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ORIGINAL REPORT

# Availability of Experimental Therapy Outside Oncology Randomized Clinical Trials in the United States

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## ABSTRACT

### Purpose
Investigational cancer therapies may be available outside trials as "off-protocol therapy" (OPRx), with implications for patient safety, trial accrual, and access to care. We conducted a literature-based analysis of recent randomized trials to evaluate the potential scope and impact of OPRx in the United States.

### Methods
A MEDLINE search identified all English-language phase III medical oncology randomized clinical trials (RCTs) published over a 2-year period ending April 17, 2008. Determination of OPRx availability was based on US Food and Drug Administration approval for any indication. We limited assessment of accrual to studies with US sites. Data from articles were extracted independently by two investigators.

### Results
Among 172 eligible RCTs, the majority (108; 63%) evaluated drugs that were available OPRx in the United States at trial initiation, while an additional 19 (11%) evaluated interventions that became available during the trial. Among trials with US sites, time to accrual was slower (41 *vs* 22 months; $P = .002$) and less efficient (8.8 *v* 22.7 patients per month; $P = .001$) when OPRx was available. Sixty-six percent of RCTs reported at least one increased grade 3 to 4 toxicity in the experimental arm, 47% reported superior efficacy for at least one major clinical outcome in the experimental arm, and 27% reported improvement in overall survival. These outcomes did not vary on the basis of OPRx availability.

### Conclusion
The majority of recent oncology RCTs involve experimental interventions that are available outside trials in the United States with potential impact on trial accrual. The safety and efficacy of novel interventions must be determined by clinical trials.

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## INTRODUCTION

Oncology clinical trials are conducted to evaluate the risk and benefits of novel interventions and to improve outcomes for future patients. Trials are conducted under highly regulated conditions to promote both the interests of research participants and our ability to address scientific questions. However, although patients may participate in oncology trials for altruistic reasons,[1] many seek access to a novel intervention in the hope of direct personal benefit.[2] In addition, oncologists may view clinical trials as a means of providing optimal treatment for a given patient.[3]

When a promising intervention is available only within a clinical trial, then the goals of access and research may converge. However, under some circumstances, an intervention being investigated within a clinical trial may also be available in routine clinical practice. This can occur when a drug is approved by the US Food and Drug Administration (FDA) for a different indication, making it commercially available off-label, subject to physician discretion.[4] Availability of an experimental intervention outside a trial may also occur when approved drugs are evaluated in a novel combination, dose, sequence, or schedule. We term the use of an experimental intervention outside a clinical trial "off-protocol therapy" (OPRx).

OPRx is, in many cases, a subset of off-label therapy, which raises issues concerning evidence-based medicine and reimbursement but is further complicated by the fact that the intervention in question is actively undergoing evaluation in a clinical trial. Although the majority of oncologists would prefer that experimental interventions be used primarily within clinical trials, most wish to retain discretion over when OPRx is considered.[5]

Patients may request OPRx to avoid random assignment, to avoid inconvenience associated with trial participation, or to avoid being ineligible for a trial. Oncologists may also recommend or agree to provide OPRx under a variety of conditions.

To date, the ethical and medical implications of OPRx have not been well explored. OPRx may prevent timely recognition of a drug's inferiority, undesired adverse effects, or toxicity or it may impair trial accrual. Conversely, OPRx can provide early access to potentially beneficial interventions for patients who may face poor outcomes with standard care.[6,7]

Although there are clear historical examples of strong demand for OPRx resulting in slow trial accrual and exposure of patients to unproven and potentially harmful interventions (including the well-documented history of bone marrow transplant for breast cancer),[8] it is unclear how prevalent this phenomenon truly is in oncology.

To assess the potential scope of OPRx in the United States, we evaluated the frequency with which experimental interventions in recent oncology randomized clinical trials (RCTs) were potentially available for off-label use by virtue of FDA approval. Given that important clinical questions with relevance for US practice (including consideration of OPRx) may be addressed in either domestic or international trials, we included all RCTs within the study period.[9,10] We evaluated reported safety and efficacy of experimental interventions compared with standard therapy in recent RCTs to inform clinical and policy discussions concerning access to OPRx. In a restricted sample of RCTs with US sites, we also evaluated the association between OPRx availability and trial accrual.

## METHODS

### Evaluation of Trials

We conducted a PubMed-based literature search to identify all English-language original reports from randomized phase III clinical trials in oncology published in the 2 years before study initiation. We used the search terms "cancer" and "phase III" and search limits of English language, human subjects, randomized controlled trials, and publication dates between April 17, 2006, and April 17, 2008 (2 years preceding initiation of this study). All published first reports of the results of a phase III RCT for any pharmaceutical intervention in oncology were included. Phase I, phase II, and pilot/feasibility studies along with quality-of-life, correlative, and follow-up publications were excluded, as were RCTs that evaluated radiation or surgical interventions. This

**Table 1.** Trial Characteristics

| Characteristic | All Trials (N = 172) | | Trials That Include US Sites* (n = 68) | | Trials With Only North American Sites† (n = 43) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Disease setting | | | | | | |
| Solid tumor, metastatic/unresectable | 88 | 51 | 30 | 44 | 15 | 35 |
| Solid tumor, adjuvant/neoadjuvant | 43 | 25 | 18 | 27 | 16 | 37 |
| Hematologic malignancy | 23 | 13 | 7 | 10 | 3 | 7 |
| Other | 18 | 10 | 13 | 19 | 9 | 21 |
| Type of intervention | | | | | | |
| Anticancer, molecularly targeted | 29 | 17 | 16 | 23 | 7 | 16 |
| Anticancer, not molecularly targeted | 120 | 70 | 42 | 62 | 27 | 63 |
| Supportive care | 23 | 13 | 10 | 15 | 9 | 21 |
| Purpose of randomized trial | | | | | | |
| New drug or combination of drugs | 130 | 76 | 56 | 82 | 38 | 89 |
| New delivery method (eg, dose, schedule) | 29 | 17 | 8 | 12 | 4 | 9 |
| New drug and new delivery method | 6 | 3 | 2 | 3 | 0 | 0 |
| Best of two or more standard options | 7 | 4 | 2 | 3 | 1 | 2 |
| Pharmaceutical involvement‡ | | | | | | |
| Pharmaceutical support | 95 | 48 | 39 | 57 | 22 | 51 |
| Pharmaceutical author | 29 | 13 | 25 | 37 | 17 | 40 |
| Author with conflict of interest | 77 | 39 | 42 | 62 | 26 | 60 |
| Location | | | | | | |
| North America/US sites only | 43 | 25 | 43 | 63 | 43 | 0 |
| US and international sites | 25 | 15 | 25 | 37 | 0 | 0 |
| International sites only | 104 | 60 | 0 | 0 | 0 | 0 |
| Cancer subtype | | | | | | |
| Breast | 27 | 16 | 10 | 15 | 6 | 14 |
| Lung | 24 | 14 | 5 | 7 | 4 | 9 |
| GI, noncolorectal | 19 | 11 | 8 | 12 | 5 | 12 |
| Colorectal | 17 | 10 | 6 | 9 | 3 | 7 |
| Gynecologic | 17 | 10 | 8 | 12 | 7 | 16 |
| Lymphoma | 14 | 8 | 5 | 7 | 2 | 5 |
| Hematologic malignancy, nonlymphoma | 13 | 8 | 3 | 4 | 1 | 2 |
| Genitourinary | 13 | 8 | 8 | 12 | 5 | 12 |

*"Trials with US Sites" includes trials that contain only US Sites as well as trials with both US and international/Canadian sites.
†"Trials with Only North American Sites" includes 37 trials with only US sites, three with one Canadian site, and three with two to three Canadian sites.
‡N > 172 because the components in this category are not mutually exclusive.

  

search identified 256 potentially eligible studies that were reviewed by abstracts or complete manuscript as appropriate, leading to 162 eligible reports. Ten reports contained two distinct trials (defined by separate randomization processes and two distinct data analyses) which were evaluated separately for a total of 172 trials.

We developed a study-specific abstraction form to extract study characteristics, including interventions, type and stage of cancer, patient population, trial purpose, trial sites, industry support, and authorship. We collected trial accrual information, including time from initiation to completion of accrual and number of patients. We abstracted trial outcomes, including grade 3 to 4 toxicities, incidence of febrile neutropenia, overall survival, time to progression/progression-free survival, disease-free survival, and overall response rate. Finally, we recorded any report of early closure of the study, reasons for closure, and instances of inferiority of the experimental intervention compared with standard therapy.

To evaluate the potential scope of OPRx in the United States, we evaluated the off-label availability of all experimental pharmaceutical interventions in any oncology RCT during the study period. We determined the potential availability of OPRx on the basis of the experimental arm's FDA approval status and date of approval for any indication, obtained from FDA's Web site (www.fda.gov). We evaluated the correlation between FDA approval status (used to categorize trials as OPRx available or unavailable), safety, and efficacy for all trials. We limited evaluation of the potential impact of OPRx on accrual to trials with at least one US site. All trials were reviewed independently by two reviewers and assigned an overall classification of "positive" or "negative" on the basis of efficacy and toxicity according to previously established methodology.[11,12] There was initial agreement for 2,742/2,752 items jointly abstracted (99.6%).

The primary outcomes of interest were time to completion of trial accrual and accrual efficiency, measured as number of patients enrolled per month in trials with US sites. Secondary outcomes, evaluated in all trials, were frequency of increased major toxicity, improved survival, and improved major clinical end point for experimental interventions compared with control.

### Statistical Methods

The time to completion of study accrual was estimated by the product limit method of Kaplan and Meier. Time to accrual completion was compared between subgroups by using the log-rank method of Mantel and Cox. After assessment of the proportionality assumption, multivariate analysis of time to complete study accrual was performed by using the proportional hazards regression method of Cox for estimating the hazard ratio (HR) for each included variable. Variables included in this model were availability of OPRx, study location, use of targeted therapies, and study sponsorship. First-order interaction was explored for all covariate pairs. The average rates of patient accrual were compared by using the nonparametric Mann-Whitney *U* statistic. For regression analysis, the average number of patients accrued per month was normalized by logarithmic transformation. Mean patient accrual per month was regressed on the above covariates by using linear regression analysis. Two-sided tests of the null hypothesis were used throughout.

## RESULTS

### Characteristics of Recent Oncology RCTs

We identified 172 eligible RCTs published between April 2006 and April 2008, including 68 RCTs with at least one US site. Characteristics of all trials and the subset of trials with US sites are presented in Table 1. The majority of trials (88; 51%) were conducted in metastatic solid tumors, 43 (25%) in adjuvant or neoadjuvant solid tumor trials, 23 (13%) in hematologic malignancies, and 18 (10%) in other settings. One hundred thirty RCTs (76%) evaluated a novel drug or combination while 29 trials (17%) evaluated a new delivery method or schedule of standard drugs, and six (3%) evaluated both a new drug or combination and a new delivery method. Seven trials (4%) compared two standard regimens.

The majority of RCTs (104; 60%) were conducted outside the United States. Among 68 trials with US sites, 43 (63%) were conducted exclusively in the United States or Canada (37 United States only, three United States and one Canadian site, three United States and two or more Canadian sites), and 25 (37%) included sites both within the United States and outside North America.

Experimental interventions were available off protocol in the United States during 127 trials (74%). Most interventions were available at trial initiation (108; 63%), while 19 (11%) became FDA-approved for different indications during the trial. Among trials with OPRx availability, 64 (55%) included experimental interventions approved for the same type of cancer but for a different stage, schedule, or mode of delivery, 40 (34%) for a different type of cancer, and 12 (10%) for a noncancer indication (Fig 1). Among the subset of 68 trials with US sites, OPRx availability was identified in 40 (59%) at trial initiation and five (7%) during the course of the trial. Pharmaceutical

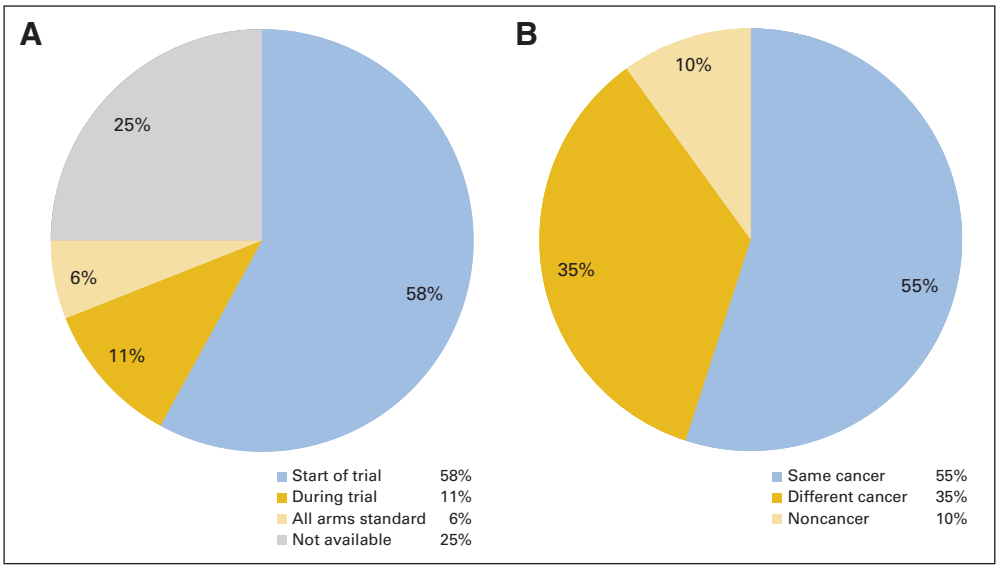


**Fig 1.** United States off-protocol availability of experimental interventions in recent oncology randomized trials on the basis of US Food and Drug Administration approval for other indications.

industry involvement was common with 97 studies (56%) receiving industry support, 46 (27%) reporting industry authorship, and 76 (44%) reporting authors with conflict of interest.

### *Association Between OPRx Availability and Trial Accrual*

Among trials with US sites, those in which OPRx was available at trial initiation had slower time to completion compared with trials in which OPRx was unavailable (median, 41 *v* 22 months; $P = .002$) and slower accrual rate (median, 8.8 *v* 22.7 patients per month; $P < .001$; Fig 2A). Trials conducted primarily in the United States accrued more slowly than trials with both US and international sites (median, 41.0 *v* 24.0 months; $P = .002$) as well as at slower accrual rate (median, 8.8 *v* 19.8 patients per month; $P = .001$; Fig 2B). Trials of targeted therapies completed accrual more rapidly (median, 29 *v* 38 months; $P = .010$) and at a greater rate (median, 16.2 *v* 9.4 patients per month; $P = .05$; Fig 2C). Trials sponsored by industry had shorter time to accrual (median, 25 *v* 44 months; $P = .001$) and faster accrual rate (median: 19.8 *v* 7.43 patients per month; $P < .001$).

In stratified analysis based on trial sponsorship, OPRx availability remained statistically significant for time to complete accrual in non-industry–sponsored studies (median, 28 *v* 54 months; $P = .0035$) but not for industry-sponsored trials (median, 21 *v* 28 months; $P = .294$). Similarly, OPRx availability was associated with statistically significantly slower accrual rate among non-industry–sponsored studies (median, 5.78 *v* 28.59 patients per month; $P = .021$) but not those sponsored by industry (median, 14.63 *v* 22.72 patients per month; $P = .573$). Five percent of all trials were closed early because of poor accrual (6% OPRx available, 2% OPRx unavailable; $P = .4$).

In proportional hazards regression analysis, the impact of OPRx availability on time to accrual remained statistically significant (HR, 0.528; $P = .05$) after adjustment for type of intervention (targeted *v* nontargeted HR, 1.581; $P = .142$) and study location (United States and Canada *v* United States and outside North America HR, 2.02; $P = .020$). Location was not significant after inclusion of study sponsorship in the model. With an interaction term for sponsorship and OPRx included in the model, both OPRx (HR, 0.256; $P = .042$) and targeted therapy trials (HR, 1.026; $P = .041$) remained statistically significant in multivariate proportional hazards regression analysis. Likewise, in linear regression analysis, the availability of OPRx was associated with a significantly lower accrual rate ($P = .012$) after adjustment for studies of targeted therapies ($P = .533$) and study locations ($P = .005$). The availability of OPRx remained statistically significant ($P = .007$) for accrual rate with an interaction term for sponsorship in the model.

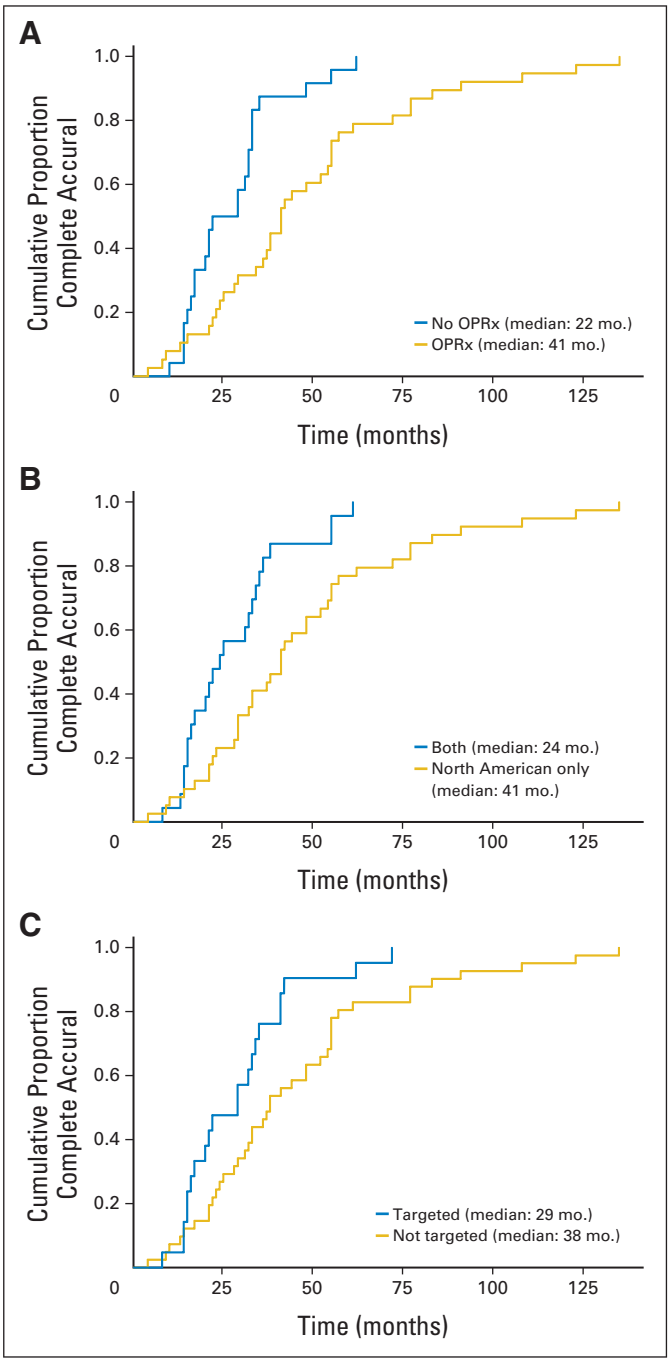


**Fig 2.** Time to trial accrual according to availability of experimental off-protocol intervention, trial center locations, and nature of intervention (Kaplan-Meier curves). (A) Availability of off-protocol therapy (OPRx) versus no availability. (B) Location of trials. "Both" refers to trials conducted at both North American and international sites. "North American only" includes 37 trials with only US sites, three trials with one Canadian site, and three trials with two to three Canadian sites. (C) Types of therapy. "Targeted" refers to therapy with novel targeted biologic agents (ie, monoclonal antibodies, small-molecule tyrosine kinase inhibitors) versus nonbiologic interventions (ie, chemotherapy, endocrine therapy).

### *Disease-Specific Outcomes in Recently Published Oncology RCTs*

Among all trials, 149 (87%) reported disease-specific outcomes including survival, progression-free survival, disease-free survival, or response rate. Among these RCTs, 70 trials (47%) reported that the experimental intervention proved superior for at least one major outcome compared with the control arm (48% OPRx available, 44% OPRx unavailable; $P = .7$). Improvement in overall survival with the experimental intervention was reported in 27% of the trials (24% OPRx available, 35% OPRx unavailable; $P = .2$; Table 2).

Inferiority of an experimental arm compared with the control arm was infrequent, occurring in 11 trials (6%). For three trials (2%), overall survival in the experimental arm was worse than that for standard therapy.[13-15] In five trials, progression-free survival,[16-18] disease-free survival,[19] or the primary symptomatic outcome measure was inferior.[20] In three trials, trial efficacy was equivalent but the

  

**Table 2.** Toxicity and Safety Outcomes in Recent Oncology Randomized Trials

| Variable | All (N = 172) | | OPRx Available in United States (n = 127) | | OPRx Not Available in United States (n = 45) | | *P* for Statistical Significance |
|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | |
| Toxicity | | | | | | | |
| Any increase in grade 3 or 4 toxicity in experimental arm | 114/172 | 66 | 87/127 | 69 | 27/45 | 60 | .3 |
| Increase in febrile neutropenia* | 28/114 | 25 | 23/89 | 26 | 5/25 | 20 | .6 |
| Efficacy | | | | | | | |
| Trials reporting any improvement in major clinical outcome for experimental arm† | 70/149 | 47 | 53/110 | 48 | 17/39 | 44 | .7 |
| Trials reporting improvement survival for experimental arm‡ | 33/122 | 27 | 22/91 | 24 | 11/31 | 35 | .2 |
| Experimental arm inferior to standard therapy | 11/172 | 6 | 6/127 | 5 | 5/45 | 11 | .2 |
| Trial stopped early | 25/172 | 15 | 16/127 | 13 | 9/45 | 20 | .2 |
| For all reasons | | | | | | | |
| Secondary to poor accrual | 9/172 | 5 | 8/127 | 6 | 1/45 | 2 | .4 |
| Positive trial | 87/172 | 51 | 63/127 | 50 | 24/45 | 53 | .7 |

Abbreviation: OPRx, off-protocol therapy.
*Calculated on the basis of the number of trials (114) reporting febrile neutropenia (ie, 28/114 indicates 28 of the 114 trials reporting an increase in febrile neutropenia).
†Calculated on the basis of the number of trials (149) reporting a major clinical outcome.
‡Calculated on the basis of the number of trials (122) reporting overall survival.

experimental intervention was markedly more toxic.[21-23] Experimental inferiority did not vary significantly with OPRx status (5% OPRx available, 11% OPRx unavailable; $P = .2$).

### *Toxicity of Experimental Interventions in Recent Oncology RCTs*

For the majority of RCTs (114; 66%), there was at least one increased grade 3 to 4 toxicity in the experimental arm compared with the control arm. This did not differ on the basis of OPRx availability (69% OPRx available, 63% OPRx unavailable; $P = .3$). Among 114 trials reporting incidence of febrile neutropenia, a significant increase in febrile neutropenia in the experimental arm compared with the standard arm was reported in 28 (25%) of 114 trials (26% OPRx available, 20% OPRx unavailable; $P = .6$; Table 2).

## DISCUSSION

Off-protocol availability of experimental drugs raises questions regarding patient safety, informed consent to treatment, and accrual to clinical trials. This study explores the potential scope of this issue in the United States and provides data regarding the efficacy and safety of recent experimental interventions in all oncology RCTs that may inform clinical and policy discussions regarding OPRx.

We found that the majority of experimental interventions in recently published oncology RCTs were FDA-approved and were therefore potentially available OPRx within the United States. Despite heterogeneity in RCTs, among trials with at least one US site, off-protocol availability of the experimental intervention correlated with longer time to completion of accrual and lower patient accrual per month, suggesting that concerns over the impact of wider availability of experimental interventions outside trials may be valid.

There are many factors beyond FDA approval that have an impact on the actual availability of a therapy outside a trial, including insurance coverage and the influence of early-phase data on physicians' willingness to prescribe an OPRx intervention. Some of the interventions identified as available OPRx on the basis of FDA approval may not have been truly available to patients outside trials, which would make our results an underestimate of the true impact of OPRx on accrual.

This study was designed to measure the potential scope of OPRx, not the true prevalence of OPRx in practice, and there are likely to be many confounding factors that impact accrual, including the study population design, sponsorship, and disease site. It is possible that in some cases, experimental interventions that are available OPRx are perceived as less novel or promising in some way (such as a trial involving a novel combination of common cytotoxic drugs) which slows accrual to the trial as a function of interest in the study rather than interest in treatment outside the clinical trial. However, in multivariate analysis, the impact of OPRx availability on time to accrual completion as well as the rate of patient accrual remained significant after accounting for more novel studies using targeted biologic therapy. Prior studies of specific interventions[24-26] and physicians' attitudes[5] support the possibility that OPRx may have an impact on trial accrual.

The explanation for differences in OPRx on the basis of study sponsorship is unclear. Although the influence of OPRx on accrual was evident in both groups, it remained statistically significant only in non-industry–sponsored studies. It is possible that OPRx has less impact on accrual for drug development trials (the common focus of industry studies) because of efficacy and safety concerns, financial incentives, or other factors, compared with studies that evaluate questions related to established drugs.

In addition to demonstrating a potential impact of OPRx on trial accrual, this study serves to document the ongoing need for evaluation of novel interventions within RCTs. Although 47% of experimental interventions proved superior for at least one major clinical outcome, only 27% demonstrated an improvement in survival. Given the potential for publication bias, this likely represents an overestimate of

improvements in clinical outcomes across all oncology RCTs.[27] In approximately two thirds of RCTs, at least one major toxicity was greater in the experimental arm compared with standard therapy. This is only one measure of potential toxicity from OPRx, and further research could evaluate the frequency of novel safety signals in RCTs compared with earlier published experience with the same interventions. Although in the vast majority of RCTs, clinical outcomes for experimental interventions were at least comparable to standard therapy, in 11 RCTs, patients in the experimental arm did worse. In seven of these trials, the entire trial or the experimental arm with inferior outcomes was stopped early. Patients considering participation in an RCT should gain some reassurance from these data, but this serves as a reminder of the need for RCTs.

This study is limited because of its reliance on published RCTs and the inability to determine whether FDA-approved interventions were truly available and provided to patients OPRx at the time of this study. Increasing scrutiny of off-label therapy in oncology may limit the relevance of FDA approval to OPRx availability in the future.[7,28] The actual impact of OPRx on accrual is likely to vary considerably for specific trials. Use of FDA approval to define OPRx availability limits the focus of this study to the United States and further limits analysis of accrual to trials with US sites. Evaluation of the scope and impact of OPRx on accrual internationally would require similar analysis of drug approval and commercial availability in each country considered. However, safety and efficacy data from recent RCTs presented here are relevant to consideration of OPRx in a broader context.

Access to experimental therapy outside clinical trials remains a complex issue. On the societal level, there are clear benefits from the practice of evidence-based medicine and efficient accrual of patients to clinical trials. However, for patients facing poor prognosis with standard options or with conditions that do not match trial eligibility criteria, there will likely continue to be strong interest in and demand for access to promising novel interventions outside clinical trials. This fact drives expanded access programs and recent FDA clarification of expanded access rules for drugs that are not commercially available.[29] For drugs that are FDA approved, oncologists are likely to want to retain some discretion over when they can treat a patient for an off-label indication.[5,30]

There is need for a better understanding of the scope and impact of OPRx in oncology. This literature-based study provides insight into potential consequences of OPRx within the United States and the potential for both benefit and harm to patients across a wide range of oncology trials. Further investigation of this area, and further debate over the appropriate policy regarding evidence-based practice and use of off-label and OPRx therapy is indicated.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Conception and design:** Erika P. Hamilton, Jeffrey Peppercorn
**Financial support:** Jeffrey Peppercorn
**Administrative support:** Erika P. Hamilton, Jeffrey Peppercorn
**Provision of study materials or patients:** Erika P. Hamilton, Jeffrey Peppercorn
**Collection and assembly of data:** Erika P. Hamilton, Jeffrey Peppercorn
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**Manuscript writing:** Erika P. Hamilton, Gary H. Lyman, Jeffrey Peppercorn
**Final approval of manuscript:** Erika P. Hamilton, Gary H. Lyman, Jeffrey Peppercorn

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