VOLUME 26 · NUMBER 36 · DECEMBER 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Self-Reported Practices and Attitudes of US Oncologists Regarding Off-Protocol Therapy

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Submitted May 19, 2008; accepted August 11, 2008; published online ahead of print at www.jco.org on November 24, 2008.

Supported by the American Society of Clinical Oncology Foundation (J.P.), Breast Cancer Research Foundation (J.P.), and by the Greenwall Foundation Faculty Scholars Program in Bioethics (J.P.).

The opinions expressed are those of the author and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/08/2636-5994/$20.00

DOI: 10.1200/JCO.2008.18.1420

ABSTRACT

Purpose
Investigational cancer therapies being tested in clinical trials may be available outside of trials, or off-protocol (OPRx). We evaluated the practices and attitudes among US oncologists with regard to this controversial practice.

Methods
We mailed an anonymous survey to a random sample of US medical oncologists evaluating frequency and prevalence of OPRx and evaluated the correlation between demographic factors, attitudes, and practice.

Results
One hundred forty-six (31%) of 471 oncologists responded. Ninety-three percent reported ever discussing and 81% ever prescribing OPRx. Academic oncologists were more likely than community oncologists to have ever provided OPRx (89% *v* 75%; $P = .06$), to discuss OPRx at least once/month (41% *v* 19%; $P = .0004$), and to deny requests for OPRx at least once/month (16% *v* 2%; $P = .004$). While 61% of oncologists believed that patients should be discouraged from OPRx, only 31% felt it should not be available. With regard to trial recruitment, 53% felt that informed consent requires discussion of OPRx, 34% disagree, and 26% feel that patients should be provided OPRx on request, while 56% disagree. There was lack of consensus on access to OPRx in scenarios based on open trials at the time of the survey, such as adjuvant trastuzumab, which 41% would provide, 59% would not.

Conclusion
US oncologists report common discussion and use of OPRx, but attitudes and practices may vary substantially. There is need for greater debate regarding OPRx in oncology, further definition of the ethical and clinical issues at stake, and development of guidelines in this area.

J Clin Oncol 26:5994-6000. © 2008 by American Society of Clinical Oncology

INTRODUCTION

In many cancer settings standard therapy remains inadequate, and clinical trials are needed to test novel interventions that may improve outcomes. Patients with cancer may participate in trials to help advance scientific knowledge,[1] but frequently are motivated by a desire for access to a promising experimental therapy.[2,3] However, under some circumstances, an experimental therapy may be available outside of a clinical trial. In medical oncology, this most frequently occurs when a drug is approved by the US Food and Drug Administration (FDA) for a different clinical indication and becomes commercially available. Off-label prescribing in oncology may be supported by well-designed clinical trials, and can constitute standard evidence-based care in some settings.[4] A dilemma emerges, however, when a drug is still undergoing evaluation in clinical trials for a given indication, but is simultaneously available for off-label use. We term such use off-protocol therapy (OPRx).

Patients may seek treatment with OPRx because they are unable or unwilling to participate in a trial, or out of concerns about random assignment to standard therapy. Oncologists may provide OPRx for their patient based on clinical judgment or patient request.

The ethical and clinical implications of availability of experimental therapy outside of clinical trials have not been well explored. OPRx may promote treatment with an unsafe or ineffective therapy or interfere with trial accrual, as was the case with high-dose chemotherapy for breast cancer.[5-7] Conversely, there is demand for greater access to potentially beneficial experimental therapy, particularly among patients facing poor outcomes with standard therapy.[8,9] Without consistent standards for use of

OPRx, there is potential for disparities in access to therapy based on physician discretion or patient demand, rather than medical considerations.

Highlighting the complexity of this issue, some have argued that disclosing the option of treatment with OPRx is a requirement of ethical recruitment to clinical trials.[10] This is based on the premise that informed consent requires disclosure of alternatives to trial participation, and treatment with an available therapy outside of the trial could be considered a valid alternative. This concern is heightened for randomized clinical trials (RCTs) in which equipoise, or clinical uncertainty regarding the superior treatment arm, is often cited as the justification for random assignment of therapy.[11] To date and to our knowledge, there has been no evaluation of how frequently this dilemma arises in oncology, and no assessment of oncologist attitudes and behavior with regard to OPRx.

In this study, we investigate the prevalence of OPRx consideration and use among US oncologists, and explore oncologists' views regarding the ethics of providing OPRx and the clinical scenarios in which it should be considered.

METHODS

Selection of Study Participants

We conducted an anonymous cross-sectional survey of US oncologists regarding their practices and attitudes toward OPRx. Using the American Society of Clinical Oncology 2004 Membership Directory, we selected a random (every 14th listing) sample of 500 medical oncologists with US addresses by the method of Helft et al[12] and attempted to obtain a balanced sample between oncologists listed in academic and nonacademic practice settings. Surgeons, pediatric oncologists, radiation oncologists, non-MDs, and entries listing a non-US address were excluded. Eligible entries were further categorized as academic or nonacademic based on address, with selection continuing until 250 entries from each practice setting were obtained. Verification of eligibility, including direct patient care at least 8 hours per week, was incorporated into the survey.

We conducted the initial mailing of the surveys in March 2005. Due to the early release of interim data from the combined analysis of North American adjuvant trastuzumab trials for breast cancer on April 25, 2005, which corresponded to one of the situations addressed in the survey, a second planned mailing was not conducted because these data were believed likely to bias subsequent responses.[13,14]

Survey Instrument

A survey was developed specifically for this study. It consisted of 39 questions divided into five domains, entitled eligibility, demographics, practice regarding off-protocol therapy, beliefs regarding off-protocol therapy, and criteria for use of off-protocol therapy. Each section contained a brief description of the nature of the questions. OPRx was defined as follows: "treatment outside of a clinical trial with a therapy that is: A) Not considered a standard therapy for your patient's condition, B) Currently under investigation in clinical trials for your patient's condition, C) FDA approved for a different indication (s), and D) commercially available." Listed examples based on ongoing trials and FDA approval at that time were trastuzumab for adjuvant breast cancer therapy, gefitinib for adjuvant lung cancer therapy, capecitabine and oxaliplatin for pancreatic cancer, and cetuximab for metastatic lung cancer. Definition and examples preceded all questions on OPRx in the survey. The survey was piloted using medical oncologists at Dana-Farber Cancer Institute and revised for clarity and comprehension.

Statistical Analysis

We explored associations between responses and subject characteristics such as age, sex, years in practice, practice setting, and frequency of enrollment of patients in clinical trials using Fisher's exact test. All statistical tests reported were two sided. Response rates to individual questions were calculated based on total responses received.

Based on response rates in published surveys of US oncologists, we estimated that the response rate to this survey would be between 45% and 60%.[12,15,16] We also estimated a 10% error rate in our screening for eligibility. Assuming a 50% response rate and a 5% α error for two-sided tests of statistical significance, we needed to survey 194 oncologists in order to detect a 20% absolute difference between academic and nonacademic oncologists with a power greater than 80%. We distributed our survey to 500 oncologists to obtain the planned sample size. A $2 incentive was provided to improve response rate.[17] The institutional review board of the Dana-Farber Cancer Institute approved this study and waived the requirement for documentation of informed consent.

RESULTS

Of 500 surveys, 20 were returned due to invalid addresses. Nine respondents were ineligible because they saw patients less than 8 hours per week or were not medical oncologists. Among 471 surveys delivered to potentially eligible US oncologists, there were 146 responders (31%). As noted previously, a second mailing was cancelled due to the

Table 1. Respondent Characteristics (N = 146)

Characteristic	No.	%
Age, years		
Mean	50.5	
Range	34-74	
Sex		
Female	24	16
Male	122	84
Years in practice		
0-15	65	45
> 15	81	55
Practice setting		
Academic	61	42
Non-academic	85	58
Time devoted to clinical care, %		
0-40	20	14
41-80	46	31
> 80	80	55
Patients/mo, No.		
< 100	25	17
100-200	49	34
> 200	72	49
New therapy starts/month, No.		
0-10	33	23
10-25	72	49
25-50	32	22
> 50	9	6
Patients considered for clinical trials, %		
< 5	32	22
6-25	56	39
> 25	57	39
Patients enrolled in clinical trials, %		
< 2	35	24
2-5	34	23
6-10	44	30
11-25	23	16
> 25	9	6

release of interim clinical trial data likely to bias subsequent responses.[13,14] Respondent characteristics are reported in Table 1.

Use of Experimental Therapy Outside of Clinical Trials Among US Oncologists

Most respondents reported discussing (93%) and providing treatment (81%) with an experimental therapy outside of a clinical trial at least once (Table 2). This practice appeared frequent, as 66% of oncologists reported prescribing OPRx at least once per year, 19% at least 5 times per year, and 12% at least once per month. At the same time, oncologists reported frequent denial of patient requests for OPRx; 68% denied requests at least once per year, 25% at least 5 times per year, and 8% at least once per month.

Academic oncologists were simultaneously more likely than community oncologists to report ever providing OPRx (89% *v* 75%; $P = .06$), discussing OPRx at least once per month (41% *v* 19%; $P = .004$), discussing OPRx at least 5 times per year (57% *v* 29%; $P = .001$), and denying patient's requests for OPRx at least once per month (16% *v* 2%; $P = .004$) and at least 5 times per year (36% *v* 16%; $P = .01$).

Attitudes Toward OPRx Among US Oncologists

Oncologists were generally opposed to treatment with experimental therapy outside of clinical trials, but wanted to retain the option of providing such therapy at their discretion. Sixty-two percent of respondents reported that they believed that patients should be discouraged from OPRx. However, only 31% felt that OPRx should not be available.

We specifically asked oncologists if they agreed with the statement that "Informed consent requires that I disclose the option of treatment with an experimental therapy outside of a trial **if** the therapy is commercially available." Fifty-three percent of oncologists agreed that patients considering trial enrollment should be informed if OPRx is available, 34% disagreed, and 13% neither agreed nor disagreed. There was no significant difference in agreement with this statement among academic versus nonacademic oncologists (60% *v* 49% respectively; $P = .3$).

Finally, we evaluated whether oncologists believed that patients' offered trial enrollment have a right to access to OPRx if they choose not to participate. Only 26% of respondents reported that patients offered enrollment had a right to OPRx, while 56% disagreed. Attitudes toward informed consent and patients rights to treatment outside of trials are summarized in Table 3.

Willingness to Provide Adjuvant Trastuzumab Outside of a Clinical Trial

At the time of this survey, in March 2005, no results from any adjuvant trastuzumab clinical trial had been presented. To assess oncologists' willingness to provide this treatment outside of a trial, we presented the following vignette: Your patient is a married 35-year-old woman with two young children who was recently diagnosed with a 3-cm, estrogen receptor– and progesterone receptor–negative, HER-2–positive, high-grade invasive breast cancer, with 12 of 15 lymph nodes positive, and no evidence of distant metastatic disease on staging studies. There is a clinical trial available at your institution in which your patient would be randomly assigned to the most aggressive standard adjuvant chemotherapy for node-positive breast cancer or the same chemotherapy regimen plus trastuzumab. The trastuzumab would be continued for 1 year. After discussing her risk of recurrence, the standard approaches to therapy, and the clinical trial, your patient expresses a strong desire to be treated according to the trastuzumab-containing arm of the trial, without participating in the trial and risking random assignment to standard chemotherapy.

There was little consensus among oncologists regarding whether they would or would not provide trastuzumab. Among all respondents, 41% stated they would prescribe adjuvant trastuzumab OPRx, while 59% would not. Factors associated with willingness to provide trastuzumab OPRx included belief that trial care and nontrial care are equivalent ($P = .01$), and belief that patients have a right to OPRx

Table 2. Use of OPRx Outside of Clinical Trials Among US Oncologists

Parameter	Total		Practice: Academic (n = 61)		Practice: Nonacademic (n = 85)		*P* for Academic *v* Nonacademic
	No.	%	No.	%	No.	%	
Ever discuss OPRx?	136	93	56	92	80	94	.74
Ever provide off-protocol therapy?	118	81	54	89	64	75	.056
Discuss OPRx							
> 5 times/year	60	41	35	57	25	29	.001
> 1 time/month	41	28	25	41	16	19	.004
Provide OPRx							
> 5 times/year	45	31	23	38	22	26	.14
> 1 time/month	17	12	9	15	8	9	.4
Patients request OPRx							
> 5 times/year	61	42	31	51	30	35	.06
> 1 time/month	29	20	19	31	10	12	.006
Deny OPRx							
> 5 times/year	36	25	22	36	14	16	.01
> 1 time/month	12	8	10	16	2	2	.004

Abbreviation: OPRx, off-protocol therapy.

Table 3. Oncologist Attitudes Toward OPRx

Parameter	Total (N = 146)				Academic (n = 61)				Nonacademic (n = 85)				Academic *v* Nonacademic
	Strongly Agree or Agree		Strongly Disagree or Disagree		Strongly Agree or Agree		Strongly Disagree or Disagree		Strongly Agree or Agree		Strongly Disagree or Disagree		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Required to inform patients of option of OPRx when discussing a trial	78	53	49	34	36	60	17	28	42	49	32	38	.3
Required to provide OPRx, if requested, when discussing a trial	38	26	82	56	14	23	35	57	24	28	47	55	.6
Patients should be discouraged from treatment with experimental therapy outside of a trial	90	62	17	12	39	64	9	15	41	48	8	9	.07
Experimental therapy should not be available outside of the context of a clinical trial	46	31	64	44	19	31	22	36	27	32	42	49	.9

NOTE. Options included strongly agree, agree, neither agree nor disagree, disagree, and strongly disagree.
Abbreviation: OPRx, off-protocol therapy.

($P = .004$). We detected no difference based on practice setting. There was a trend toward greater willingness to provide OPRx among those with longer than 15 years in practice ($P = .08$), compared with those with fewer years in practice (Table 4).

We compared these results with a second vignette involving a physician patient with metastatic colon cancer eligible for an RCT of fluororacil, leukovorin, and oxaliplatin (FOLFOX) with or without bevacizumab as first-line therapy. Bevacizumab was FDA–approved for first-line treatment with any fluorouracil-containing regimen, but its safety and efficacy in combination with the FOLFOX regimen in this setting was unknown. This information was described in the vignette. Overall, 79% of oncologists were willing to provide FOLFOX plus bevacizumab outside of the trial, while 21% were not. In contrast to the case with trastuzumab, nonacademic oncologists were significantly more likely to provide OPRx than academic oncologists (85% *v* 70%; $P = .04$).

Factors Affecting Willingness to Provide OPRx

Respondents were asked a series of questions about factors that might influence willingness to provide OPRx (Table 5). More than one third of oncologists reported that lack of trial availability at their institution, incurable disease, and evidence for efficacy in a different setting for the disease in question made them more likely to treat with OPRx. Evidence that the therapy was safe and well tolerated increased

Table 4. Willingness to Provide OPRx in Clinical Scenarios Based on Demographic Characteristics and Attitudes Among US Oncologists

Characteristic	OPRx					
	Trastuzumab			Bevacizumab		
	No.	%	*P* for Comparison	No.	%	*P* for Comparison
Total	59/143	41*		115/145	79*	
Practice setting						
Academic	24/58	41	1.0	115/145	70	.04
Nonacademic	35/85	41		115/145	85	
Years in practice						
> 15	38/79	48	.08	115/145	81	.5
< 15	21/64	33		115/145	77	
Sex of physician						
Male	53/119	45	.1	115/145	80	.5
Female	6/24	25		115/145	75	
Attitude toward trial care *v* care outside of trials						
Trial care is superior to non–trial care	23/75	31	.01	115/145	75	.2
Trial care is equivalent	36/68	53		58/69	84	
Attitude toward discussion of OPRx in informed consent						
Discussion of OPRx required	33/76	43	.4	67/77	87	.03
Discuss OPRx not required	17/49	35		35/49	71	
Attitude toward OPRx access for patients offered trial enrollment						
Right to OPRx	21/38	55	.004	31/38	82	1.0
No right to OPRx	22/81	27		65/82	79	

Abbreviation: OPRx, off-protocol therapy.
*Indicates $P < .001$ for differences in willingness to provide OPRx between scenarios.

Table 5. Factors Influencing Willingness to Provide OPRx

Parameter	Much More Likely to Treat Outside of a Trial		More Likely to Treat Outside of a Trial		Slightly More Likely to Treat Outside of Trial		No Effect on My Decision to Treat Outside of a Trial		Less Likely to Treat Outside of a Trial	
	No.	%	No.	%	No.	%	No.	%	No.	%
My patient refuses to enroll in the clinical trial	17	12	34	24	29	20	46	32	17	12
The trial is not available at my institution or practice	17	12	44	31	35	24	40	28	7	5
I think the experimental therapy is better than standard therapy	18	13	44	31	37	26	33	23	11	8
My patient's cancer is incurable with current treatments	25	17	38	27	29	20	42	29	9	6
The therapy works in the metastatic setting, and my patient has high-risk early-stage disease	11	8	33	23	33	23	44	31	21	15
The therapy is safe and well tolerated	21	15	54	38	35	24	30	21	3	2
My patient will have to pay for treatment outside of a trial	3	2	4	3	8	6	47	33	80	56

Abbreviation: OPRx, off-protocol therapy.

willingness to provide OPRx among most oncologists. Most oncologists reported decreased willingness to provide OPRx if the patient had to pay for therapy outside of trial.

DISCUSSION

Our survey, which to our knowledge is the first to measure the prevalence of OPRx in oncology, suggests that OPRx is common. However, practices appear varied and there is little consensus in the oncology community regarding when access to OPRx should be provided. We found that more than 90% of oncologists report discussing OPRx with their patients and more than 80% report providing OPRx at least once. Academic oncologists appear more likely than nonacademic oncologists both to provide OPRx and to deny patients' requests for OPRx, which may reflect an association between consideration of OPRx and consideration of trial enrollment.

These results must be interpreted in light of our response rate of 31%. Although within the range reported for physician surveys,[18] this raises the possibility that our results are not representative of all US oncologists, particularly with regard to the prevalence of OPRx. However, it is highly unlikely that the heterogeneity of views and practices observed among respondents would have disappeared had the response rate been higher. In addition, even if confined to a sizeable minority of oncologists, this apparent variation in practice and lack of consensus would signal a need for further evaluation of OPRx in oncology.

There are several well-documented examples from oncology that illustrate the potential for increased use of OPRx when a therapy with promising results in single-arm studies is available outside of an RCT. In a review of the use of autologous bone marrow transplant for breast cancer during the early 1990s, Antman et al[7] demonstrated a six-fold increase in use of this therapy over 6 years, during the period that RCTs were ongoing. Only 11% of patients with stage II/III disease and 1% of patients with stage IV disease who received this experimental therapy were treated in one of the national RCTs. While some patients continued to receive bone marrow transplants in the context of single-arm studies (guaranteeing access), many were treated outside of trials, bolstered by significant public pressure to ensure access to OPRx while trials were ongoing.[7]

Similarly, Harari[19] noted that induction chemotherapy for locally advanced head and neck cancer was widely used outside of clinical trials while RCTs were ongoing and in the absence of proven benefit beyond historical comparisons from phase II studies. In a survey of 218 community-based cancer specialists, he found that 61% of respondents reported that induction chemotherapy was the most common treatment approach for locally advanced head and neck cancer and that only 4% of patients were treated with this approach as part of an RCT.[19]

The very existence of an RCT appears to increase the frequency of OPRx at both trial and nontrial centers.[20] Clark et al studied the use of therapeutic apheresis for three conditions—multiple sclerosis, thrombocytopenic purpura, and myeloma nephropathy—during three concurrent RCTs at 19 major medical centers in Canada. Apheresis was an available but unproven therapy for all three conditions at the time of this study. The investigators found a large increase in the use of apheresis during the period of the RCT, with the majority of the increase due to treatment of patients outside of clinical trials.[20]

In the era of molecularly targeted therapy, which in recent years has led both to significant changes in outcomes in some cancer settings[21-23] and to increased cost of cancer care,[24] the issue of access to OPRx is likely to become more prominent. As with the examples mentioned earlier, data from single-arm studies may drive both the imperative for rapid accrual to RCTs and the demand for access outside of a trial.

The OPRx dilemma emerges not only when patients actively seek this option, but also when oncologists present patients with the option of clinical trial participation and the experimental intervention is available outside of the trials. Our study demonstrates that oncologists are divided as to whether a discussion of OPRx

should be included in the informed consent process. While most respondents (53%) agreed that informed consent requires a discussion of OPRx, one third disagreed. Discussing OPRx is distinct from providing it, but a substantial minority of oncologists felt that failure to provide OPRx on request to a patient offered trial enrollment was a violation of the principle of voluntary trial participation (26%). This suggests uncertainty among oncologists over whether the patient's decision to undergo treatment with an experimental therapy (as a therapeutic option) can or should be uncoupled from the decision to participate in a clinical trial (as a contribution to clinical science).

A full exploration of the complex ethical issues surrounding OPRx is beyond the scope of this article, but some of the questions that should be addressed are clear. Key ethical issues include access to potentially beneficial experimental therapy, protection of patients from treatments that lack a favorable benefit-to-risk ratio, and society's interest in rigorous assessment of safety and efficacy before treatments are introduced into clinical practice. Also central are conceptual questions: Should an experimental intervention be considered therapy? Is there a spectrum of experimental interventions from first use in humans to proven in a different setting for the same disease that is ethically relevant to considerations of access outside of clinical trials? These and related ethical questions that require future investigation and analysis are summarized in Table 6.

Our study was intended to be a first assessment of the scope of OPRx in oncology, and should therefore be viewed as descriptive and hypothesis generating. As noted earlier in this Discussion, one of the most important limitations of this study is the possibility of response bias. In addition, though our study was anonymous, it is unclear how comfortable oncologists are in describing their use of OPRx. Further, self-report may not accurately reflect behavior. The size of our survey and lack of prior evidence in this area preclude detailed exploration of the association between practice, attitude, and demographic factors, and a more comprehensive evaluation of oncology practice and OPRx will be pursued in subsequent research. Decisions about OPRx may vary significantly based on the disease setting and the level of evidence from prior research that bears on the intervention in question. Finally, respondents may have differed in their interpretation of OPRx. Our definition, examples, and use of case scenarios attempted to minimize these differences.

Nonetheless, we believe that the findings in our survey underscore the potential prevalence of this practice and a lack of consensus among oncologists. This diversity of views may lead to variable access to and options for care among patients with comparable medical conditions, depending on where they seek treatment. There is a need for greater discussion regarding OPRx in the oncology community, further definition of the ethical and clinical issues at stake, and development of guidelines in this area.

Table 6. Ethical Questions Related to Experimental Therapy Outside of Trials in Oncology

Basic question
How and when should an experimental intervention be discussed or offered to a patient outside of a clinical trial?
Questions related to patient safety
What constitutes a legitimate treatment option for a patient?
Are there factors related to the intervention or the patient's medical condition that should make an ethical difference regarding access to treatment outside of a trial?
What role does the safety of the intervention in other settings play in determining the ethics of providing access in an unknown setting?
How does treatment inside a trial differ from treatment outside of a trial in terms of patient safety?
Questions related to access to treatment
As a rule, should access to experimental treatments be limited to clinical trials?
Is it acceptable for access/nonaccess outside of the trial to be at the physician's discretion?
If an experimental intervention is being tested in a trial, but a patient does not have access to the trial (due to distance, or treating facility), should they have access to the intervention outside of the trial?
If a patient is not eligible for a trial (due to clinical parameters, or due to protocol restrictions to a certain population) should they have access to treatment outside of a trial?
Are there populations of patients who do not have the resources to seek an experimental therapy outside of a trial? Do these populations have equal access to the products of any research?
Questions related to professional integrity
Are there obligations particular to the academic oncologist regarding providing access outside of clinical trials?
Does the oncologist who is offering an intervention in a randomized trial have a greater or lesser obligation to discuss or provide the option of off-protocol therapy?
How does compensation to the physician impact willingness to provide care outside of a trial (compensation for trial enrollment, insurance reimbursement)?
Questions related to policy implications for RCTs and evidence-based medicine
What will happen to our ability to conduct trials if patients gain wider access to experimental treatments outside of RCTs?
How does availability of an intervention due to FDA approval change the ethical issues in access to experimental therapy outside of trials, if at all?
Should access be provided after completion of a trial, but before presentation of results?
Questions related to informed consent
Is disclosure of an "off-protocol" experimental option required under the ethical imperative to discuss options with patients considering trials as part of informed consent?
If an option becomes available for another indication during a trial, should this be disclosed to trial participants so they can assess ongoing participation?
If an experimental intervention is considered a reasonable treatment option in an RCT, and it is clinically available, by what justification should patients be required to participate in the trial for access?
Is restricting access to experimental but FDA-approved treatments to clinical trials coercive?
What is the impact of disclosure of an off-protocol option on informed consent?

Abbreviations: RCT, randomized controlled trial; FDA, US Food and Drug Administration.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Jeffrey Peppercorn, Genentech (C) **Stock Ownership:** None **Honoraria:** Jeffrey Peppercorn, Genentech **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

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