

SPECIAL ARTICLE

## Risks and Benefits of Phase 1 Oncology Trials, 1991 through 2002

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### ABSTRACT

#### BACKGROUND

Previous reviews of phase 1 oncology trials reported a rate of response to treatment of 4 to 6 percent and a toxicity-related death rate of 0.5 percent. These results may not reflect the rates in current phase 1 oncology trials.

#### METHODS

We reviewed all nonpediatric phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program at the National Cancer Institute between 1991 and 2002. We report the rates of response to treatment, of stable disease, of grade 4 toxic events, and of treatment-related deaths.

#### RESULTS

We analyzed 460 trials involving 11,935 participants, all of whom were assessed for toxicity and 10,402 of whom were assessed for a response to therapy. The overall response rate (i.e., for both complete and partial responses) was 10.6 percent, with considerable variation among trials. "Classic" phase 1 trials of single investigational chemotherapeutic agents represented only 20 percent of the trials and had a response rate of 4.4 percent. Studies that included at least one anticancer agent approved by the Food and Drug Administration constituted 46.3 percent of the trials and had a response rate of 17.8. An additional 34.1 percent of participants had stable disease or a less-than-partial response. The overall rate of death due to toxic events was 0.49 percent. Of 3465 participants for whom data on patient-specific grade 4 toxic events were available, 14.3 percent had had at least one episode of grade 4 toxic events.

#### CONCLUSIONS

Overall response rates among phase 1 oncology trials are higher than previously reported, although they have not changed for classic phase 1 trials, and toxicity-related death rates have remained stable. Rates of response and toxicity vary, however, among the various types of phase 1 oncology trials.

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THE ETHICAL ISSUES RAISED BY PHASE 1 oncology trials have been debated for decades.<sup>1-6</sup> These trials enroll patients with advanced cancer whose disease is usually refractory to available treatment in order to evaluate the safety and toxicity of new therapeutic agents, to establish the pharmacokinetic properties of those agents, and to determine a safe dose for subsequent testing.<sup>7</sup> Published reviews report that a tumor response occurs in 4 to 6 percent of the participants in these trials and that about 0.5 percent of participants die as the result of toxicity.<sup>8-16</sup> Critics of such trials cite these data when raising concerns about the poor prospect of benefit and the potential for severe harm. Some contend that the enrollment of patients with advanced disease in risky research studies with little chance of direct benefit exploits a vulnerable population.<sup>17</sup> The response rates of 4 to 6 percent and the toxicity-related death rate of 0.5 percent continue to be viewed as representative of phase 1 oncology trials, but these rates are based on reviews of single-agent trials. They do not take into full account the development of new types of anticancer agents, trials of combinations of agents, new trial designs, or improvements in supportive care, and they do not present a comprehensive picture of the benefits and risks associated with phase 1 trials.<sup>18-20</sup>

To better inform the discussion of the risks and benefits involved in phase 1 oncology trials, we reviewed studies that began between 1991 and 2002 and were sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute, the major sponsor of phase 1 oncology trials in the United States. Reflecting the full spectrum of phase 1 oncology trials, our review included trials of chemotherapeutic agents and newer, targeted agents such as antiangiogenesis factors, vaccines, and gene therapies; trials of combinations of agents, including some already approved by the Food and Drug Administration (FDA); and published and unpublished trials. To extend our understanding of the benefits and risks associated with phase 1 oncology research, data on stable disease and grade 4 toxic events are reported in addition to conventional measures of outcome.

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#### METHODS

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All nonpediatric phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program that began between 1991 and 2002 were eligible for this

review, including trials that evaluated solid tumors and hematologic cancers and trials conducted at the National Institutes of Health (NIH) Clinical Center and other institutions around the United States. Excluded were phase 1–phase 2 trials, trials of radiation therapy alone, of stem-cell or bone marrow transplantation, of supportive care without anticancer agents, and of therapies for diseases other than cancer (e.g., human immunodeficiency virus disease).

The staff of the Cancer Therapy Evaluation Program plan, review, coordinate, and oversee clinical trials of investigational anticancer agents.<sup>21</sup> The program receives comprehensive trial data at regular intervals from investigators and actively monitors all trials through routine data submission and periodic audits. Between 1991 and 2002, data from phase 1 trials sponsored by the Cancer Therapy Evaluation Program were monitored by five different sources: the Clinical Trials Monitoring System, the Clinical Data Update System, the Annual Update System, the Quarterly Data Update, and Study Summary reports.

The Clinical Trials Monitoring System, which has been managed for the Cancer Therapy Evaluation Program by Theradex since 1979, is a database of electronically submitted case-report forms for first trials of agents in humans as well as trials of combinations of investigational new drugs and at least one FDA-approved drug that may be associated with a risk of overlapping toxic effects. Extensive data are submitted every two weeks for quality control and are maintained in a relational KnowledgeMan database (Micro Data Base Systems). Each participating institution is audited for quality assurance three times a year.

The Clinical Data Update System, managed by Capital Technology Information Systems, has received electronic data according to course of therapy and according to patient every three months since 1998. The Clinical Data Update System is generally used for late phase 1 trials of agents whose toxicity profile has been established in earlier studies. Data are maintained in a relational Oracle database. Before 1998, summary data for these trials were submitted as paper reports yearly (by the Annual Update System or by Study Summary reports), quarterly (by Quarterly Data Update), or twice a year in printed trial summaries prepared by the cooperative groups. For trials monitored by the Clinical Data Update System, the Annual Update System, Study Summary reports, and Quarterly Data Update,

each institution is audited every three years. Auditors examine the consistency of reporting, including references to source documents concerning toxic events among subjects and assessments of responses. Data reported in this article include selected variables from the database of the Cancer Therapy Evaluation Program and combine data from the program's five monitoring sources. A subgroup of 110 trials, primarily those monitored by the Annual Update System, was excluded because complete data in regard to toxicity were unavailable. None of the excluded trials were from the Clinical Trials Monitoring System's database of studies involving agents used for the first time in humans, studies involving agents filed as investigational new drugs with the FDA, or other early phase studies. The Cancer Therapy Evaluation Program provided the data on May 16, 2003.

Trials were grouped by an experienced investigator of phase 1 trials into one of six categories according to the mechanism of action of the agent or agents under investigation: cytotoxic chemotherapeutic agents, immunomodulators, receptor-transduction or signal-transduction agents (including those affecting gene reexpression), antiangiogenesis agents, gene-transfer agents, and vaccines. Each of these categories was further subdivided into four types of trials: those for single investigational agents, for multiple investigational agents, for both investigational and FDA-approved agents, and for only those agents approved by the FDA. Trials involving multiple investigational agents with different mechanisms of action were grouped according to the agent predicted to be the most toxic. Thus, any trial involving a combination of therapies that included a chemotherapeutic investigational agent was coded as a chemotherapy trial, and any trial that included an immunomodulating investigational agent but no chemotherapeutic agents was categorized as an immunomodulator trial. Trials that included both investigational and FDA-approved agents were categorized according to the mechanism of action of the investigational agent. For purposes of classification, radiation was considered an FDA-approved agent.

In cases in which the study title identified a specific disease, the study was considered disease-specific. Studies of single investigational cytotoxic chemotherapeutic agents were labeled "classic" phase 1 trials. Studies of agents being used in humans for the first time were selected from all five databases. These included the very first study of an agent con-

ducted after the agent was filed as an investigational new drug with the FDA and trials that were initiated within seven months of the first study, before any information was available about dose-limiting toxicity from the very first trial.

Potentially beneficial effects of agents under investigation were categorized as complete response, partial response, less-than-partial response, and stable disease. Response to treatment was reported for each protocol according to guidelines of the World Health Organization (WHO),<sup>22</sup> the Response Evaluation Criteria in Solid Tumors,<sup>23</sup> or other established criteria approved by the Protocol Review Committee of the Cancer Therapy Evaluation Program. A complete response was defined as the disappearance of a tumor; a partial response as an overall 50 percent reduction in the tumor, measured as the sum of the products of the two longest diameters (according to the WHO criteria), or as an overall 30 percent reduction in tumor size, measured as the sum of the longest diameters (according to guidelines of the Response Criteria in Solid Tumors); and stable disease as neither a partial response nor progressive disease.<sup>23</sup> For this analysis, less-than-partial response and stable disease are combined into one category.

Toxicity was reported with the use of the Common Toxicity Criteria.<sup>24</sup> Protocols specified which version of these criteria were used, depending on when the protocols were initiated. All deaths reported by investigators as "possibly," "probably," or "definitely" related to treatment were considered toxicity-related deaths. Data on patient-specific grade 4 toxic events that were available from the Clinical Data Update System are reported; for the other trials, only the data on cumulative toxicity according to trial were available.

#### STATISTICAL ANALYSIS

Response rates, death rates, and rates of grade 4 toxic events were calculated for participants who were assessed according to trial category (i.e., therapeutic modality, single agent or combination, disease-specific or not, and first-in-human or other). Rates were calculated by dividing the total number of events (responses, deaths, or grade 4 toxic events) by the total number of patients assessed for response or toxicity. Response rates and toxicity-related death rates were also calculated for three-year intervals to evaluate trends. For the subgroup of trials monitored by the Clinical Data Update System, the percentage of patients who had grade 4

toxic events and the average number of grade 4 toxic events per affected patient were reported. Comparisons of response rates and of toxicity-related death rates — in particular, between the current sample and prior samples — were made descriptively. Calculation of statistical significance was intentionally avoided in cases where patient samples may have been divergent and hypothesis test-

ing not prospectively defined. Statistical analyses were performed with the use of SAS software, version 8.02.

## RESULTS

The sample of 460 phase 1 oncology trials sponsored by the Cancer Therapy Evaluation Program

**Table 1. Rates of Response to Treatment in Phase 1 Oncology Trials.**

Trial	No. of Trials	No. of Patients Assessed for Response	Rate of Response			
			Overall Response (Complete and Partial)	Complete Response	Partial Response	Stable Disease and Less-Than-Partial Response
<i>percent</i>						
Total	460	10,402	10.6	3.1	7.5	34.1*
Cytotoxic chemotherapy						
One investigational agent	92	2,341	4.4	1.5	2.9	40.8
Multiple investigational agents	12	273	11.7	1.5	10.3	27.5
Combination of investigational and FDA-approved agents	88	2,251	16.4	5.6	10.8	31.3†
FDA-approved agents only	29	792	27.4	8.0	19.4	27.2†
Immunomodulator						
One investigational agent	13	203	11.3	3.0	8.4	35.5
Multiple investigational agents	28	651	6.9	2.2	4.8	22.3†
Combination of investigational and FDA-approved agents	19	392	26.0	5.6	20.4	26.7†
Receptor or signal transduction						
One investigational agent	51	1,347	3.2	0.7	2.5	39.3
Multiple investigational agents	7	81	7.4	1.2	6.2	27.2
Combination of investigational and FDA-approved agents	61	935	11.7	2.1	9.5	37.4
Antiangiogenesis						
One investigational agent	15	335	3.9	0.6	3.3	31.0
Combination of investigational and FDA-approved agents	9	135	14.8	5.2	9.6	37.0
Gene transfer						
One investigational agent	7	89	3.4	0	3.4	30.3
Combination of investigational and FDA-approved agents	1	3	0	0	0	0
Vaccine						
One investigational agent	15	265	3.4	3.0	0.4	24.9
Multiple investigational agents	7	198	1.0	1.0	0	35.4
Combination of investigational and FDA-approved agents	6	111	5.4	2.7	2.7	19.8

\* For 630 of 10,402 participants, data on stable disease and less-than-partial response are not reported. The percentage was calculated with 9772 as the denominator.

† Percentages were calculated with a denominator adjusted to exclude participants for whom data on stable disease and less-than-partial response were unavailable.

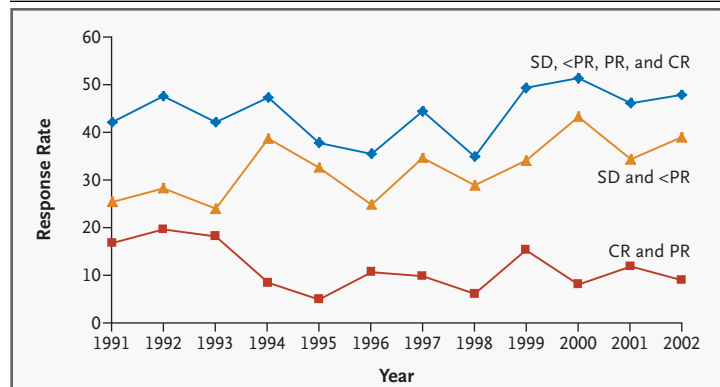
that opened between 1991 and 2002 included 11,935 participants. All participants were assessed for toxicity, and 10,402 were assessed for a response (Table 1). Trials of cytotoxic chemotherapeutic agents accounted for 48.0 percent (221) of all trials and for 54.4 percent (5657) of participants assessed for response. Trials involving receptor transduction or signal transduction were the second-largest group (119 trials, or 25.9 percent), representing 22.7 percent (2363) of participants assessed for response. There were only eight trials involving gene transfer, with 92 participants (Table 1).

#### RESPONSE RATES

Among the trials of all types of agents, 10.6 percent of the 10,402 participants assessed for response had either a partial or a complete response to therapy. Of these, 7.5 percent had a partial response and 3.1 percent had a complete response. In addition, 34.1 percent of the participants in phase 1 trials had either stable disease or a less-than-partial response (Table 1).

Response rates varied according to the type of agent used and the characteristics of the trial (Table 1). The overall response rate was 3.0 percent among trials of vaccines and 13.6 percent among studies of immunomodulators (data not shown). Furthermore, response rates varied within categories according to the type of trial. For classic phase 1, single-agent chemotherapy studies, the overall response rate was 4.4 percent. The rate among chemotherapy studies involving more than one investigational agent was 11.7 percent; for combinations of investigational and FDA-approved agents, the rate was 16.4 percent; and for phase 1 trials including only FDA-approved chemotherapeutic agents, the rate was 27.4 percent (Table 1). A similar variation was seen in the other categories of trials (Table 1). The response rate among 3420 participants in 184 disease-specific trials was 19.3 percent; among trials that were not specific to disease, the rate was 6.3 percent.

Response rates also varied over time, with the highest rate (19.5 percent) occurring in 1992 and the lowest (5.0 percent) in 1995. When the rates were grouped according to three-year periods, a downward trend in complete and partial responses was noted (18.3 percent for 1991 to 1993 and 9.4 percent for 2000 to 2002). However, when stable disease was taken into account, the rate remained relatively constant over time (34.6 to 51.3 percent) (Fig. 1).



**Figure 1. Response Rates According to Year.**

Response to therapy was classified as complete (CR), partial (PR), less than partial (<PR), or as stable disease (SD). When the rates were grouped according to three-year periods, a downward trend was observed for complete and partial responses, but when stable disease and less-than-partial responses were taken into account, the rate remained relatively constant over time.

#### TOXICITY

Among the 11,935 participants in all 460 phase 1 studies, there were 58 deaths (0.49 percent) that were determined to be at least possibly related to the treatment (Table 2). Of those deaths, 18 were reported as definitely related to the treatment and 7 as probably related (for a combined toxicity-related death rate of 0.21 percent). When calculated in three-year intervals for 1991 through 2002, the toxicity-related death rate remained relatively constant (range, 0.45 to 0.61 percent). Of the 58 deaths, 43 (74.1 percent) occurred in participants in chemotherapy trials, with the highest toxicity-related death rate (0.77 percent) occurring in trials involving both investigational and FDA-approved agents (Table 2). Classic phase 1 trials of single investigational chemotherapeutic agents had a toxicity-related death rate of 0.57 percent. Thirteen deaths were reported among trials of receptor-transduction or signal-transduction agents (0.47 percent) and one death each among trials of immunomodulators (0.07 percent) and antiangiogenesis factors (0.17 percent). There were no reported deaths in phase 1 gene-transfer or vaccine studies.

In a subgroup of 168 studies that involved 3465 patients assessed for toxicity, 14.3 percent of participants had had grade 4 toxic events; an average of 1.9 grade 4 events occurred per affected patient (Table 3). On average, trials of chemotherapeutic agents were associated with the highest rate of tox-

**Table 2. Deaths from Toxic Events in Phase 1 Oncology Trials.**

Trial	No. of Trials	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events*
			no. (%)
Total	460	11,935	58 (0.49)
Cytotoxic chemotherapy			
One investigational agent	92	2,621	15 (0.57)
Multiple investigational agents	12	305	2 (0.66)
Combination of investigational and FDA-approved agents	88	2,594	20 (0.77)
FDA-approved agents only	29	925	6 (0.65)
Immunomodulator			
One investigational agent	13	235	0
Multiple investigational agents	28	730	1 (0.14)
Combination of investigational and FDA-approved agents	19	443	0
Receptor or signal transduction			
One investigational agent	51	1,565	3 (0.19)
Multiple investigational agents	7	99	2 (2.02)
Combination of investigational and FDA-approved agents	61	1,081	8 (0.74)
Antiangiogenesis			
One investigational agent	15	402	0
Combination of investigational and FDA-approved agents	9	171	1 (0.58)
Gene transfer			
One investigational agent	7	107	0
Combination of investigational and FDA-approved agents	1	5	0
Vaccine			
One investigational agent	15	297	0
Multiple investigational agents	7	218	0
Combination of investigational and FDA-approved agents	6	137	0

\* Deaths include all those reported as possibly, probably, or definitely related to the treatment.

icity, with 17.4 percent of participants experiencing at least one grade 4 toxic event; vaccine trials had the lowest rate, with no grade 4 toxic events reported (Table 3). Among all 11,935 participants assessed in the 460 studies, 5251 grade 4 toxic events were reported.

#### FIRST-IN-HUMAN TRIALS

Of 460 trials, 117 (25.4 percent) involving a total of 3164 participants assessed for a response to therapy were considered first-in-human trials — that is, studies designed to establish initial information on

toxicity and dose for agents not previously tested in humans (Table 4). The overall response rate in these studies was 4.8 percent, as compared with 13.1 percent in the other studies. The toxicity-related death rate in first-in-human studies was 0.26 percent, as compared with 0.58 percent in studies not considered first-in-human trials. Studies of cytotoxic chemotherapeutic agents made up the largest group of first-in-human trials (36.8 percent). Of the vaccine studies sponsored by the Cancer Therapy Evaluation Program, 82.1 percent were first-in-human trials.

**Table 3. Grade 4 Toxic Events in Phase 1 Oncology Trials.**

Trial	No. of Trials	No. of Patients Assessed for Toxic Events	Patients with a Grade 4 Toxic Event %	Average No. of Grade 4 Toxic Events per Patient
Total	168	3465	14.3	1.9
<b>Cytotoxic chemotherapy</b>				
One investigational agent	20	408	15.0	1.6
Multiple investigational agents	3	23	4.3	2.0
Combination of investigational and FDA-approved agents	17	475	14.5	1.8
FDA-approved agents only	3	159	34.0	2.4
<b>Immunomodulator</b>				
One investigational agent	2	43	2.3	1.0
Multiple investigational agents	10	207	9.7	2.2
Combination of investigational and FDA-approved agents	5	101	4.0	1.8
<b>Receptor or signal transduction</b>				
One investigational agent	29	839	13.0	1.7
Multiple investigational agents	6	67	19.4	2.0
Combination of investigational and FDA-approved agents	51	752	18.1	2.0
<b>Antiangiogenesis</b>				
One investigational agent	9	143	5.6	1.6
Combination of investigational and FDA-approved agents	6	101	17.8	1.8
<b>Gene transfer</b>				
One investigational agent	1	26	11.5	1.7
Combination of investigational and FDA-approved agents	1	5	0	0
<b>Vaccine</b>				
One investigational agent	3	20	0	0
Multiple investigational agents	2	96	0	0

**TRIALS WITH FDA-APPROVED AGENTS**

Overall, 213 studies (46.3 percent) included at least one FDA-approved anticancer agent. Response rates were higher in trials with FDA-approved agents than in trials without FDA-approved agents (Table 5). These studies had an overall response rate of 17.8 percent, as compared with 4.8 percent for studies not including FDA-approved anticancer agents. The toxicity-related death rate was higher (0.65 percent) than for trials that did not include FDA-approved anticancer agents (0.35 percent).

Program between 1991 and 2002. The overall response rate in these trials was 10.6 percent, which is higher than previously reported, whereas the toxicity-related death rate, 0.49 percent, is similar to that of previous reports. Rates of response and of toxicity-related death among classic phase 1 trials of single chemotherapeutic agents are similar to those reported in other reviews, but classic trials account for only 22 percent of participants in this review.

Response rates in phase 1 oncology trials have been reported to be 4 to 6 percent, with toxicity-related death rates reported to be 0.5 percent or lower.<sup>8-16</sup> In our review, however, we found that response rates in recent phase 1 oncology trials exceeded 10 percent, with stable disease or less-than-partial re-

**DISCUSSION**

We comprehensively reviewed phase 1 oncology trials sponsored by the Cancer Therapy Evaluation

**Table 4. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials Involving the First Use of an Agent in Humans.**

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate* %	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events† no. (%)
Total					
First use of an agent in humans	117	3164	4.8	3498	9 (0.26)
All other trials	343	7238	13.1	8437	49 (0.58)
Cytotoxic chemotherapy					
First use of an agent in humans	43	1298	5.0	1422	7 (0.49)
All other trials	178	4359	15.0	5023	36 (0.72)
Immunomodulator					
First use of an agent in humans	16	404	7.4	431	1 (0.23)
All other trials	44	842	16.6	977	0
Receptor or signal transduction					
First use of an agent in humans	27	742	3.8	853	1 (0.12)
All other trials	92	1621	8.0	1892	12 (0.63)
Antiangiogenesis					
First use of an agent in humans	8	200	7.0	228	0
All other trials	16	270	7.0	345	1 (0.29)
Gene transfer					
First use of an agent in humans	0	0	0	0	0
All other trials	8	92	3.3	112	0
Vaccine					
First use of an agent in humans	23	520	3.1	564	0
All other trials	5	54	1.9	88	0

\* The overall response rate includes both complete and partial responses.

† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

sponse having been achieved in an additional 34.1 percent of participants. Rates of toxicity-related death have not increased over time, and more than 85 percent of participants had no grade 4 toxic events. As compared with other reviews, these data suggest that participants may benefit more from current phase 1 oncology trials than previously believed.

A recent review of single-agent trials showed that there was a decrease in tumor-response rates over time,<sup>13</sup> which was attributed to the use of newer, more specific agents and changes in trial design. In our review, response rates per year varied without a clear pattern. When these rates were grouped in three-year intervals, there was a decrease in complete or partial responses from 1991 to 2002 but an increase in rates of stable disease. Little change in the benefit to participants over time was seen when response rates were grouped with stable disease.

In our view, it is inaccurate to refer to phase 1

oncology studies as if they are all similar to one another. Nearly half of the trials we studied included at least one FDA-approved agent, and less than half included chemotherapeutic agents. Different types of phase 1 oncology studies are associated with very different response rates. For instance, the response rate among patients who were treated with immunomodulators was 13.6 percent, yet the rate was just 3.0 percent for patients treated with vaccines. Trials that included one or more FDA-approved anticancer agents showed higher response rates than did those involving only investigational agents. For these reasons, it may be misleading to summarize phase 1 oncology trials with the use of a single response rate.

Risk, as measured by toxicity-related death rates and grade 4 toxic events, also varies according to the type of trial. The average toxicity-related death rate for trials of cytotoxic chemotherapeutic agents was 0.67 percent but just 0.07 percent for those in-

**Table 5. Response Rates and Deaths from Toxic Events in Phase 1 Oncology Trials, According to Whether FDA-Approved Agents Were Used.**

Trial	No. of Trials	No. of Patients Assessed for Response	Overall Response Rate*	No. of Patients Assessed for Toxic Events	Deaths from Toxic Events†
			%		no. (%)
Single investigational agent	193	4580	4.2	5227	18 (0.34)
Multiple investigational agents	54	1203	7.1	1352	5 (0.37)
Combination of investigational and FDA-approved agents	184	3827	15.8	4431	29 (0.65)
FDA-approved agents only	29	792	27.4	925	6 (0.65)

\* The overall response rate includes both complete and partial responses.

† Deaths include all those reported as possibly, probably, or definitely related to the treatment.

volving immunomodulators, and no toxicity-related deaths were reported in gene-transfer or vaccine trials. Grade 4 toxic events were more common in chemotherapy trials, especially those involving multiple agents, than in all other trials. Trials of FDA-approved drugs, which evaluated the safety of higher doses or combinations of drugs, appeared to be associated with the highest rates of toxicity (a death rate from toxic events of 0.65 percent, vs. 0.35 percent for other trials) but also had the highest overall response rate (17.8 percent, vs. 4.8 percent for other trials). Overall, newer, nonchemotherapeutic agents are associated with lower rates of toxic events.

Classic phase 1 studies of single investigational chemotherapeutic agents, which were the only trials included in previous reviews, showed an overall response rate of 4.4 percent and a toxicity-related death rate of 0.57 percent. These rates are almost identical to those previously reported.<sup>8–16</sup> In this study of trials sponsored by the Cancer Therapy Evaluation Program and initiated between 1991 and 2002, classic phase 1 trials accounted for only 22 percent of all participants. Similarly, the testing of investigational agents never before studied in humans is commonly thought of as a defining characteristic of phase 1 oncology trials. In our review, these first-in-human studies represented less than a quarter of phase 1 studies and enrolled less than a third of participants. Response rates, but also toxicity-related death rates, are lower in studies that test agents for the first time in humans than in those that do not test agents for the first time.

When the risks and benefits associated with phase 1 oncology trials are weighed, factors other than response rates and toxicity should be taken

into account. Investigational treatments may have clinically meaningful benefits — reduced pain, increased appetite, energy, and activity, weight gain, reduced fatigue, or increased ability to perform daily activities.<sup>20,25,26</sup> Some of these benefits might accrue from research participation itself; for some persons, contributing to research and potentially helping future cancer patients may also be an important benefit.<sup>27</sup> At the same time, participation in research may involve additional burdens: multiple visits or long hours at the clinic, unpleasant procedures, and the possible financial costs associated with participation in research studies.<sup>28</sup>

This study has several limitations. First, our data are derived only from trials sponsored by the Cancer Therapy Evaluation Program. Although the program is a major sponsor of phase 1 oncology trials in the United States<sup>29</sup> and the use of data from the program avoids publication bias, any differences that might be found in the phase 1 trials with other sponsors have not been captured. It is possible that the response rates associated with trials of promising agents sponsored by pharmaceutical companies could be higher than those reported here. Second, for trials involving gene transfer, the findings should be interpreted with caution because of the small number of trials and the possibility that outliers influenced the data. Finally, our reporting of grade 4 toxic events is limited. Patient-specific data on grade 4 toxic events came from one monitoring source, which, although it includes some first-in-human trials, is generally used to monitor later phase 1 studies and may not be entirely representative of phase 1 oncology studies. Moreover, the data on grade 4 toxic events are reported without distinguishing among the types of toxic events.

Since not all toxic events have similar medical consequences, evaluation of the risks in phase 1 trials should include both the types and the frequency of events experienced by participants.

In conclusion, reliance on a single estimate of the response rate or the toxicity-related death rate for phase 1 oncology trials is misleading, since rates of response and toxicity vary according to the type of trial. Potential participants and their families, oncologists, investigators, members of institutional review boards, ethicists, and others interested in weighing the risks and benefits of phase 1 studies and making decisions about their acceptability should be aware of the complexity and variety of such trials, know the details about the trial

they are considering, and carefully evaluate all relevant risks and benefits.

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#### REFERENCES

- Lipsett MB. On the nature and ethics of phase I clinical trials of cancer chemotherapies. *JAMA* 1982;248:941-2.
- Kodish E, Stocking C, Ratain MJ, Kohrman A, Siegler M. Ethical issues in phase I oncology research: a comparison of investigators and institutional review board chairpersons. *J Clin Oncol* 1992;10:1810-6.
- Agrawal M, Emanuel EJ. Ethics of phase 1 oncology studies: reexamining the arguments and data. *JAMA* 2003;290:1075-82.
- Miller M. Phase I cancer trials: a collusion of misunderstanding. *Hastings Cent Rep* 2000;30:34-43.
- Idem*. Phase I cancer trials: a crucible of competing priorities. *Int Anesthesiol Clin* 2001;39:13-33.
- Emanuel EJ. A phase I trial on the ethics of phase I trials. *J Clin Oncol* 1995;13:1049-51.
- Markman M. The needs of science vs the needs of patients: ethical concerns in cancer clinical trials. *Cleve Clin J Med* 2003;70:1008-9, 1013-4, 1016.
- Itoh K, Sasaki Y, Miyata Y, et al. Therapeutic response and potential pitfalls in phase I clinical trials of anticancer agents conducted in Japan. *Cancer Chemother Pharmacol* 1994;34:451-4.
- Estey E, Hoth D, Simon R, Marsoni S, Leyland-Jones B, Wittes R. Therapeutic response in phase I trials of antineoplastic agents. *Cancer Treat Rep* 1986;70:1105-15.
- Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. *Ann Oncol* 1990;1:175-81.
- Bachelot T, Ray-Coquard I, Catimel G, et al. Multivariable analysis of prognostic factors for toxicity and survival for patients enrolled in phase I clinical trials. *Ann Oncol* 2000;11:151-6.
- Han C, Braybrooke JP, Deplanque G, et al. Comparison of prognostic factors in patients in phase I trials of cytotoxic drugs vs new noncytotoxic agents. *Br J Cancer* 2003;89:1166-71.
- Roberts TG Jr, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA* 2004;292:2130-40.
- Sekine I, Yamamoto N, Kunitoh H, et al. Relationship between objective responses in phase I trials and potential efficacy of non-specific cytotoxic investigational new drugs. *Ann Oncol* 2002;13:1300-6.
- Smith TL, Lee JJ, Kantarjian HM, Legha SS, Raber MN. Design and results of phase I cancer clinical trials: three-year experience at M.D. Anderson Cancer Center. *J Clin Oncol* 1996;14:287-95.
- Von Hoff DD, Turner J. Response rates, duration of response, and dose response effects in phase I studies of antineoplastics. *Invest New Drugs* 1991;9:115-22.
- Annas GJ. The changing landscape of human experimentation: Nuremberg, Helsinki, and beyond. *Health Matrix Clevel* 1992;2:119-40.
- Dent SF, Eisenhauer EA. Phase I trial design: are new methodologies being put into practice? *Ann Oncol* 1996;7:561-6.
- Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. *J Clin Oncol* 2000;18:684-92.
- Chen EX, Tannock IF. Risks and benefits of phase 1 clinical trials evaluating new anticancer agents: a case for more innovation. *JAMA* 2004;292:2150-1.
- Ansher SS, Scharf R. The Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute: industry collaborations in new agent development. *Ann N Y Acad Sci* 2001;949:333-40.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
- Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205-16.
- Cancer Therapy Evaluation Program. Common Toxicity Criteria (CTC), version 2.0. Bethesda, Md.: National Cancer Institute, 1999. (Accessed February 14, 2005, at <http://ctep.cancer.gov/reporting/ctc.html>.)
- Markman M. Partial responses to antineoplastic drug therapy: what do they mean? *J Cancer Res Clin Oncol* 1992;119:5-6.
- Shanafelt TD, Loprinzi C, Marks R, Novotny P, Sloan J. Are chemotherapy response rates related to treatment-induced survival prolongations in patients with advanced cancer? *J Clin Oncol* 2004;22:1966-74.
- Daugherty CK, Siegler M, Ratain MJ, Zimmer G. Learning from our patients: one participant's impact on clinical trial research and informed consent. *Ann Intern Med* 1997;126:892-7.
- Goldman DP, Berry SH, McCabe MS, et al. Incremental treatment costs in National Cancer Institute-sponsored clinical trials. *JAMA* 2003;289:2970-7.
- Takimoto CH. Anticancer drug development at the US National Cancer Institute. *Cancer Chemother Pharmacol* 2003;52: Suppl 1:S29-S33.

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