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Purpose and Benefits of Early Phase Cancer Trials: What Do Oncologists Say? What Do Patients Hear?

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Abstract

Cancer patients overestimate benefits of early phase trials but studies have not reported what oncologists say to patients about trials. We audiotaped oncologists talking to cancer patients about Phase I or II trials and interviewed patients about the purpose and expected outcomes of trials presented to them. Oncologists gave mixed messages, saying Phase I trials measure safety and dosing, yet referring to trials as treatment with uncertain therapeutic effects. Seventeen percent of Phase I respondents said the trial's purpose related to safety/dosing ($p = 0.017$); 17% of Phase I respondents said the purpose was "to cure my cancer." Patients may find it important to believe trials offer significant benefit. Oncologists, while respecting patients' hopes, should be precise in their language, particularly regarding Phase I trials, distinguishing early stages of research from treatment.

Keywords

cancer; ethics; research; informed consent; Phase I; Phase II; therapeutic misconception

Patients with cancer enter clinical research for many reasons, including hope, altruism, or doctors' recommendations (Advisory Committee, 1995; Daugherty et al., 1995; Daugherty, Banik, Janish, & Ratain, 2000; Cassileth, Lusk, Miller, & Hurwitz, 1982; Moore, 2001; Schutta & Burnett, 2000). Many patients have difficulty distinguishing research from clinical care, or

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view participation solely as therapy (Joffe, Cook, Cleary, Clark, & Weeks, 2001; Riecken & Ravich, 1982; Rodenhuis et al., 1984; Kass, Sugarman, Faden, & Schoch-Spana, 1996). Further, patients who join early phase clinical trials (EPCTs—defined here as Phase I or Phase II trials) may overestimate the likelihood of direct personal benefit (Daugherty et al., 2000; Cheng et al., 2000; Tomamichel et al., 2000).

Many commentators have discussed the ethical challenges presented by Phase I cancer trials, which are designed to find a safe dosage, to identify how a cancer agent should be given, and/or to observe how the agent affects the human body (National Cancer Institute, accessed July 2008). Because these studies often are the first time the agent is given to a human or the first time they are given for the particular type of cancer, the doses provided often are low and considered "subtherapeutic." As such, since the drugs given generally are not expected to have much clinical effect, cancer patients generally are eligible only if efficacious treatment options are not otherwise available to them. Thus, patients recruited for Phase I cancer trials generally are those who have exhausted other treatment options and often are nearing the end of their lives. Ethics tensions are raised in these trials if patients, desperate for an intervention that might work, do not appreciate that the chance of personal clinical benefit is modest, at best (von Huff & Turner, 1997; Estey et al., 1986; Smith, Lee, Kantarjian, Legha, & Raber, 1996). Agrawal and Emanuel, however, suggest that patients may well understand the limits of benefit, but may want to fight aggressively until the end, and/or that enrolling may appropriately reflect patients' values (Agrawal & Emanuel, 2003). While there is growing literature on patients' understanding of Phase I trials, there are quite limited data on what oncologists say to patients during recruitment. Jenkins et al. documented oncologists' statements to patients being recruited for Phase III trials (Jenkins, Fallowfield, Souhami, & Sawtell, 1999), and Brown et al. analyzed seven transcripts from either Phase II or III trials (Brown, Butow, Butt, Moore, & Tattersall, 2004). We are aware of no studies documenting what oncologists say to patients regarding EPCTs and, in particular, how this relates to patients' understanding of EPCTs. Further, there are scant data regarding patients' understanding of Phase II trials.

This paper provides data from two U. S. medical centers on how oncologists explain Phase I and Phase II trials to patients. It also provides data on what cancer patients understand to be the purpose and benefits of these trials when enrolling, and several weeks later. This study builds on existing literature by situating patients' beliefs in light of what they are actually *told* by oncologists, and by including both Phase I and Phase II trials.

Methods

STUDY SAMPLE

Oncologists at the Johns Hopkins Medical School and Duke University Medical Center were eligible if they referred patients to EPCTs, were willing to have appointments audiotaped, and provided consent.

Patient-subjects were eligible if referred by participating oncologists. Oncologists referred patients whose medical history suggested EPCT participation might be discussed that day. Oncologists asked eligible patients' permission for our staff to audiotape appointments; written consent for surveys and interviews was requested later by our staff, when these instruments were administered. Johns Hopkins and Duke University Institutional Review Boards approved this study.

SOURCES OF DATA

Audiotapes—Medical appointments were taped when oncologists and patients discussed possible participation in an EPCT. We call these "options discussions."

Patient Surveys—After the "options discussion," we sought patients' written consent for a survey and possible in-depth interview. The 45–60 minute structured survey elicited beliefs about purpose, expected benefits and risks, intended decision, and attitudes. Some items were drawn from previous studies (Sugarman et al., 1998; Roter et al., 1977). Instruments were reviewed at two meetings with oncologists. The survey was administered after the clinical appointment or, if patient-subjects preferred, within the next week by telephone. Patients who had not yet decided whether to join an EPCT were re-contacted 1–2 weeks later. All participants were asked permission for a follow-up survey, 13 weeks after baseline. This interval was shortened to 5 weeks as many participants had died or were too sick to respond at 13 weeks.

In-depth Patient Interviews—Every third survey respondent was asked to complete an in-depth interview. If a survey respondent refused the in-depth interview, the next respondent was asked. In-depth interviews covered similar topics to surveys but were longer and all questions were open-ended. Interviews were conducted in person or by telephone, approximately one week after the survey and lasted 1–1½ hours.

Data on Trials—In the survey, patient-subjects were asked to describe or name the trial or study drug just offered so our project staff could retrieve blank copies of the appropriate study's consent forms. Consent forms were used to classify trials by phase. Respondents were classified as Phase I if they were offered participation in Phase I trials *only* and classified as Phase II if offered enrollment in at least one Phase II trial. Anyone offered enrollment in at least one Phase III trial and those for whom trial phase could not be determined were excluded from analyses by phase.

Analysis

Audiotapes—Options discussions were recorded. We expected we would reach informational redundancy after analyzing only a subset of tapes, and thus made an initial decision to transcribe, code, and analyze approximately one-third of options discussions. Tapes were chosen for transcription and qualitative analysis if the patient-subject also had completed a survey; further, it was a goal for analysis to include tapes from all participating oncologists. Once satisfying those criteria, tapes were selected randomly for analysis. The same coding scheme was used for in-depth interviews and options discussions (below). A subset of transcripts was hand-coded by two staff members and discrepancies were resolved. Remaining transcripts were hand-coded by one investigator, reviewed by the other, and entered into NUD*IST qualitative software (QSR International Pty Ltd N6: Melbourne, Australia) for electronic coding to facilitate further analysis. Our initial code book significantly followed the domains of interest to the study including, for this paper, those related to study purpose and potential study outcomes. Subcodes were developed iteratively from the large body of text related to the large domains (e.g., the large body of text on study purpose and the large body of text on study outcomes) by the two investigators responsible for qualitative coding. Subcodes were listed based on the different types of purposes oncologists mentioned during discussions (e.g., scientific purpose; purpose related to helping the patient clinically, etc.) and on the different types of outcomes they mentioned during discussions (e.g., outcomes of value to other patients; outcomes relevant to the patient him or herself, etc.).

Quantitative Survey Data—Univariate, descriptive statistics were generated for all survey variables. Bivariate analyses (using chi-square statistic) tested the association between

demographic variables and dependent variables of interest (e.g., perceived study benefit, purpose, reasons for decision) and between trial phase and relevant outcomes.

In-depth Interviews—Interviews were transcribed, read in their entirety, and hand coded. The coding scheme was based on interview questions and themes that emerged from data. Transcripts were double coded, discrepancies resolved, and codes entered electronically using NUD*IST.

Results

Response Rates

Twelve oncologists agreed to have options discussions between themselves and their eligible patients audiotaped; one oncologist refused. All oncologists had been investigators on an EPCT and ten were male. Eighty-four patients agreed to have appointments taped; none refused. Four proved ineligible and three later refused to have their tape used, leaving 77 eligible "options discussions"; 29 tapes were transcribed for analysis. Seventy-five patient-subjects completed surveys; two refused to complete a survey; 56 (75%) completed follow-up surveys. Follow-up survey respondents had higher education than those lost to follow-up; 34% of the follow-up group, but only 5% of those lost to follow-up, had graduate education ($p = 0.002$). Also, 50% of follow-up respondents had incomes >$80,000, compared to 12% lost to follow-up ($p = 0.14$). Twenty-seven patient-subjects agreed to in-depth interviews, and two refused. Table 1 shows demographic data, and Table 2 shows the background characteristics of the participating oncologists.

Of the 75 survey respondents, 5 patient-subjects had been offered a Phase III or Phase II/III trial, and for 5 patient-subjects there was insufficient information to determine the phase of trial offered. Thus 10 survey respondents were excluded from analyses by phase. Of the remaining 65, 30 patient-subjects had been offered enrollment in Phase I trials and 35 had been offered enrollment in Phase II.

OPTIONS DISCUSSIONS

Phase I—Of the 29 options discussions transcribed and analyzed, 18 related exclusively to Phase I trials. In these, almost all oncologists mentioned a purpose related to safety or dosing, that the drug was early in testing, and/or that many investigational drugs never come to market. Some oncologists were quite candid about the purpose of EPCTS:

> Now I would be careful to emphasize that this is a Phase I study, so the purpose of what we're doing right now is to try and determine what the ideal dose of the treatment is. From there we take that dose and we go on to do a study where we try to determine whether it's actually effective or not (Interview #34, Phase I).

The majority of oncologists, however, while describing the need to measure safety and dosing, quickly moved to discuss at much greater length the therapeutic intent of the trial. One oncologist said,

Now we do have experimental treatments and these are new treatments that we think are good ideas that … are too new to have any proof…. So if you join any one of these protocols, you're in the process of helping us figure out if they work (Interview #85, Phase I).

Across all conversations, words like "therapy" and "medicine" were used, words often associated with clinical practice rather than research. An oncologist described the trial's intervention by saying, "It is unproven therapy … but if you're somebody … who doesn't need to be shown the rainbow in order to undergo treatment … then you would be an ideal

candidate" (Interview #15, Phase I). Several oncologists suggested that the research question being examined was one of *efficacy*. One oncologist said, "So I can't tell you for sure how well this medicine will work for you, if at all. It does look promising enough that we're probably going to be doing more studies with this medicine, particularly with this kind of cancer" (Interview #13, Phase I).

Reinforcing perhaps a therapeutic intent, the majority of oncologists explained the process for EPCTs was for the patient to enroll for 1–2 months and then see "how well the drug was working."

> The usual way we go through this is to see whether or not it's helping you. We look at the CT scan about every two months. If things look like they're helping, we keep going. If it looks like the cancer is growing despite the treatment, clearly we don't want to continue that, and we'll sort out what other options make sense (Interview #26, Phase I).

Indeed it was striking that many more oncologists described that participating would be stopped if the cancer was progressing than if side effects could not be tolerated. In a small number of discussions, the investigational nature was not discussed, and oncologists simply implied the trial was another treatment option. One introduced a Phase I trial as, "I have another medicine that I think would be very suitable, possibly something that works for you" (Interview #82, Phase I).

In several discussions, the suggestion was offered that taking action is preferable to taking none. "It's better than doing nothing. It's, at least, the treatment is worth trying," said one (Interview #34, Phase I), while another said, "At least we've done everything we can" (Interview #04, Phase I).

Phase II—As one might expect, Phase II options discussions differed in nature somewhat from Phase I discussions. To varying degrees, all oncologists discussed the question of whether the drug offered would work against the patient's cancer. What varied was the degree to which uncertainty of benefit was stressed, and how promising the investigational drug was described as being. At one end, one oncologist said, "Chemotherapy is basically poison. The idea behind it is that hopefully it poisons the cancer more than it poisons you but you might say, it's no proof that it can help, why do it?" (Interview #38, Phase II) At the other extreme, an oncologist voiced:

> I've had patients taking this medicine for months or in excess of that. These are patients who are having a rapidly progressing tumor, all of a sudden, they're taking this medicine, and the tumor stops (Interview #12, Phase II).

Several oncologists raised examples of other drugs that eventually proved successful, perhaps suggesting by implication potential long-term effectiveness of the intervention in question:

> They already have a clue that it does have some activity so, for example, Taxol started out and basically was in the same ball park where they had some activity, and they did Phase II studies … and eventually it has worked its way up to be one of the first drugs they give (Interview #36, Phase II).

SURVEY DATA

After discussions with their oncologists about possibly joining a Phase I or Phase II trial, patient-subjects were asked on our survey about the purpose of the "investigational study" just offered. The question about purpose was open-ended, and interviewers coded responses. If the patient-subject identified several purposes, multiple responses were coded. Of the 65 survey respondents with trial phase data, 54% said the purpose was to see if the drug works, and 11%

said the purpose was to cure their cancer. Responses differed by phase of trial offered. Those offered Phase II enrollment were significantly more likely than those offered Phase I to say the trial's purpose was to see if the drug works (70% vs. 40%; $p = 0.016$). By contrast, those offered only Phase I enrollment were significantly more likely to mention dosing than those offered Phase II (17% vs. 0%, $p = 0.017$), but those offered Phase I also were more likely to mention "cure" as the trial's purpose (17% vs. 3%, $p = 073$) (Table 3). Overall, 12% of respondents mentioned *only* purposes related to safety or dosing (and did not mention a purpose related to benefit, working, or effectiveness), while 71% mentioned purposes related to efficacy or benefit only (Table 4). Phase II respondents were significantly more likely to mention efficacy/benefit purposes than Phase I respondents ($p = 0.039$), although the majority of patient-subjects in both groups believed the trial's purpose related to efficacy or benefit.

IN-DEPTH INTERVIEW DATA

Eighteen of 27 respondents described the trial's purpose on in-depth interviews. Five (three Phase I; two Phase II) described a purpose related to side effects or dosing. Ten more (five Phase I, three Phase II, two phase unknown) suggested the trial was research or a scientific endeavor. For example, one said, "They know about the rat, but they don't know about the human" (Interview #13, Phase I). Twelve (six Phase I, four Phase II, two unknown) of 18 respondents mentioned purposes related to efficacy, although many also mentioned scientific purposes. Three (two Phase I, one unknown) explicitly answered the question about purpose as, "to find a cure." Others more generally referred to efficacy, saying the trial was to stop or slow tumor growth, or learn about "effectiveness."

Enrollment Decision

SURVEY DATA—In the survey, 68% of respondents planned to join the EPCT, 11% planned to decline, and 22% were undecided. Ultimately, 81% decided to enroll. Those offered Phase I or Phase II trials were equally likely to enroll. Among those age 60 or older, 92% reported being likely to join compared with 69% of those < 60 ($p = 0.14$).

Table 5 shows answers to an open-ended question about the patient-subjects' primary reason for enrolling. Overall, 58% said the investigational treatment has promise and 25% said they wanted to contribute or be part of the cure. Participants then were provided possible reasons for enrolling and asked if each contributed a lot, a little, or not at all to their decision. Responses did not differ by phase of trial offered. Those 60 or older were more likely to say they joined because the physician-researcher thought it would be a good idea (63% vs. 35%, $p = 0.049$), because their families thought it would be a good idea (55% vs. 25%, $p = 0.036$), and because it was a way to advance medical science (60% vs. 25%, $p = 0.015$). Seven respondents overall decided not to join; reasons offered on the survey did not explain why they declined.

IN-DEPTH INTERVIEW DATA—Most in-depth interview respondents, regardless of phase, said they enrolled because they thought it would improve their chance of survival. A few cited particular events for which they wanted to stay alive, such as a child's graduation. Several said the particular approach taken in the EPCT sounded promising, using language like "cutting edge" and suggesting newer meant better. One specifically said his immune system needed something "more than standard treatment" and said, "I would have looked until I found a clinical study" (Interview #26, Phase I). Four said they had few choices.

> At this stage of the game, this far along, you don't have a lot of options. You sort of look for whatever seems to be the best right now. And hopefully it is going to help you and other people. It's not a lot of options (Interview #71, Phase II).

Twenty of the 27 in-depth interview respondents mentioned altruism, although most also stated, explicitly, that this was secondary to the possibility of personal benefit. Mentioning altruism

did not differ by phase of trial. Respondents often said they were aware and pleased they were helping others, but this was not what *motivated* them to join. One exceptional patient-subject considered enrollment a duty: “So far cancer, you know they just aren’t getting it, and it’s killing a lot of people. Now I have it and so now it’s my duty as a human being to participate in whatever area that I can” (Interview #46, Phase II).

Four respondents, all offered Phase I trials, described their *refusal* of enrollment. All believed the trial would be no better, or believed the marginal benefit was not worth additional inconvenience or unknown effects. One said, “I just didn’t think that the possibility of 5% was worth being that much sicker and having to travel two and a half hours in each direction to be that much sicker” (Interview #48, Phase I). Two described wanting to avoid the additional burden on family who would be responsible for transporting them to study visits.

Expectation of Benefit from Enrollment

SURVEY DATA—Survey respondents were asked what outcome was likely for “most cancer patients” who enroll in EPCTs and, later, what they expected from their *own* participation (Table 6). Specifically, patient-subjects were asked to complete the sentence “Most cancer patients who enroll in investigational studies like the one presented to you...” with one of the following five answers: “have their cancer get worse; experience no change in their cancer; experience some short-term improvement in their cancer; experience some long-term improvement in their cancer; or experience a complete cure of their cancer.” Then, later in the survey, they were asked to complete a similar sentence about themselves: “While participating in the investigational study, do you expect …” and respondents were given five response choices: “your cancer to get worse; to experience no change in your cancer; to experience some short-term improvement in your cancer; to experience some long-term improvement in your cancer; or to experience a complete cure of your cancer.”

The majority (60%) of those who enrolled said that they, personally, expected long-term benefit or cure, while fewer (33%) believed that “most cancer patients” would have these benefits. There were no differences in what benefit subjects personally expected by phase. None of the trial refusers believed that “most cancer patients” would have long-term benefit or cure from enrollment.

At follow-up, 30% said their cancer got better or tumors shrank, while 45% said they did not know the benefits yet (Table 7). There was no difference by phase of trial in saying their cancer got better. Twenty-five percent (11 of 44) were no longer on trial at follow-up, citing tumor progression or bad reactions. There was no difference by phase in likelihood of no longer being enrolled.

There were few significant differences between responses at baseline and follow-up. Comparing only those participants completing both baseline and follow-up surveys, there were no differences in reports of why they joined or beliefs about whether the study’s purpose related to safety or dosing. Participants *were* significantly less likely to report at follow-up that the trial purpose related to efficacy (whether the drug works, whether the drug can help them). At baseline, 68% of respondents gave a purpose related to efficacy, compared to 34% of those at follow-up ($p < 0.001$).

IN-DEPTH INTERVIEW DATA—Twenty-two follow-up *in-depth* interviews were completed; 13 described clinical outcome. Five reported clinical benefit (stabilization or reduction of tumors), four said they had progression, and four said it was too early to tell. Many said interacting with research staff was itself a great benefit, and one mentioned interacting with other patients. Two referred to the benefit of taking action:

> I guess what I'm doing with these protocols … is reaffirming to myself that if I do die, which is very likely, that I had done everything in my power…. Whereas, if I just died and said, boy, I should have really went on that test, you know, I would have never known.

Two mentioned helping others, or being a "contributor". One said, "It didn't help. But I'm glad I went through it anyway, 'cause the negative finding is good for their research as well as the positive finding."

In-depth interview responses conveyed more ambivalence, uncertainty, or sophistication than responses to survey data. For example, compared to survey data, where the majority of respondents said they expected long-term benefit or cure, in-depth interview respondents often said that they hoped for reduction in tumor growth. One patient-subject who said "cure" on the survey suggested a broader perspective in the in-depth interview:

> The reason is … to see if we can put this in remission or find a cure for it, maybe not in my lifetime, but the purpose of doing this study is maybe it would help someone else in their lifetime (Interview #66, Phase I/II).

Another said early in the in-depth interview that the purpose was to kill the cancer, find a cure, and "It's going to work." Later, however, this same participant was more tempered: "We don't know. He didn't know. I don't know. You don't know. Only God knows" (Interview #21, Phase I). One subject said that he did not ask details about benefit because he wanted to remain optimistic, suggesting that the truth might dampen his hopes. Some explicitly cited oncologists telling them that benefit was uncertain: "I was just told that it may work, it may not" (Interview #18, Phase I). A few in-depth interview respondents continued the theme that newer was better, and one reasoned that benefit from Phase I participation is greater than Phase II because Phase I approaches are even newer.

Discussion

The survey component of this study replicates findings from previous research that suggests that patients who join Phase I cancer trials have unrealistically high expectations for clinical benefit from enrolling. This study contributes further to this literature in three ways. First, by using a mixed-methods approach, our data reveal that patient-subjects have a more nuanced understanding of how much clinical benefit might be expected from enrollment than suggested by our and others' survey data alone. Second, our data demonstrate a difference in what patients recruited to Phase I vs. Phase II trials understand about the purpose of EPCTs. Third, and importantly, by recording oncologists' discussions with patients, this study documents that oncologists give mixed messages about the purpose and benefits of EPCTs. Trials were described as investigations testing substances for the first time in humans to see whether they were safe, and yet patient-subjects were then told that their clinical status would be checked to see if the cancer was progressing and to see whether the drug was "working." Further, while oncologists said in most discussions that Phase I studies were being conducted in order to determine the reasonable tolerated dose for a drug, they generally did not explain that, at least in traditional Phase I trials, most patients receive subtherapeutic doses (Miller, 2000). Even oncologists who were most conservative regarding clinical benefit never directly said it was highly *unlikely* the patient would benefit significantly from the investigational drug. Similarly, none of the oncologists in this sample ever gave patients statistics or numerical ranges about expected clinical benefit. This is despite data showing that cancer patients believe benefit to be higher when oncologists provide trial information using non-quantitative terms such as "somewhat likely" or "possible" than when information is provided numerically (Siminoff & Fetting, 1989).

In the survey component of this study, only 17% of patient-subjects offered participation in a Phase I trial named a purpose related to dosing, safety, or side effects, while 60% reported a trial purpose related to efficacy. Further, 17% of Phase I respondents believed that the trial promised a complete cure. While other investigators have documented that patients join Phase I trials believing that their purpose is related to efficacy, including possible cure (Daugherty et al., 2000), cure is highly unlikely for Phase I trials. Qualitative data, however, indicate that patient-subjects' expectations are more tempered. Only two patient-subjects spoke in qualitative interviews about the trial leading to cure, with most instead voicing *hope* that the trial might slow tumor growth or prolong life a few months. Some qualitative responses were nuanced, suggesting that the patient-subjects' hope for cure was perhaps a hope for the trajectory of this *type* of research, rather than necessarily a cure for themselves from joining the specific trial at hand. Several acknowledged that, if the trial did not help them, it might help future patients. These themes of hope and altruism also were found in the qualitative interviews in a British study (Cox, 1999). Our respondents typically voiced differing beliefs within the same interview, declaring at one point the trial would work, and later saying, "only God knows." The qualitative responses from the small number of refusers also were important. Their comments that joining the trial did not seem to them to be a better option suggest that they *did* understand the trial's limited benefit and, indeed, further suggests that patients' differing values allowed them, importantly, to make different decisions. Thus, in qualitative interviews, where patient-subjects had the chance to discuss topics at length, the beliefs about significant clinical benefit voiced by so many respondents started to sound more like a hope than an expectation. On surveys, however, where patient-subjects were forced to provide one response to what they thought would happen, they articulated an extremely positive outcome. This finding raises the question of whether previous studies that have documented inflated patient-subject expectations of benefit on surveys might have yielded different results if they had used a mixed-methods approach. Agrawal and Emanuel have also noted that a survey questions asking patients what they believe to be the "purpose" of a trial may be interpreted by patients instead to be asking why they personally decided to join the trial (Agrawal & Emanuel, 2003). A hope for benefit, in this light, becomes a more coherent response.

The differences in patient-subjects' responses by phase of trial seen in this study also were revealing. While only a small minority of patient-subjects—17%—mentioned that the purpose of the Phase I study they were offered related to safety or dosing as opposed to active treatment, it is nonetheless reassuring that more patient-subjects recruited to Phase I trials stated this type of purpose than did those recruited to Phase II. This suggests that the oncologists *did* discuss this feature of Phase I trials, at least to some extent, and/or with at least some of their patients.

Argawal and Emanuel's commentary on ethics and Phase I cancer trials suggested that it is not unreasonable for patients facing serious illnesses to make different assessments of the risks they are willing to take than healthy individuals would make. Thus, patients' seemingly irrationally high estimates of clinical benefit from EPCTs may simply reflect their hopes, and their decision to join what seems to outsiders to be an activity with a particularly gloomy risk-benefit balance may nonetheless seem favorable to them (Agrawal & Emanuel, 2003). Our recordings of discussions between oncologists and patients reveal that oncologists may share some of these same values. Oncologists, for example, suggested to several patients that taking action is better than doing nothing. And while such values may have emerged from empathically experiencing the hopes and fears of their very sick patients, the medical literature suggests that some physicians have difficulty giving bad news to patients (Buckman, 1992). Furthermore, compassionate oncologists may be voicing their *own* hopes that their patients' conditions will improve. Some commentators have suggested that patients' and oncologists' optimism about trial benefit is beneficial itself. The published literature is inconsistent concerning whether optimism improves clinical outcomes (Buckman, 1992; Schofield et al., 2004; Scheier & Carver, 1987; Taylor, Kemeny, Reed, Bower, & Gruenewald, 2000;

Mondloch, Cole, & Frank, 2001). One recent article urges oncologists to encourage patients to "hope for the best, and prepare for the worst" (Back, Arnold, & Quill, 2003).

Research Agenda

This study documents areas where patients may misunderstand the nature of clinical research, particularly early phase trials. Future work is needed to design and test interventions, in real life clinical settings, to enhance patients' understanding of the purpose and potential outcomes of Phase I and Phase II trials. Related, additional work should be conducted to examine what oncologists in other settings say to cancer patients about the different stages of clinical research and the degree to which this relates to patients' own understanding.

Best Practices and Educational Implications

This study had several limitations. It was conducted at two academic referral hospitals, and data may not be generalizable to other settings. Nonetheless, academic medical centers are where significant proportions of oncology EPCTs are conducted (Horstmann et al., 2005). Second, although one of the largest studies of EPCTs to date, our sample size was insufficient to perform certain subgroup analyses. Generalizability may be further limited since most patient-subjects were white, with good incomes, and the number of oncologists was small. Audiotaping may have caused clinicians, who underwent informed consent for our study, to be more likely to mention scientific purposes of early phase trials; if anything, however, this would make our findings conservative. Respondents may have understood the meaning of important questions differently than we intended. While we were interested in what patient-subjects understood to be the purpose of EPCTs, respondents may have interpreted this question instead to be asking them why they joined an early phase trial. It is a further limitation that we did not also explore qualitatively with oncologists their own views about the purpose and expected outcomes of these trials. Related, there are a variety of other factors that may be associated with understanding and patients' beliefs about trials, including their prognosis, the type of cancer they have, how much previous knowledge or experience they have with clinical research, and their own personalities. None of these were explored in these analyses. Finally, an important limitation is that, while we determined the phase of trial offered to most patients in this sample, we did not determine the nature of the trial. Recent publications have demonstrated that clinical response differs based on the number of tumor types treated, source of funding, route of administration, and whether the trial includes FDA-approved substances (Roberts et al., 2004). Indeed, one review suggests that first–in-human studies are least likely to provide clinical response, but that only 25% of Phase 1 trials now are of this sort (Horstmann et al., 2005).

In this sample from two large medical centers, oncologists were candid about the purpose of EPCTs but spent significantly more time in discussions with cancer patients using language related to potential treatment efficacy and how it is determined whether "treatments" might be "working." We heard immediately afterwards from patient-subjects that they assumed that early phase cancer trials are designed to test the efficacy of the investigational treatment, although in-depth discussion with patients revealed a more tempered expectation of personal benefit. While patients at the end of life will legitimately hold a variety of values and views about risks, preferences, and choices of intervention, oncologists should pay attention to the language they use when discussing trial participation with this group of patients. It may be useful for oncologists to provide objective information on trials' likely outcome to patients and remind patients that participating primarily contributes to the care of future patients. Every oncologist-patient dyad will and should have its own dynamic, and each trial has a slightly different profile in terms of what is already known about the drug under investigation. Patients, through informed consent, can and should make whatever decisions are important to them, and

yet they should expect that the information provided to them by their oncologist is accurate and complete. Taking care about how and what we say to patients who may be near the end of their lives is essential to the enormous trust cancer patients place in the physicians who care for them.

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TABLE 1

Demographic Characteristics of Patient-Subjects Completing Baseline Questionnaire.

Characteristic	Percent
Sex	
Male	67
Race	
White	87
African-American	10
Other	3
Education	
Some high school or high school graduate	28
Some college or college graduate	43
Some post graduate or graduate degree	25
Employment	
Full time	19
Part time	9
Retired/Not employed	72
Income	
<$20,000	10
$20,000–39,999	16
$40,000–59,999	21
$60,000–79,999	13
$80,000	40
Self-Rated Health Status	
Excellent	16
Very Good	25
Good	30
Fair	11
Poor	18

TABLE 2

Background Characteristics of Participating Oncologists (*N* = 12).

White race	12/12	
Male gender	10/12	
	Median	**Range**
Age	39	33–51
Years working with oncology patients	10.5	3–20
# patients seen face-to-face each week	30	10–55
% of professional time spent on research	36.5%	20–75%
% of patients enrolled in an EPCT	30%	5–75%
Currently or previously PI or co-investigator on investigational study?	100%	
Involved in obtaining informed consent from patients who decide to enroll in investigational study?	100%	
Routinely offer patients enrollment in investigational study?	100%	

TABLE 3

Percent Respondents Mentioning Different Purposes of Investigational Trial. Respondents could Offer Multiple Responses to this Open-ended Question.

Purpose mentioned	Phase I $N = 30$	Phase II $N = 35$	Overall $N = 65$	p-value
To see if drug works	40%	70%	54%	0.016
To see if drug is safe/to learn side effects	6%	7%	6%	0.87
To figure out the best dose	17%	0%	9%	0.017
To see if drug will help me	11%	17%	14%	0.54
To cure my cancer	17%	3%	11%	0.073

TABLE 4

Purpose of Trial Mentioned by Participants by Phase Trial in which Offered Enrollment (N = 65).

	Phase I	Phase II	TOTAL	*p*-value
Mentioned safety/dosing	17%	7%	12%	0.200
Mentioned benefit	60%	83%	71%	0.039
Mentioned both Safety/dosing and personal benefit	6%	3%	5%	0.648

TABLE 5

Reasons for Participation in Early Phase Cancer Trial.

What is the main reason you decided to enroll in an investigational study?*	**Percent**
No other treatment option	14
Best chance for cure	15
To help in quest for cure/to help gain knowledge	25
Treatment under investigation has promise	58

Did each of the following possible reasons contribute a lot, a little, or not at all to your decision to participate?**	**Percent Responding "Contributed a lot"**
I felt pressure to join from the physician who presented the investigational study.	0
I felt pressure from my family to join.	6
The investigational study was the best way to pay for treatment.	10
I would get extra medical attention from being in the investigational study.	18
I wanted to continue to see the physician who presented the investigational study at Hopkins/Duke.	50
My family thought it would be a good idea to join.	43
Joining the investigational study would give me peace of mind.	44
The investigational study sounded interesting.	45
Joining the investigational study was a way to advance medical science.	46
Because of my diagnosis, I felt I had little choice.	48
The investigational study offered a chance to get better treatment.	50
The physician who presented the investigational study thought it would be a good idea to join.	52
The investigational study was a way to help others.	58
Joining the investigational study gave me hope.	60
I had no reason not to join.	61
I trust the physician who told me about the investigational study.	76

* This was an open-ended question; response options for possible reasons were not provided.

** This was a closed-ended question; possible reasons and response options were provided. Order of questions reorganized to list responses in order from those most to least likely to have "contributed a lot" to their decision to join.

TABLE 6

Expectations for Benefit and Side Effects for Themselves and for Most Cancer Patients.

	Potential Benefits from Participation	
	Most cancer patients who enroll in investigational studies like the one presented to you experience …	**While participating in the investigational study, do you expect …**
Their/your cancer gets worse	3%	3%
No change in their/your cancer	9%	3%
Some short term improvement in their/your cancer	56%	33%
Some long term improvement in their/your cancer	18%	39%
A complete cure of their/your cancer	15%	21%

TABLE 7

Self-reported Results of Trial Participation at Follow-up.

"Did your tumor shrink or did your cancer get better?" (*n* = 44)	
Yes	30%
No	25%
Don't know	45%
"Did you receive any other clinical benefit?"	
Yes	30%
No	46%
Don't know	24%
"Did you experience any non-medical benefits or advantages as a result of participation?"	
Yes	35%
No	58%
Don't know	7%
Reasons Why No Longer Enrolled (*n* = 11)	
Had a bad reaction, physician took me off	18%
Tumor growth/disease progressed	46%
Study was over	27%
Other	36%