

The Changing Face of Phase 1 Cancer Clinical Trials

New Challenges in Study Requirements

Barbara S. Craft, MD¹, Razelle Kurzrock, MD¹, Xiudong Lei, DPHIL², Roy Herbst, MD³, Scott Lippman, MD³, Siqing Fu, MD^{1,4}, and Daniel D. Karp, MD⁵

Phase 1 studies in cancer have changed in recent years. Now, with the advent of new, less toxic, targeted agents, more patients may be candidates for new drug studies earlier in the course of their disease. It is to the advantage of the members of the oncology community to know more regarding the details and requirements for participation in early-phase clinical trials so they can advocate for their patients and help them decide when such trials may be an appropriate choice. To examine the work intensity of early phase cancer clinical trials, the authors of this report compared the study requirements of phase 1 and 2 protocols. Five parameters were studied as a surrogate of study complexity—the number of physical examinations, vital sign determinations, electrocardiograms (ECGs), nonpharmacokinetic laboratory tests, and pharmacokinetic (PK) sampling—in the first 4 weeks of protocol in 90 studies (49 phase 1 studies and 41 phase 2 studies). From July 2004 through March 2007, there were 49 phase 1 trials in the phase 1 Program, 9 phase 2 studies that were conducted by physicians appointed in that program, and 32 phase 2 trials with accessible data in the Department of Thoracic/Head & Neck Medical Oncology. In the phase 1 trials versus the phase 2 trials, there were significantly more ($P < .05$) physical examinations (mean $\pm$ standard error, 3.16 ± 0.24 vs 2.22 ± 0.13), vital sign determinations (5.63 ± 0.61 vs 2.80 ± 0.26), ECGs (4.36 ± 1.16 vs 0.80 ± 0.17), nonpharmacokinetic laboratory tests (18.08 ± 1.31 vs 10.12 ± 0.65), and PK sampling (15.14 ± 1.79 vs 1.02 ± 0.53). These values also differed significantly ($P < .005$ for each) when the median values were compared in nonparametric tests. Although both phase 1 and phase 2 trials had substantial study requirements, those for the phase 1 studies were significantly higher. The successful conduct of early-phase clinical trials requires significant research infrastructure. **Cancer** 2009;115:1592-7. © 2009 American Cancer Society.

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Phase 1 cancer clinical trials play a crucial role in drug development. Commonly known as ‘first-in-human’ studies, phase 1 trials also encompass new combinations and/or new dosing schedules of US Food and Drug Administration-approved drugs.¹ Although several different designs for these trials have been

Corresponding author: Daniel D. Karp, MD, Department of Thoracic/Head and Neck Medical Oncology, Unit 432, The University of Texas M.D. Anderson Cancer Center, 1400 Holcombe Boulevard, Houston, TX 77030; Fax: (713) 792-1220; dkarp@mdanderson.org

¹Phase I Program, Division of Cancer Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; ²Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; ³Department of Thoracic/Head and Neck Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; ⁴Department of Gynecologic Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; ⁵Clinical and Translational Research Center, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

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used, the standard design in phase 1 studies is to enroll cohorts of 3 to 6 patients at increasing dose levels until dose-limiting toxicity is reached.²⁻⁵ Traditionally, the primary endpoints of phase 1 studies of chemotherapy included determining the pharmacokinetics of the drug⁶ as well as the maximum tolerated dose⁷ and subsequent recommendations of a dose and schedule with which to proceed to phase 2 studies. In contrast to phase 1 trials, the primary endpoint for phase 2 studies is efficacy. However, for newer, targeted agents, other endpoints for phase 1 trials, such as the optimal biologic dose (eg, the dose at which the target is modulated best), increasingly are becoming important along with describing response signals and any early evidence of a correlation between these signals and target inhibition and/or patient/tumor characteristics.^{8,9} These endpoints are more complex to obtain, because they require measuring target impact in tumor tissue and/or assessing genomic expression patterns in the host or the tumor.^{10,11} In addition, over the last decade, there has been increasing scrutiny of clinical trials research with an emphasis on tight adherence to protocol requirements as well as careful monitoring of patient safety.¹²⁻¹⁴ All of these factors have contributed to the impression that phase 1 trials have become increasingly complex.

Much has been written concerning the risks and benefits¹⁵⁻¹⁷ and the design and importance of phase 1 trials¹⁻³ as well as the cost of clinical trials versus standard care.¹⁸⁻²⁵ There also is literature regarding the work involved in clinical research, but mostly with regard to phase 2 and 3 protocols.^{19,26} Until now, little has been done to examine the intensity of the phase 1 protocol schedule. This information is important, because the intensity of phase 1 trials impacts both the patient and the clinical research staff. In the current study, we analyzed a series of phase 1 and 2 trials conducted at M. D. Anderson Cancer Center to further examine and compare the work intensity required for the 2 different phases of clinical research.

MATERIALS AND METHODS

Protocol Selection

The requirements for all phase 1 and 2 protocols managed by the Phase 1 Program or by physicians with an appointment in that program at M. D. Anderson Cancer Center,

as well as the phase 2 protocols with accessible data managed by the Department of Thoracic/Head & Neck Medical Oncology during fiscal years 2003 through 2007 were reviewed. (For the phase 1 trials, only studies that were approved by the Internal Review Board and that had accessible data were analyzed. The time frame for these studies was July 2004 through March, 2007.) After the exclusion of 7 trials (5 were phase 1 trials, and 2 were phase 2 trials) because of either past closure or inaccessible data, 49 phase 1 trials and 41 phase 2 trials remained for investigation. Each trial and its requirements were reviewed by tabulating data from the Clinical and Translational Research Center database, the institution's Protocol Document Online System, the M. D. Anderson-mandated protocol abstract, and/or the protocol order sets. All trials had been approved by the Institutional Review Board. In preparing this report, we obtained protocol requirements from sources that contained no patient-specific information.

Correlative Studies and Data Collection

We analyzed several parameters as representatives of the complexity of requirements. These included 1) physical examination, 2) vital sign monitoring, 3) electrocardiography monitoring, 4) nonpharmacokinetic (non-PK) laboratory testing, and 5) and pharmacokinetic (PK) sampling conducted in the first 28-day cycle of each protocol. To evaluate our findings, we developed a comprehensive database along with a Microsoft Excel spreadsheet matrix to analyze the number of correlative studies.

Statistical Analysis

The statistical objectives of this study included comparison of differences in each of the 5 variables (physical examinations, vital signs, electrocardiograms [ECGs], non-PK laboratory draws, and PK time points) by 1) phase of study (ie, phase 1 vs phase 2), 2) sponsorship within phase (industry, nonsponsored/investigator-initiated, National Cancer Institute [NCI]/peer-reviewed group), and 3) sponsorship (industry, nonsponsored/investigator-initiated, NCI/peer-reviewed group). All statistical analyses were performed by our biostatistician (X.L.).

Summary statistics were used to report the number of observations and the mean, standard deviation,

Table 1. Correlative Tests: Phase 1 Versus Phase 2 Cancer Trials

Test	Phase 1, N = 49	Phase 2, N = 41	P*
Physical examination total	155	91	
Median (range)	3 (1-8)	2 (1-5)	.0023
Mean $\pm$ SE	3.16 $\pm$ 0.24	2.22 $\pm$ 0.13	
Vital sign total	276	115	
Median (range)	5 (1-27)	2 (1-7)	<.0001
Mean $\pm$ SE	5.63 $\pm$ 0.61	2.80 $\pm$ 0.26	
ECG total	214	33	
Median (range)	1 (0-49)	1 (0-5)	<.0001
Mean $\pm$ SE	4.36 $\pm$ 1.16	0.80 $\pm$ 0.18	
Non-PK laboratory total	886	415	
Median (range)	16 (7-50)	10 (3-21)	<.0001
Mean $\pm$ SE	18.08 $\pm$ 1.31	10.12 $\pm$ 0.65	
PK total	742	42	
Median (range)	13 (0-51)	0 (0-18)	<.0001
Mean $\pm$ SE	15.14 $\pm$ 1.79	1.02 $\pm$ 0.53	

SE indicates standard error; ECG, electrocardiogram; PK, pharmacokinetic.
* *P* value for median.

standard error, median, and range of each of the 5 variables by phase of study (phase 1 and phase 2) and by sponsor (industry, investigator-initiated, or NCI/peer-reviewed group). Nonparametric methods of comparison were implemented. If the number of groups for comparison was 2, then the Wilcoxon rank-sum test was used. If the number of groups for comparison was >2 , then the Kruskal-Wallis test was used. *P* values were reported, and differences between protocol phase and sponsor were considered statistically significant if the *P* value for a given test was $<.05$. All the statistical analyses were performed in SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

We reviewed a total of 90 trials, including 49 phase 1 trials and 41 phase 2 trials, that were approved and managed during the same period. The parameters were those assessed during the first 4 weeks of the study. For all correlative tests that we investigated, there were significantly more tests required in phase 1 trials than in phase 2 trials (Table 1). Physical examination time points differed between the 2 groups, with significantly more required in phase 1 (mean $\pm$ standard error, 3.16 ± 0.24 time points vs 2.22 ± 0.13 time points). The number of vital sign

Table 2. Sponsorship: Phase 1 Versus Phase 2 Cancer Trials

Sponsor	No. of Trials	
	Phase 1	Phase 2
Industry	38	19
Nonsponsored/investigator-initiated	8	6
NCI/peer-reviewed group	3	16

NCI indicates National Cancer Institute.

measurements differed significantly between phase 1 and 2, with a greater mean number required in phase 1 (5.63 ± 0.61 vital sign measurements vs 2.80 ± 0.26 vital sign measurements). For ECGs, the mean number also was significantly greater in phase 1 trials versus phase 2 trials (4.36 ± 1.16 ECGs vs 0.80 ± 0.18 ECGs). The mean number of non-PK laboratory draws also differed between phase 1 and phase 2 (18.08 ± 1.31 non-PK laboratory draws vs 10.12 ± 0.65 non-PK laboratory draws). Very noteworthy was the difference in the mean number of PK samplings between phase 1 trials (15.14 ± 1.79) and phase 2 trials (1.02 ± 0.53). These parameters also differed significantly ($P < .005$) for each when the median values were compared using nonparametric tests. Therefore, in the current study, although while both phases of clinical trials required significant numbers of correlatives, the requirements for phase 1 were considerably greater.

Similar to previous studies that investigated work requirements,²⁶ we also looked at how the sponsorship of different trials affected the number of requirements (Table 2). Of the phase 1 trials, 38 of 49 were industry-sponsored trials, 8 of 49 were nonsponsored/investigator-initiated trials, and 3 of 49 were NCI-sponsored trials. Of the phase 2 trials, 19 of 41 were industry sponsored, 6 of 41 were nonsponsored/investigator initiated, and 16 of 41 were NCI/Department of Defense or other peer-review group sponsored. (Trials that were investigator initiated but were funded by a sponsor who held the investigational new drug are listed as industry sponsored or NCI sponsored). Among the phase 1 trials, as noted previously, 78% were sponsored by private industry, and only 6% had NCI or peer-reviewed sponsorship—a trend we have witnessed for several years. This limited number of phase 1 NCI studies precluded an analysis of sponsorship within each of the phase 1 and phase 2 trials. In that context, for

Table 3. Summary Statistics for Variables by Sponsor

Variable	Industry, N = 57	Nonsponsored, Investigator-Initiated, N = 14	NCI/Peer Review Group, N = 19	P
Physical examinations				
Mean ± SD	2.79 ± 1.52	2.57 ± 1.40	2.68 ± 1.16	.8252
Median	2	2	2	
Range	1-8	1-6	1-5	
Vital signs				
Mean ± SD	5.07 ± 4.28	2.79 ± 1.42	3.32 ± 1.67	.0434
Median	4	2.5	3	
Range	1-27	1-6	1-7	
ECGs				
Mean ± SD	3.93 ± 7.65	0.86 ± 0.86	0.58 ± 0.84	.0002
Median	1	1	0	
Range	0-49	0-3	0-3	
Non-PK laboratory tests				
Mean ± SD	15.81 ± 9.70	13.50 ± 4.40	11.11 ± 4.04	.1261
Median	14	12.5	10	
Range	3-50	8-21	5-20	
PK				
Mean ± SD	13.07 ± 12.74	1.86 ± 5.11	0.68 ± 2.21	<.0001
Median	11	0	0	
Range	0-51	0-18	0-9	

NCI indicates National Cancer Institute; SD, standard deviation; ECG, electrocardiogram; PK, pharmacokinetic.

Table 4. P Values for Pairwise Comparison of Variables between Sponsors

Variable	Industry-Sponsored vs Nonsponsored Investigator-Initiated	P	
		Investigator- vs NCI-Sponsored	Industry- vs NCI-Sponsored
Physical examination	.5747	.5888	.9090
Vital signs	.0271	.4099	.1156
ECGs	.0160	.2615	.0002
Non-PK laboratory tests	.7228	.1388	.0515
PKs	.0003	.7238	<.0001

NCI indicates National Cancer Institute, ECGs, electrocardiograms; PK, pharmacokinetic.

each of the 5 parameters studied, industry-sponsored trials required an overall greater number of measurements than both the nonsponsored/investigator-initiated trials and the NCI/peer-review group trials (Table 3). However, only the difference in number of ECGs (mean $\pm$ standard deviation: 3.93 $\pm$ 7.65 ECGs [industry-sponsored trials] vs 0.86 $\pm$ 0.86 ECGs [nonsponsored/investigator-initiated trials] vs 0.58 $\pm$ 0.84 ECGs [NCI/peer-review group trials]), and PK time points (13.07 $\pm$ 12.74 time points vs 1.86 $\pm$ 5.11 time points vs 0.68 $\pm$ 2.21 time points,

respectively) reached statistical significance (Table 4). However, our sense was that NCI trials, when controlled for study phase, were every bit as rigorous as industry-sponsored studies.

DISCUSSION

New drug development is essential for making progress in the treatment of cancer. During the last few years, concern for patient safety in clinical trials has resulted in strict

regulatory requirements.¹²⁻¹⁴ In addition, with the advent of targeted agents, correlative studies to understand pharmacodynamic effects and target impact have become crucial to optimal drug development.⁶ These requirements have resulted in the impression of a greater workload assumed by investigators and institutions participating in early-phase clinical trials.

Because there are few data on this aspect of study conduct for phase 1 protocols, our analysis focused on them. And, although many activities are required to run a successful phase 1 clinical trial, including the workload of clinical study coordinators, imaging, etc, we did not specifically address those activities. Instead, we chose to examine a set of 5 requirements of current, successful, early-phase cancer clinical trials. We chose these variables because of their prevalence and importance in phase 1 studies. For instance, determining PK is often a primary endpoint.⁶ With more targeted agents being developed, the strategy is evolving to find a less toxic/more effective dose versus the maximal tolerated dose.⁸⁻¹¹ Frequent ECG monitoring also has become a common requirement to monitor QT interval and rhythms²⁷; and vital signs, physical examinations, and non-PK laboratory draws are required for safety assessment,¹²⁻¹⁴ which is another primary endpoint of phase 1 trials. We observed that, for all 5 parameters (physical examination, vital sign monitoring, ECGs, non-PK laboratory testing, and PK sampling), there were significantly greater demands in phase 1 trials versus phase 2 trials.

These results are supported by earlier findings in the literature that examined the requirements of phase 2 and 3 studies. For instance, a study by Roche et al²⁶ reviewed the time requirements of clinical research associates involved in clinical trial coordination and data collection. Those authors observed that the work intensity of phase 2 and 3 studies (and a small number of phase 1 studies) was greater than had been acknowledged previously. Furthermore, phase and sponsor were identified as significant independent factors that predicted an increased workload after controlling for disease stage. Similar to our results, Roche et al demonstrated that earlier phase studies and those sponsored by industry were more time consuming than later phase trials or those that were investigator initiated.

Issues that have been at the forefront in the past several decades regarding phase 1 trials are fading with the development of newer, more targeted therapies. Concerns

have included the possibility of serious toxicity with minimal benefit from experimental agents. These issues, along with concerns about patient safety, have resulted in increasingly stringent regulatory requirements.¹²⁻¹⁴ In the largest analysis of phase 1 studies, which included almost 12,000 patients, Horstmann et al¹⁵ demonstrated that the toxic death rate was <0.5%, which is surprisingly low considering that these patients, by definition, are afflicted by terminal, untreatable cancer. In addition, although previous studies demonstrated an overall response rate for phase 1 studies of only 4.4%, their data revealed an overall response rate (partial and complete remissions) of 10.6%. When less than partial responses and stable disease were included, then the percentage of patients 'benefiting' was 44.7%.^{15,16}

Currently, successful clinical trials remain the cornerstone of new drug development. Both phase 1 and phase 2 clinical trials recently have endured an increase in the number of requirements and workload. The data from our study are consistent with those from previous studies that focused on phase 2 and 3 requirements. However, our findings indicate that phase 1 studies are even more complex, as demonstrated here by extensive correlative testing and safety monitoring, indicating that these studies require substantial resources and infrastructure.

Conflict of Interest Disclosures

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