J Clin Oncol. Author manuscript; available in PMC 2017 July 10.

Published in final edited form as:
J Clin Oncol. 2017 January 10; 35(2): 135–138. doi:10.1200/JCO.2016.67.9902.

Is Participation in Cancer Phase I Trials Really Therapeutic?

Jonathan Kimmelman, PhD
STREAM Research Group, Biomedical Ethics/Experimental Medicine, McGill University, 3647 Peel St, Montreal, Quebec, Canada H3A 1X1, Ph: 514 398-3306

Jonathan Kimmelman: jonathan.kimmelman@mcgill.ca

Phase I trials are a key step in developing anticancer treatments. But because they administer unproven drugs to populations with life-threatening disease, their design and ethics are often debated.[1–4] In 1995, ASCO issued a policy declaring the importance of phase I studies as a treatment modality for patients with cancer who have advanced disease. ASCO revisited its policy in 2014.[5] The new policy amplifies the earlier position, reasserting two closely connected claims: first, that phase I cancer studies have therapeutic intent, and second, that they potentially "provide patients [who enroll with clinical benefit."[5(p1)]

In this article, I reinforce the first assertion and qualify the second. The therapeutic intent of many phase I cancer studies is attested to by the fact that most studies measure disease response, and many use designs aimed at maximizing clinical benefit. However, intent alone does not underwrite an actual therapeutic claim. The assertion that phase I trials offer a vehicle for pursuing cancer treatment (the "therapeutic position") rests on weak evidence and has counterproductive implications for human protection. It also erodes the ability of oncologists to rigorously evaluate new treatments and support evidence-based practice. Instead I propose a different view—the "research position"—that stresses the investigational orientation of phase I trials while accommodating exceptional cases and the therapeutic yearnings of patients and their caregivers. I close by suggesting how groups such as ASCO might refine their recommendations.

Evidence

The kernel of the therapeutic position expressed by ASCO is that investigators can and should present phase I trial participation as providing "the prospect of a direct medical benefit."[5(p2)] Because direct benefit relates to the pharmacologic action of a drug, and because benefit in medicine is always measured against how patients would be treated otherwise, the therapeutic position is equivalent to saying that the risk/benefit for receiving experimental drugs in phase I trials is consistent with and possibly superior to standard of care.

Proponents of this view draw on several streams of evidence. First, meta-analyses show objective response rates (ORRs) in the neighborhood of 5% and fatal toxicities of approximately 0.5% for monotherapy studies.[6–8] Proponents argue that these response rates

Conflict of Interest Statement: No relationship to disclose

are consistent with those for several US Food and Drug Administration (FDA) approved anticancer drugs. [5,9] Moreover, risk/benefit may be improving because of the growing emphasis on strategies like immunotherapy and personalized medicine. Therefore, the offer of participation in a phase I study is consistent with the use of drugs deemed safe and effective by an authoritative regulatory body.

Appeals to meta-analyses rest on assuming that ORR is a reliable surrogate for clinical benefit. Sometimes, it seems that it is.[5,10] Other times, it is not.[11–13] Moreover, full FDA approval decisions for drugs cited by ASCO, such as ipilimumab for melanoma[14] and gemcitibine for pancreatic cancer,[15] were ultimately based on survival data from controlled trials, not on ORRs. Approval decisions have often been bolstered by quality-of-life outcomes, a type of evidence that is not generally available for phase I oncology studies.[16] Further complicating the reliance on phase I meta-analyses, open-label phase I studies cannot exclude natural regression[17–20] or radiography error. One systematic review of cancer trials found that patients in placebo arms showed a 2.4% response rate.[21] Finally, although it is true that oncology drug development has evolved, I am not aware of any meta-analyses showing significantly improved risk/benefit for recent phase I trials. In the meantime, the attrition rate for oncology products remains stubbornly high.[22] If the category of activities we call phase I studies constituted a drug that could be bottled for sale, it seems highly improbable that FDA would grant full approval.

A second stream of evidence supporting the therapeutic position is the occasional occurrence of grand slam trials, such as the first-in-human trial of imatinib (70% response rate in an otherwise refractory population[23]). However, argument from anecdote is, by definition, unsystematic. One can also point to instances of major unexpected toxicities in phase I trials, [24,25] or t compelling surrogate evidence failed to translate into survival advantage.[26–30]

One study often cited for the therapeutic position showed that patients with solid tumors who received higher doses of molecularly targeted agents had longer survival than patients who received lower doses.[31] However, because most phase I studies do not involve randomization and blinding, it is impossible to rule out that clinical investigators enroll hardier patients in high-dose groups and feebler patients in lower-dose cohorts (there is some evidence that such selective enrollment occurs[32]).

Without rigorous trials that test the clinical value of participation phase I studies, perhaps the best way of inferring their therapeutic value is to ask what fraction of patients receive drug regimens that are ultimately vindicated in randomized trials. Although reasonable people will disagree about where to draw the line, one might posit that participation in phase I studies is therapeutic if a patient, on entry, has a one-in-ten chance of receiving a drug treatment regimen that is ultimately vindicated in randomized trials that use a clinical end point. Because only one in 20 cancer drugs introduced into trials is ultimately approved by the FDA, and because most drugs are put to phase I trials in a variety of schedules, doses, and combinations or against different indications, we suspect that an analysis of these trials would find a far smaller fraction of patients with cancer receiving regimens that are ultimately vindicated.

Conceptual Problems

There are three conceptual problems with the therapeutic position. First, that category of phase I trials captures many different compounds, applied along different regimens. Some studies are first in human; others involve drugs for which there is already a clinical evidence base. An emerging literature on preclinical study quality suggests that the strength of evidence supporting phase I studies is highly variable.[33–36] Furthermore, studies generally entail numerous procedures that are demonstrably nontherapeutic (eg, blood draws for pharmacokinetics or biopsies for pharmacodynamics or marker exploration). Another reason FDA would probably not approve phase I studies, if they could be packaged and marketed as a product, is that their precise composition is highly variable.

A second conceptual problem with ASCO's therapeutic position is its appeal to intent. That phase I cancer studies have therapeutic intent seems unassailable. However, the warrant for a therapeutic claim derives from evidence, not intention. That clinical investigators *intend* effective cancer care does not make their therapeutic claims justified. If it did, it would license any number of quack cures. Note further that critics of the therapeutic position often posit erroneously—on the exact same logic—that because phase I studies are aimed at testing safety, they cannot be therapeutic (in any event, benefits count whether intended or not).

Third, drugs do not constitute therapies until researchers identify the necessary conditions for unlocking their therapeutic activity. These include dose, schedule, diagnostic eligibility, necessary medical monitoring, and in some cases, cointerventions. The very purpose of phase I studies is to sample these conditions. Unless these conditions are well understood at the point of phase I testing-which may be the case for some pediatric phase I trials or for trials involving highly targeted drugs supported by exemplary preclinical evidence - this sampling requires testing conditions that lie outside a therapeutic window of conditions (eg, testing doses below those that are minimally effective or testing patients on either side of a diagnostic cut point for marker positivity). This means that the scientific objective of phase I studies demands exposing at least some patients to conditions that are, by definition, nontherapeutic.[37]

Policy Problems

Perhaps the most problematic aspects of the therapeutic position relate to its policy implications. First, the therapeutic position raises questions about why we restrict drug access to patients enrolling in trials. If drugs are considered potentially clinically advantageous at the population level on the basis of preclinical or related early-phase clinical evidence alone, why should regulators condition access to drugs on participation in studies? Currently, compassionate use policies restrict patient access until after phase I studies have been completed, a policy that suggests that drugs should not be considered therapeutic until *after* phase I studies are completed. Right-to-try laws or challenges to the authority of the FDA to restrict drug access before trialing recapitulate the logic of the therapeutic position (these policies, in some ways, are more restrictive than the therapeutic position in that their provisions often activate only *after* completion of phase I testing, not during). If, in fact,

drugs entering phase I trials are potentially advantageous against the natural course of refractory illness, drug regulators' policies of restricting drug access or limiting commercial claims of therapeutic value are ethically questionable. Taking this view implies that drug regulators do, as some activists and many regulation critics argue, sacrifice the welfare of present-day patients so that future patients may benefit.

Many patients are ineligible for phase I trials. Eligibility criteria are driven by the scientific objectives of the study. A patient's performance status may be too low, or their tumors may be inaccessible for biopsy. Patients in early cohorts may be given drug at doses on the basis of the same animal testing that supports the therapeutic claim, are believed to be inactive. These design practices become ethically problematic insofar as they potentially discriminate against patients who are equally entitled to the medical opportunity but lack characteristics needed for scientific investigation. phase I studies also disproportionately enroll advantaged populations and patients living near urban centers.[38] Declaring drug administration in phase I studies therapeutic raises profound questions about the fairness of the geography of testing, or the failure to recruit more diverse populations to trials.

The therapeutic position also antagonizes practices that are important for a sustainable drug development effort or for enabling downstream efforts that are crucial for generating reliable evidence of clinical utility. Consider, for example, dose escalation designs that begin at low doses, or that exclude patients with certain comorbidities. The use of such cautionary approaches in part reflects that unexpected deaths can derail drug development efforts.[39] Or consider the evidentiary value of randomized trialing. If drug access in phase I studies is considered therapeutic, how can investigators downstream of successful phase I studies ethically deprive half their patients of study product in randomized trials?

Toward a More Nuanced View

A major factor driving the debate over the therapeutic status of phase I cancer trials is insurance coverage. In the United States, Medicare coverage for routine patient costs in trials is not pegged to trial phase, but instead to therapeutic intent.[5] As noted, the therapeutic intent of many phase I cancer studies is hard to dispute. Therefore, as long as Medicare bases coverage on intent, nothing in the above analysis threatens the coverage of routine patient costs associated with trial participation (I will not take up the question of whether intent alone *should* underwrite Medicare coverage).

An alternative to the therapeutic position is to consider phase I study participation as being consistent with competent medical care, but drug administration in particular as a research procedure, akin to a research biopsy (the "research position"). Therapeutic claims can only be evaluated against the context in which they are being made. One contextual variable is the type of phase I study and the quality of evidence supporting it. Certain types of phase I studies can mount a stronger claim to therapy (eg, when they are supported by prior clinical experience or when they explore a narrower dose range in, for example, pediatric phase I studies). Another variable is the party making a therapeutic claim. Patients and caregivers make decisions about individuals, not populations. They can legitimately view participation as therapeutic provided that two conditions are met: (1) patients adequately understand that,

at least on a population level, major benefit is highly unlikely but adverse events are probable, and (2) that patients attach sufficient value to the remote prospect of disease control. Nothing in the research position denies the meaning that many patients derive from participation, or the psychological benefits that patients might experience from closer contact with caregivers. Above all, phase I trials do not ask patients to forego proven effective therapy or supportive care, and there is no evidence to suggest that there is a survival *disadvantage* for study participation. However, the therapeutic position articulated by most proponents rests on drug access being therapeutically advantageous at a population level. In most policy contexts, there are good reasons to reject this view.

The ASCO statement closes with a series of recommendations on enrollment and design of phase I trials. Alternative recommendations that build on the more nuanced position argued above would include the following:

- Improving patients' understanding of goals. Professional societies that prepare educational materials and investigators who conduct informed consent should generally stress that only a small fraction of treatments tested in phase I studies eventually show efficacy and that study participation is unlikely to result in major direct benefit.
- Increasing enrollment in trials. Professional societies and investigators should use careful review of preclinical and clinical evidence to prioritize those phase I studies that have the greatest promise for clinical translation. This will help prevent less meritorious trials from crowding out important studies.
- Improving the phase I research process. Recognizing that phase I trials are primarily experiments, not treatment platforms, professional societies should articulate benchmarks for their conduct. In particular, they should stress the importance of grounding trials on a reproducible preclinical evidence base. They should also denounce the common nonpublication of phase I trial results[40] and the incomplete reporting[41] of pharmacodynamic analyses within them.

Favoring the research position coheres with standards of evidence-based medicine, and it deflates the unscrupulous marketing of unproven interventions to desperate patients.[42] It places a greater onus on rigorous scientific design and reporting of studies. This more nuanced view might not enhance recruitment, but it will encourage frank discussions during informed consent. The research position anchors the moral basis of drug administration in phase I cancer trials in scientific advance. In the end, this is the best way to safeguard individual patients, payers, and a productive research enterprise.

Acknowledgments

The author thanks Adelaide Doussau, members of the Studies of Translation, Ethics and Medicine research group, and two anonymous referees for helpful comments.

Funding: Supported by a Humboldt Foundation Fellowship and Grant No. EOG111391 from the Canadian Institutes of Health Research

References

1. Miller FG, Joffe S. Benefit in phase I oncology trials: therapeutic misconception or reasonable treatment option? Clin Trials. 2008; 5:617–23. [PubMed: 19029210]
2. Schüklenk U, Lowry C. Terminal illness and access to phase I experimental agents, surgeries and devices: reviewing the ethical arguments. Br Med Bull. 2009; 89:7–22. [PubMed: 19056723]
3. Ross L. Phase I research and the meaning of direct benefit. J Pediatr. 2006; 149:S20–4. [PubMed: 16829237]
4. Miller M. Phase I cancer trials. A collusion of misunderstanding. Hastings Cent Rep. 2000; 30:34–43.
5. Weber JS, Levit LA, Adamson PC, et al. American Society of Clinical Oncology policy statement update: the critical role of phase I trials in cancer research and treatment. J Clin Oncol. 2015; 33:278–84. [PubMed: 25512456]
6. Roberts TG Jr, Goulart BH, Squitieri L, et al. Trends in the risks and benefits to patients with cancer participating in phase I clinical trials. JAMA. 2004; 292:2130–40. [PubMed: 15523074]
7. Horstmann E, McCabe MS, Grochow L, et al. Risks and benefits of phase I oncology trials, 1991 through 2002. N Engl J Med. 2005; 352:895–904. [PubMed: 15745980]
8. Italiano A, Massard C, Bahleda R, et al. Treatment outcome and survival in participants of phase I oncology trials carried out from 2003 to 2006 at Institut Gustave Roussy. Ann Oncol. 2008; 19:787–92. [PubMed: 18042834]
9. Agrawal M, Emanuel EJ. Ethics of phase I oncology studies: reexamining the arguments and data. JAMA. 2003; 290:1075–82. [PubMed: 12941681]
10. Bruzzi P, Del Mastro L, Sormani MP, et al. Objective response to chemotherapy as a potential surrogate end point of survival in metastatic breast cancer patients. J Clin Oncol. 2005; 23:5117–25. [PubMed: 15955906]
11. Burzykowski T, Buyse M, Piccart-Gebhart MJ, et al. Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. J Clin Oncol. 2008; 26:1987–92. [PubMed: 18421050]
12. Ciani O, Buyse M, Garside R, et al. Meta-analyses of randomized controlled trials show suboptimal validity of surrogate outcomes for overall survival in advanced colorectal cancer. J Clin Epidemiol. 2015; 68:833–42. [PubMed: 25863582]
13. Chen TT, Chute JP, Feigal E, et al. A model to select chemotherapy regimens for phase III trials for extensive-stage small-cell lung cancer. J Natl Cancer Inst. 2000; 92:1601–7. [PubMed: 11018096]
14. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010; 363:711–23. [PubMed: 20525992]
15. ODAC recommends full approval for Gemzar for pancreatic cancer. Oncology (Williston Park). 1995; 9:799–800. [PubMed: 8562322]
16. Revicki DA, van den Eertwegh AJ, Lorigan P, et al. Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. Health Qual Life Outcomes. 2012; 10:66. [PubMed: 22694829]
17. Loeve F, Boer R, Zauber AG, et al. National Polyp Study data: evidence for regression of adenomas. Int J Cancer. 2004; 111:633–9. [PubMed: 15239144]
18. Printz C. Spontaneous regression of melanoma may offer insight into cancer immunology. J Natl Cancer Inst. 2001; 93:1047–8. [PubMed: 11459861]
19. Hero B, Simon T, Spitz R, et al. Localized infant neuroblastomas often show spontaneous regression: results of the prospective trials NB95-S and NB97. J Clin Oncol. 2008; 26:1504–10. [PubMed: 18349403]
20. Elhilali MM, Gleave M, Fradet Y, et al. Placebo-associated remissions in a multicentre, randomized, double-blind trial of interferon gamma-1b for the treatment of metastatic renal cell carcinoma. The Canadian Urologic Oncology Group. BJU Int. 2000; 86:613–8. [PubMed: 11069364]
21. Chvetzoff G, Tannock IF. Placebo effects in oncology. J Natl Cancer Inst. 2003; 95:19–29. [PubMed: 12509397]

22. Hay M, Thomas DW, Craighead JL, et al. Clinical development success rates for investigational drugs. Nat Biotechnol. 2014; 32:40–51. [PubMed: 24406927]
23. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001; 344:1031–7. [PubMed: 11287972]
24. Morgan RA, Yang JC, Kitano M, et al. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. Mol Ther. 2010; 18:843–51. [PubMed: 20179677]
25. Wall L, Talbot DC, Bradbury P, et al. A phase I and pharmacological study of the matrix metalloproteinase inhibitor BB-3644 in patients with solid tumours. Br J Cancer. 2004; 90:800–4. [PubMed: 14970856]
26. Rettig, RA. False hope: bone marrow transplantation for breast cancer. Oxford ; New York: Oxford University Press; 2007.
27. Sharma SP. Avastin saga reveals debate over clinical trial endpoints. J Natl Cancer Inst. 2012; 104:800–1. [PubMed: 22673590]
28. Fleming TR. Objective response rate as a surrogate end point: a commentary. J Clin Oncol. 2005; 23:4845–6. [PubMed: 15955898]
29. Han K, Ren M, Wick W, et al. Progression-free survival as a surrogate endpoint for overall survival in glioblastoma: a literature-based meta-analysis from 91 trials. Neuro Oncol. 2014; 16:696–706. [PubMed: 24335699]
30. Walker, Joan, Lari Wenzel, MB. A phase III trial of bevacizumab with IV versus IP chemotherapy for ovarian, fallopian tube, and peritoneal carcinoma: An NRG Oncology Study. Abstract. Annual Meeting on Women's Cancer; 2016;
31. Gupta S, Hunsberger S, Boerner SA, et al. Meta-analysis of the relationship between dose and benefit in phase I targeted agent trials. J Natl Cancer Inst. 2012; 104:1860–6. [PubMed: 23169991]
32. Mick R, Lane N, Daugherty C, et al. Physician-determined patient risk of toxic effects: impact on enrollment and decision making in phase I cancer trials. J Natl Cancer Inst. 1994; 86:1685–93. [PubMed: 7966396]
33. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. Nature. 2012; 483:531–3. [PubMed: 22460880]
34. Amarasingh S, Macleod MR, Whittle IR. What is the translational efficacy of chemotherapeutic drug research in neuro-oncology? A systematic review and meta-analysis of the efficacy of BCNU and CCNU in animal models of glioma. J Neurooncol. 2009; 91:117–25. [PubMed: 18813876]
35. Henderson VC, Demko N, Hakala A, et al. A meta-analysis of threats to valid clinical inference in preclinical research of sunitinib. Elife. 2015; 4
36. Ocana A, Amir E, Yeung C, et al. How valid are claims for synergy in published clinical studies? Ann Oncol. 2012; 23:2161–6. [PubMed: 22314859]
37. Kimmelman J, London AJ. The STRUCTURE of Clinical Translation: Efficiency, Information, and Ethics. Hastings Center Report. 2015; 45:27–39. [PubMed: 25628068]
38. Seidenfeld J, Horstmann E, Emanuel EJ, et al. Participants in phase I oncology research trials: are they vulnerable? Arch Intern Med. 2008; 168:16–20. [PubMed: 18195190]
39. London AJ, Kimmelman J, Emborg ME. Research ethics. Beyond access vs. protection in trials of innovative therapies. Science. 2010; 328:829–30. [PubMed: 20466907]
40. Camacho LH, Bacik J, Cheung A, et al. Presentation and subsequent publication rates of phase I oncology clinical trials. Cancer. 2005; 104:1497–504. [PubMed: 16116590]
41. Freeman GA, Kimmelman J. Publication and Reporting Conduct for Pharmacodynamic Analyses of Tumor Tissue in Early Phase Oncology Trials. Clin Cancer Res. 2012
42. Bianco P, Sipp D. Regulation: Sell help not hope. Nature. 2014; 510:336–7. [PubMed: 24955467]