</b>	34	3.2 (1.8, 5.5)	16 (10, 23)	39 (31, 48)	5	0.7 (0.2, 1.3)	19 (13, 25)	12 (6.4, 20)
<b>Other</b> (Not reported)	26	0.8 (0.2, 1.6)	8.0 (4.2, 12)	27 (20, 34)	10	2.3 (0.7, 5.1)	24 (19, 30)	5.4 (3.1, 8.4)

**TABLE 6: Geography in Phase I Oncology Trials published in 2002.**

	<b>Number of Trials</b>	<b>Complete Response Rate (CR) (%)</b>	<b>Response Rate (CR+PR) (%)</b>	<b>Total Response Rate (CR+PR+SD)</b>	<b>Total Deaths</b>	<b>Toxic Death Rate (%)</b>	<b>Grade 3-4 non-hematologic toxicity (%)</b>	<b>Grade 4 hematologic toxicity (%)</b>
<b>Total</b>	221	3.8 (2.8, 5.0)	19 (17, 22)	48 (44, 52)	63	1.1 (0.8, 1.6)	22 (19, 24)	19 (16, 23)
<b>U.S.</b>	114	3.5 (2.3, 5.1)	14 (11, 18)	38 (33, 43)	35	1.3 (0.8, 2.1)	20 (17, 23)	13 (10, 18)
<b>Europe</b>	80	4.6 (2.9, 7.0)	24 (19, 30)	56 (49, 62)	23	1.1 (0.7, 1.7)	25 (21, 30)	25 (19, 32)
<b>Other</b>	27	2.6 (1.3, 4.2)	25 (18, 34)	64 (53, 75)	5	0.8 (0.3, 1.7)	18 (12, 23)	26 (20, 34)

**TABLE 7: Patient Characteristics for PART II**

<i>Demographics</i>	<i>Number of patients (%)</i>
# of patients	4,532
# evaluable for toxicity	4,350
# evaluable for response	4,027
Male/Female	2610:1922 (58/42)
Median Age (age range)*	56.5 (0.9-90)
25 <sup>th</sup> percentile/75 <sup>th</sup> percentile	53/61
<i>Prior Treatment History**</i>	
Prior Chemotherapy	3,084 (76)
Prior Radiation	1135 (28)
Prior Surgery/Transplant	758 (19)
No Prior Cancer Treatment	105 (2.5)

\* Calculated as the median of the median age.

\*\*Percentages were determined with denominator of 4,051 patients for whom these data were provided.

**TABLE 8: Frequency and Bivariate Analysis**

Study Design	% [Number] of Studies	Complete + Partial Response* % [N] (95% CI)	Complete + Partial Response + Stable Disease % [N] (95% CI)	Grade 4 Hematological Toxicity % [N] (95% CI)	Grade 3/4 Non Hematological Toxicity % [N] (95% CI)	Patients Receiving Recommended Phase II Dose % [N] (95% CI)
<b>Total</b>	100% [149]	3% [141]	25% [127]	15% [124]	17% [155]	60% [134]
<i>Dose Escalation</i>						
<b>Conservative</b>	40% [59]	6% [55] (4-9)	32% [46] (25-39)	17% [50] (13-21)	20% [54] (15-25)	71% [52] (63-77)
<b>Traditional</b>	26% [37]	2% [35] (1-3)	21% [32] (15-28)	10% [30] (7-14)	13% [33] (9-18)	46% [35] (37-57)
<b>Aggressive</b>	34% [49]	1% [47] (1-2)	23% [45] (17-29)	17% [41] (13-21)	17% [45] (13-22)	55% [45] (46-63)
<i>Intra-patient Dose Escalation</i>						
<b>Yes</b>	22% [32]	2% [29]	24% [27]	15% [24]	16% [28]	66% [30]
<b>No</b>	78% [112]	3% [108]	26% [97]	15% [97]	17% [103]	57% [101]
<i>Minimum Patients per dose for first course of therapy</i>						
<b>&lt;3 patients</b>	28% [40]	2% [38]	20% [36] (14-26)	16% [32]	17% [35]	65% [39]
<b>3+ patients</b>	72% [105]	3% [100]	28% [90] (24-33)	14% [90]	17% [98]	57% [94]
<i>FDA approved agent</i>						
<b>FDA approved</b>	26% [38]	10% [34] (6-17)	40% [29] (31-49)	18% [30] (13-23)	19% [33] (14-25)	65% [35]
<b>not FDA approved</b>	74% [111]	2% [107] (1-3)	22% [98] (19-26)	14% [94] (12-16)	16% [102] (14-19)	58% [99]

\*Numbers in columns are rates with number of studies in brackets and 95% credible intervals in parentheses.

**TABLE 9: Mean # patients needed for completion of phase I trials**

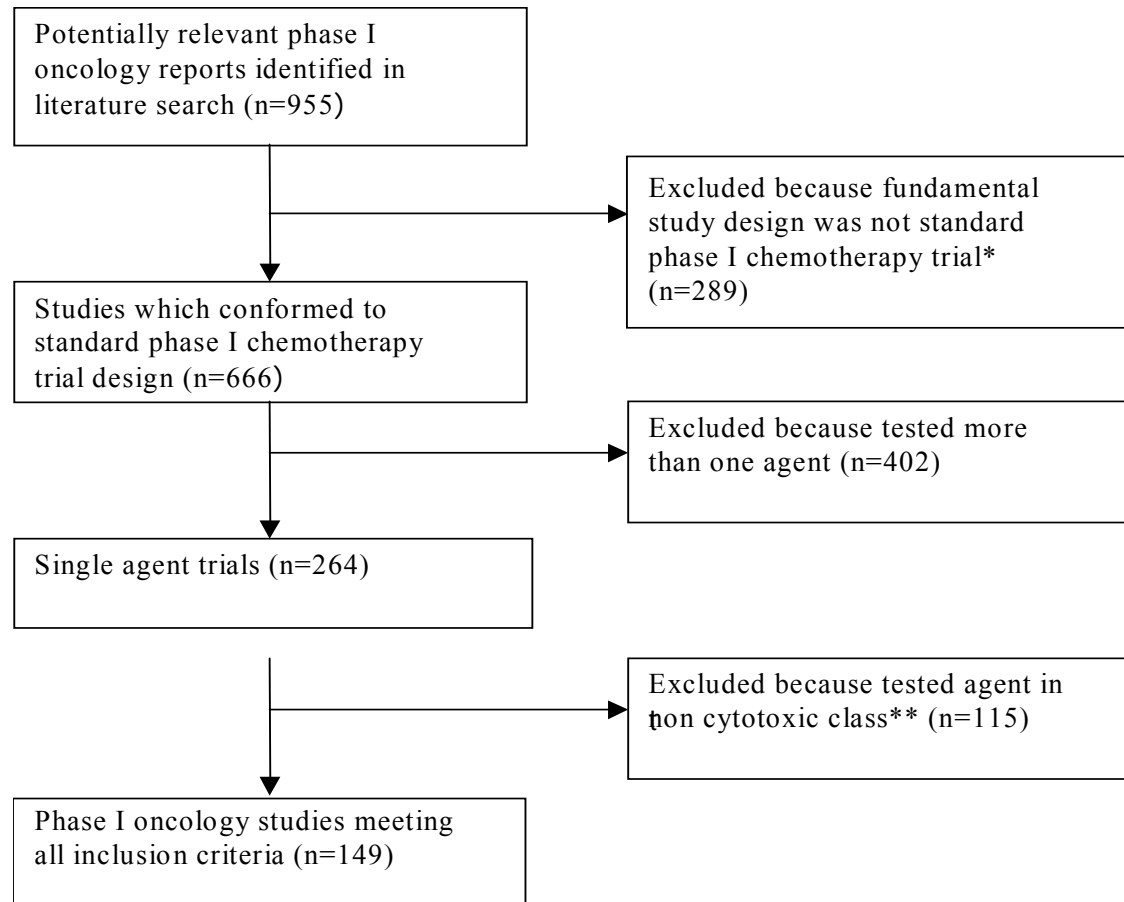
Category of dosing strategy or agent		Mean # pts needed per trial
<i>Dose Escalation</i>	Conservative	26.2
	Traditional	31.9
	Aggressive	33.6
<i>IPDE</i>	Allowed	30.4
	Not Allowed	29.9
<i>Minimum Patients per dose in first course</i>	<3	31.7
	3 or more	30.1
<i>Approval Status</i>	FDA approved	25.2
	unapproved	32.2

**TABLE 10: Comparison of Response and Toxicity Rates in Published Meta Analyses**

Lead Author	Type of trials/agents studied	Years Studied	# studies (# patients)	Toxic deaths (%)	Grade 4 Hematologic toxicity (%)	Grade 3/4 non-hematologic toxicity (%)	CR (%)	PR (%)	CR +PR +SD (%)
Decoster <sup>24</sup>	Single agent cytotoxics	1972-1987	211 (6,639)	0.5	N/R	N/R	0.3	4.2	N/R
Von Hoff <sup>22</sup>	Single agent cytotoxics	1970-1983	228 (7,960)	N/R	N/R	N/R	1.0	5.0	N/R
Estey <sup>23</sup>	Single agent cytotoxics	1974-1982	187 (6,447)	N/R	N/R	N/R	0.7	3.5	N/R
Itoh <sup>25</sup>	Single agent cytotoxics	1981-1991	56 (2,200)	N/R	N/R	N/R	1.1	2.2	N/R
Roberts <sup>1</sup>	All single agent	1991-2002	213 (6,474)	0.54	10.3 overall		3.8 overall		N/R
Horstmann <sup>28</sup>	All	1991-2002	460 (11,935)	0.49	14.3 overall		3.1	7.5	34.1
Current Study	All	2002	221 (6,008)	1.1	19.0	22.0	3.8	15.2	48.0

Abbreviations: N/R not recorded; CR complete response; PR partial response; SD stable disease

**Figure 1: Study Selection**

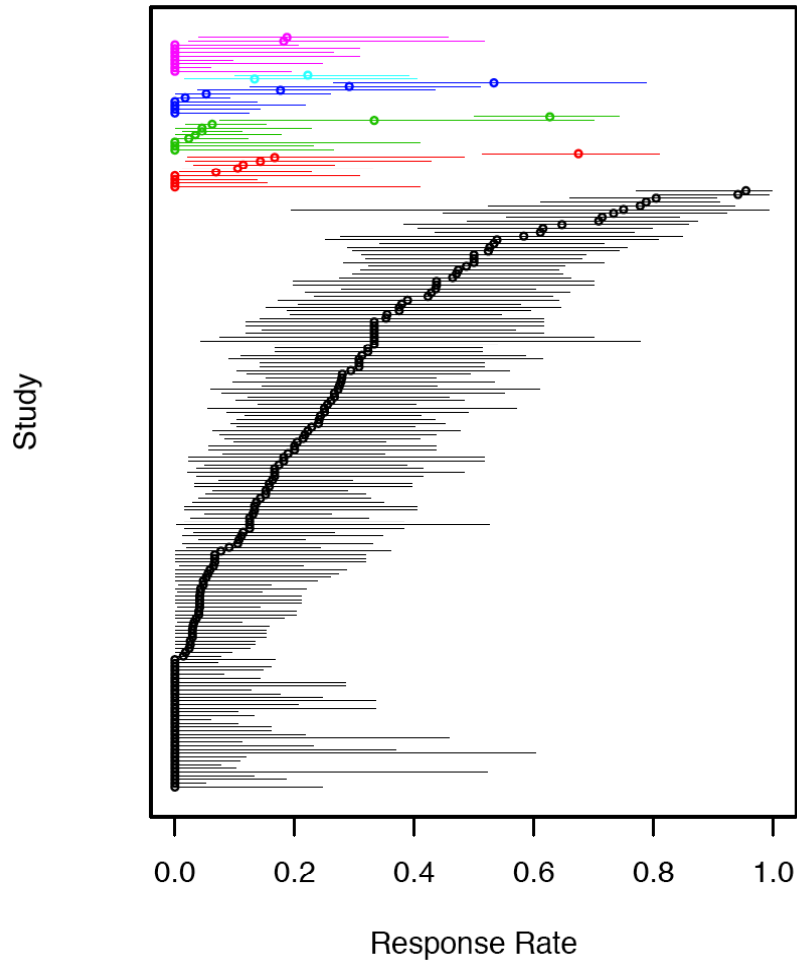


\* Includes studies which were not cancer related, not Phase I studies, or dose finding studies; those that did not assess the safety profile of the agent; those that included the use of radiotherapy, cryotherapy or photodynamic therapy; and those for which the trial data was inaccessible or incomplete.

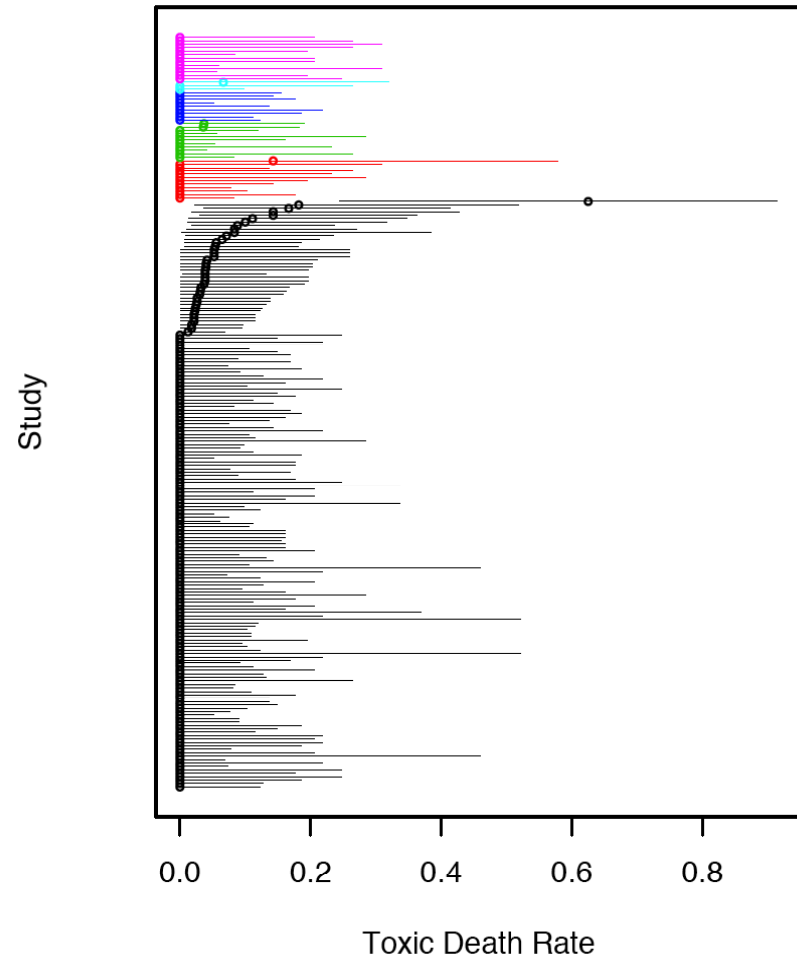


\*\* This includes signal transduction inhibitors, angiogenesis inhibitors, immunotherapy and gene therapy.

**A. CR + PR Rate**

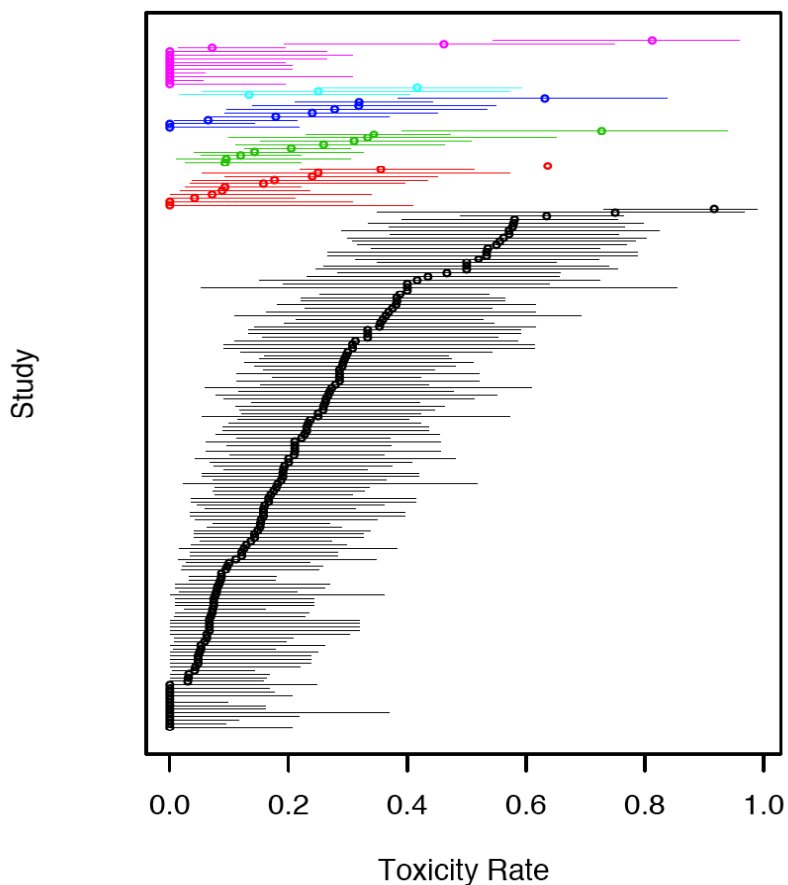


**B. Toxic Death Rate**

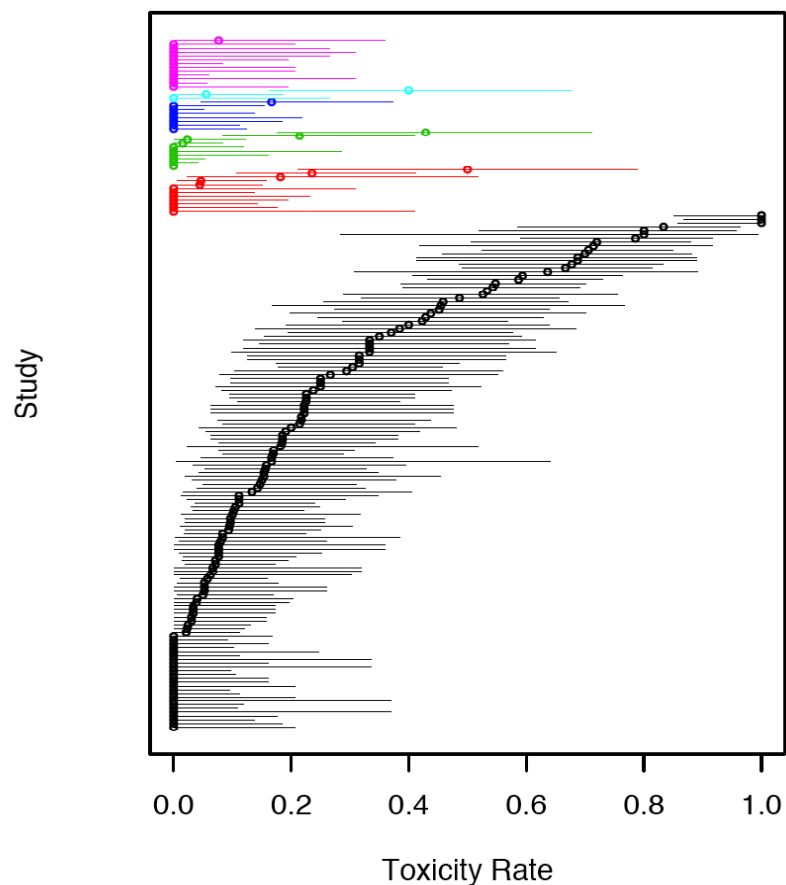


**Figure 2A and 2B**

C. NonHem Grade 3-4 Rate



D. Hem Grade 4 Rate

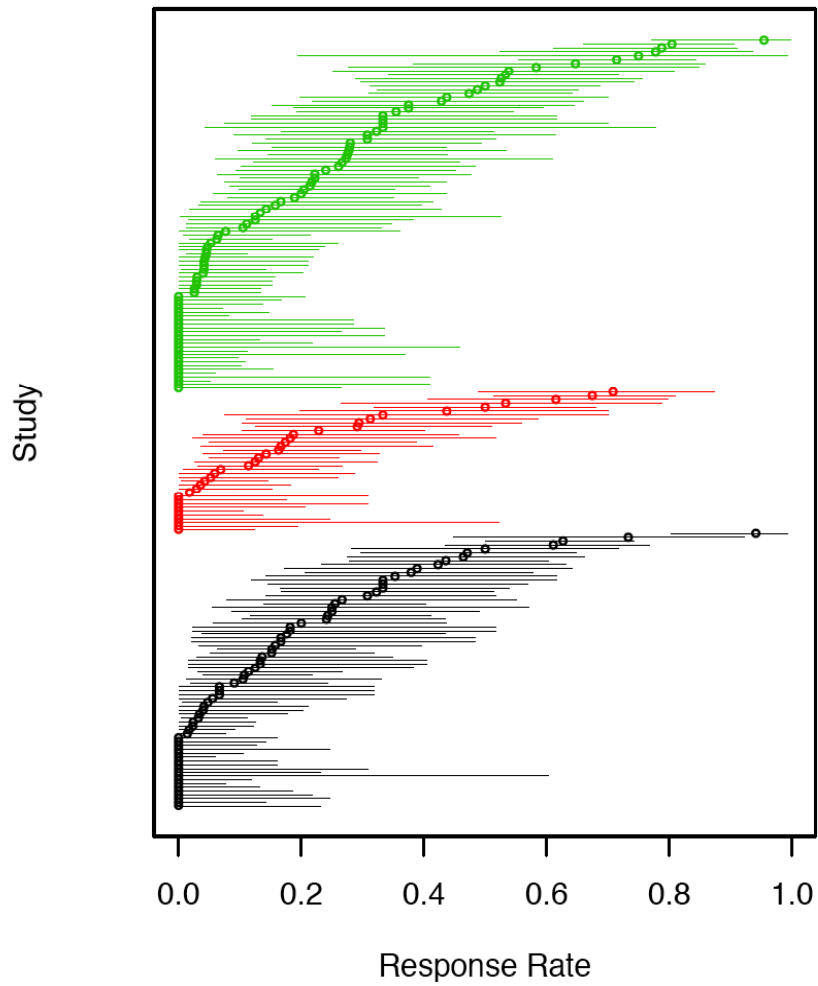


**Figure 2C and 2D**

**Figure 2.** Response rates and toxicity of phase 1 oncology trials published in 2002 stratified by chemotherapy, immunomodulator, receptor/signal transduction, gene therapy, angiogenesis, vaccines. Panel A. CR+PR Panel B. Rate of Toxic Deaths Panel C. Non-hematological Grade 3/4 toxicity Panel D. Hematological Grade 4 toxicity.

Agent: black=chemotherapy, red=immunomodulator, green=receptor/signal, blue=angiogenesis, light blue=gene therapy, pink=vaccines.

A. CR + PR Rate



B. Toxic Death Rate

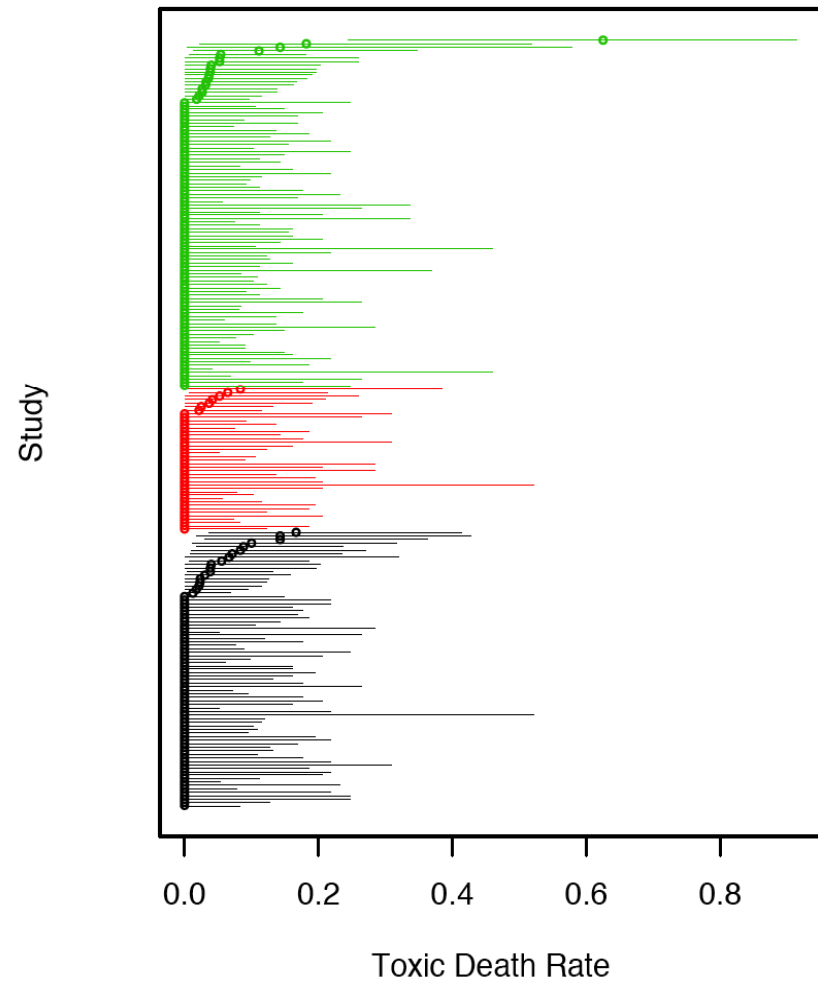
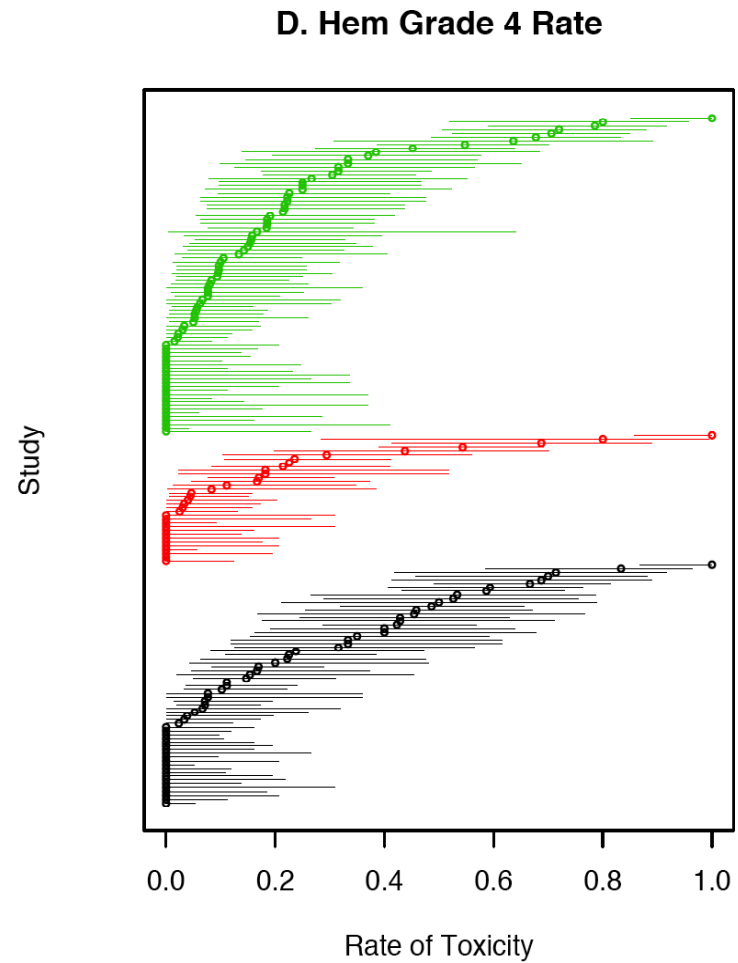
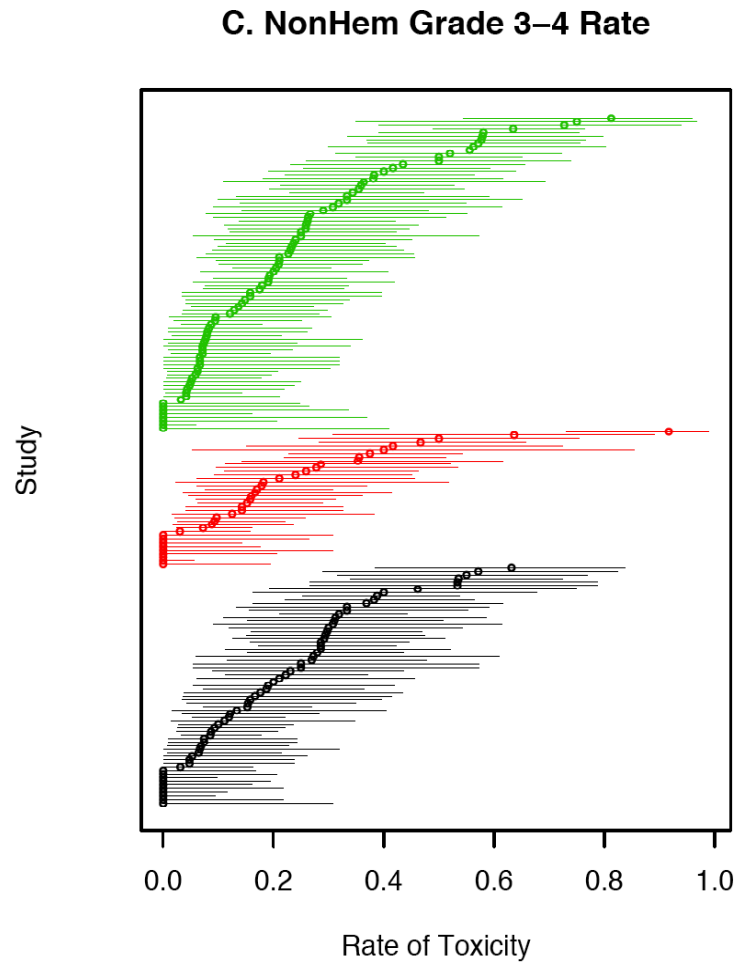


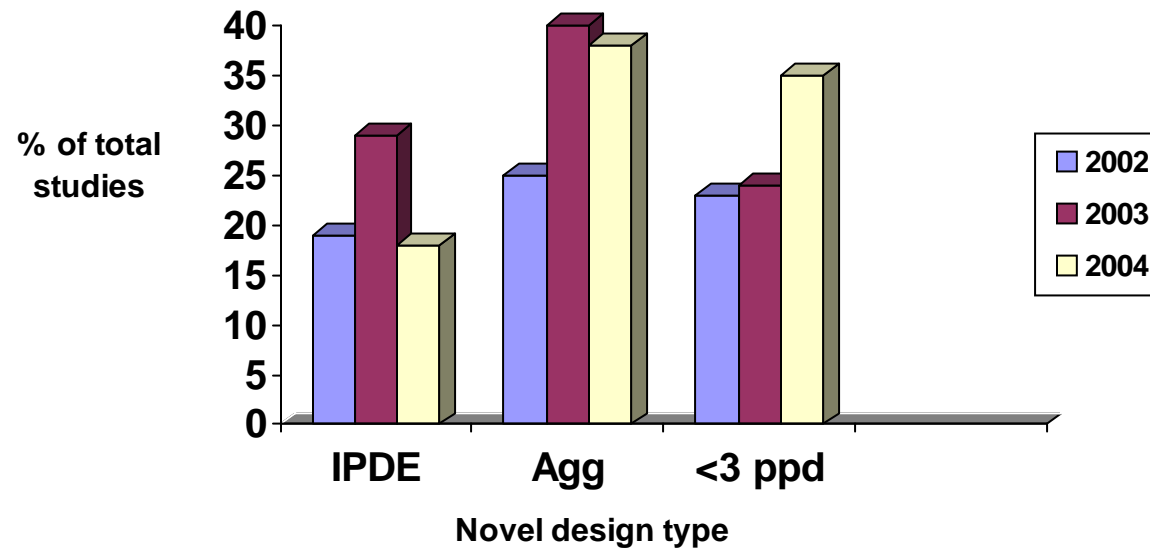
Figure 3A and 3B



**Figure 3C and 3D**

**Figure 3.** Response rates and toxicities of phase 1 oncology trials published in 2002 stratified by sponsorship (profit, non-profit, other) Panel A. CR+PR Panel B. Rate of Toxic Deaths Panel C. Non-hematological Grade 3/4 toxicity Panel D. Hematological Grade 4 toxicity. Support: black=drug/device manufacturer, red=not for profit, green=other/not-specified.

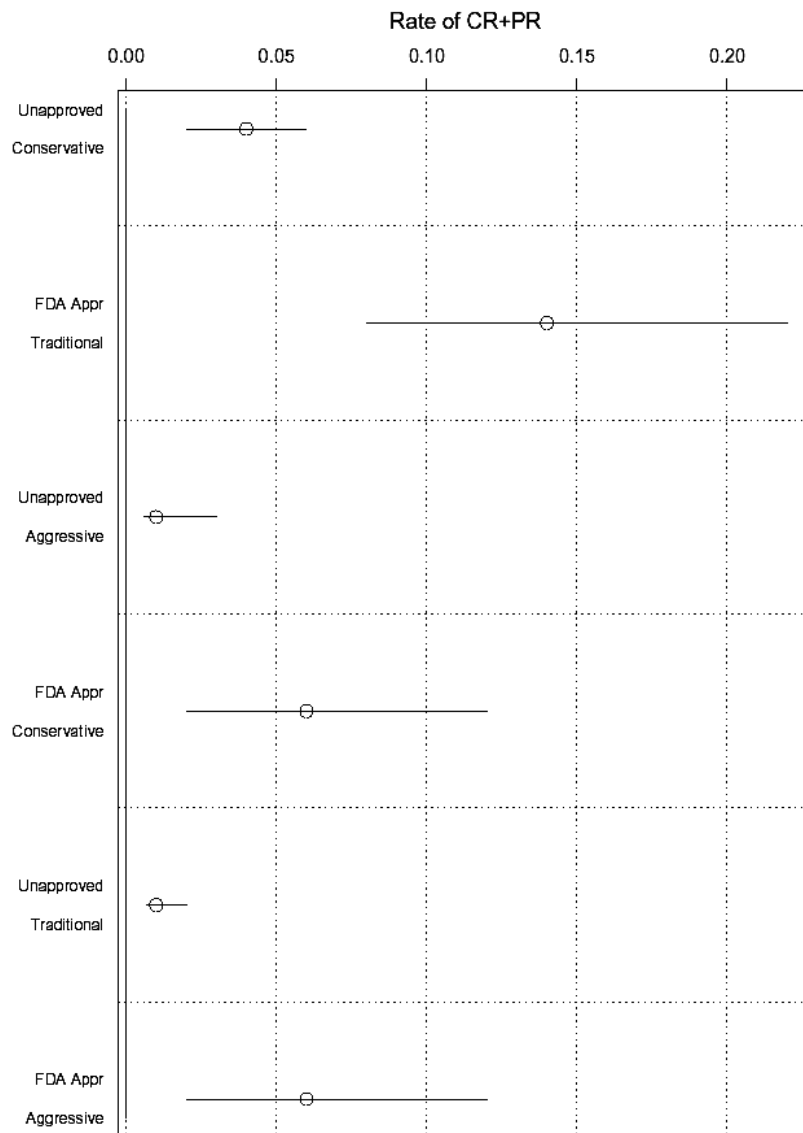
**Figure 4: Frequency of Novel Design Strategies by Year**



IPDE: Studies that allowed intra-patient dose escalation

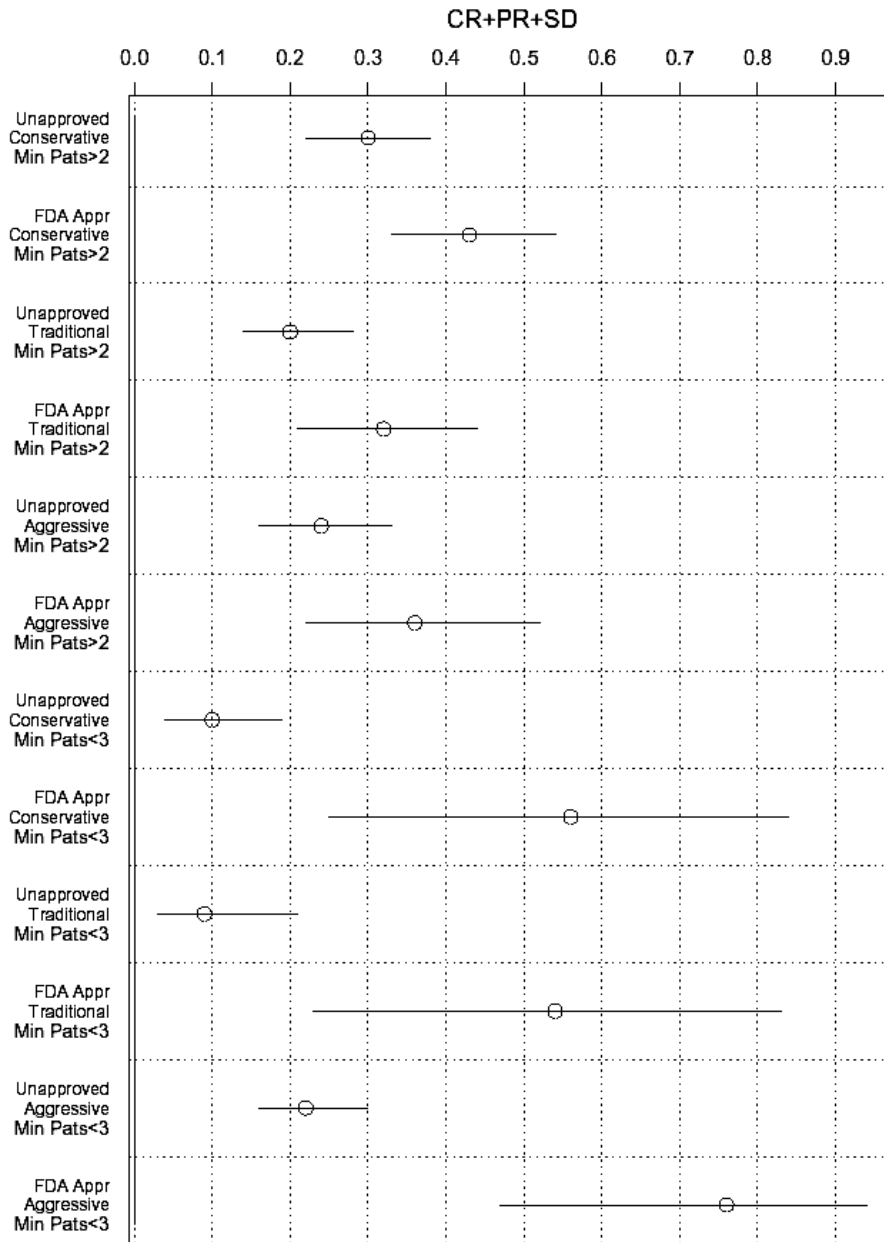
Agg: Studies that used an aggressive titration design

<3ppd: Studies that used less than 3 patients per dose in initial dose levels



**Figure 5:** Multivariate regression analysis of association between FDA approval status and dose escalation strategy with outcome of rate of complete response (CR) + partial response (PR).





**Figure 6:** Multivariate Regression Analysis of association of FDA approval status and dose escalation strategy with rate of complete response (CR), partial response (PR) and disease stabilization (SD) stratified by minimum patients required per dose of either >2 or <3.



## **APPENDIX:** Search Criteria for Parts 1 and 2

*PART 1:* The Medline database was searched to identify Phase I clinical oncology trials published in 2002. The search criteria were as follows: neoplasms (mh) NOT (review (pt) OR meta-analysis (pt) OR editorial (pt) OR practice guideline (pt) OR (clinical trial, Phase ii (pt) NOT clinical trial, Phase i (pt)) OR radiotherapy (mh)) AND (clinical trial, Phase i (pt) OR "Phase i") AND (drug therapy (mh) OR antineoplastic agents (mh) OR drug evaluation (mh) OR cancer vaccines (mh) OR adjuvants, immunologic (mh) OR signal transduction (mh) OR angiogenesis inhibitors (mh) OR gene expression regulation, neoplastic (mh) OR gene therapy (mh) OR cell transplantation). The search was performed on all fields of the database, but was limited to articles that were written in the English language and were published in 2002. Also, the publication type was defined as 'clinical trials' and the subset was designated as 'cancer.'

*PART 2:* The Medline database was searched to identify single agent phase I oncology trials of cytotoxic agents published between 2002 and 2004. The search criteria initially included *antineoplastic or chemotherapy or cytotoxic* and was limited to humans and the English language. The subset was defined as 'cancer,' the publication type was designated as 'clinical trial - phase I' and the year of interest was selected.