The Effect of Receiving Treatment Within a Clinical Trial Setting on Survival and Quality of Care Perception in Advanced Stage Non–Small Cell Lung Cancer

Taher Abu-Hejleh, MD, Elizabeth A. Chrischilles, PhD,† Thorvardur R. Halfdanarson, MD,* Christian Simon, PhD,‡ Jane F. Pendergast, PhD,§ Dingfeng Jiang, MS,§ Carmen J. Smith, MS,§ Aaron T. Porter, PhD,§ Knute D. Carter, MS,§ Robert B. Wallace, MD, PhD,† and Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)*

Objectives: Treatment outcomes of advanced stage (IIIB and IV) non–small cell lung cancer (NSCLC) are poor. In this study, we explore the survival outcomes and the perception of the quality of care delivered in stage IIIB and IV NSCLC patients treated within versus outside a clinical trial.

Materials and Methods: Data were obtained from the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS). Baseline characteristics according to clinical trial participation were determined. The association between clinical trial enrollment and survival was assessed using a Cox proportional hazard model after adjusting for age, income, primary data collection and research site, comorbidities, self-reported performance status, presence of brain metastasis, stage IIIB versus IV, and cancer histology.

Results: Of 815 stage IIIB and IV NSCLC patients, 56 (7%) were enrolled in clinical trials. Median survival for the patients treated within versus outside a clinical trial was 20.5 versus 16.7 months, respectively ($P = 0.21$). Using a multivariate survival model, clinical trial enrollment did not correlate with longer survival ($P = 0.81$). Comparing patients according to clinical trial enrollment, patients treated within a clinical trial setting perceived a better overall quality of care ($P < 0.01$).

Conclusions: Management of stage IIIB and IV NSCLC patients within a clinical trial setting conveyed a perception of superior care that did not translate into survival benefit. These findings suggest that providing cancer care within a clinical trial should not imply a survival benefit when counseling stage IIIB and IV NSCLC patients about entering clinical trials.

Key Words: lung cancer, clinical trials, quality of care, chemotherapy, radiation therapy

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Lung cancer is the leading cause of cancer death in the United States and the world.[1] Despite the progress made in managing and treating this disease, outcomes for advanced stage non–small cell lung cancer (NSCLC), which comprises the majority of the cases, are poor.[2] Consequently, enrolling lung cancer patients in clinical trials is viewed as potentially the best available treatment whenever possible.

Although clinical trials are primarily designed to test an experimental intervention, there is an argument that participation in a clinical trial may confer survival benefit through enhancing quality of care, stringent patient selection criteria, and adapting aggressive measures for treating patients in trials.[3] This favorable gain from being in a trial is often referred to as the "trial effect" or "inclusion benefit." Although survival advantage for patients in clinical trials was noticed in various cancers,[4–11] including small cell lung cancer and resectable NSCLC, this association is not established in advanced stage NSCLC. Further, most studies that explored the "trial effect" did not adjust for important survival covariates and suffered from small sample size.

Boosting patient accrual to cancer clinical trials has been a major challenge for research institutions.[12,13] Recognizing the crucial need to enroll more patients in trials, it is important to ensure that patients have realistic expectations of the benefits from trial.

The purpose of this study was to examine the survival outcomes, the specifics of the care delivered, and the patient perception of the quality of care provided for advanced stage (IIIB and IV) NSCLC patients managed within versus outside a clinical trial. The study used the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) database, which represents a large cohort of patients across the United States.[14] We believe this study will improve our understanding of the "trial effect" in stage IIIB and IV NSCLC and will be of benefit when counseling patients about entering clinical trials.

MATERIALS AND METHODS

Study Population

The study population included all CanCORS participants with advanced stage NSCLC (stage IIIB or IV per the

From the *Department of Internal Medicine, Division of Hematology, Oncology, Blood & Marrow Transplantation, University of Iowa Hospitals and Clinics; ‡Department of Internal Medicine and Program in Bioethics and Humanities, University of Iowa Hospitals and Clinics; †University of Iowa Hospitals and Clinics; and §Department of Biostatistics, University of Iowa, Iowa City, IA.

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Reprints: Taher Abu-Hejleh, MD, Department of Internal Medicine, Division of Hematology, Oncology, Blood & Marrow Transplantation, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242. E-mail: taher-hejleh@uiowa.edu.

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American Joint Committee on Cancer "AJCC" staging, sixth edition) who had completed a full baseline interview. CanCORS is a broadly representative,[14] large study of care and outcomes in lung and colorectal cancer patients who were diagnosed between September 2003 and June 2005. The study was funded by the National Cancer Institute and involved 7 primary data collection and research (PDCR) sites, which include geographically defined areas, health care delivery systems, and Veterans Administration Hospitals across the United States.

The CanCORS instruments for data collection include baseline and follow-up patient and surrogate interviews, medical record abstraction by trained abstracters, and physician surveys. The baseline interviews were either full length or brief, wherein the latter were for ill patients unable to take the full interview. The surrogate interviews were used if death or sickness prevented the patient from completing the initial interview. All baseline interviews were completed within an average of 4 months after diagnosis. The follow-up interviews/surveys were completed 11 to 14 months after diagnosis (detailed methodology for CanCORS has been previously described).[14] Of the 5207 patients in CanCORS with lung cancer, 2941 had advanced stage NSCLC and 815 completed the full baseline survey.

Study Measures

Data collected from the surveys and the abstracted medical records included sociodemographic and clinical characteristics, symptom management, quality of care delivered, and participation in a clinical trial. All variables were obtained from the full baseline interviews except for location of patient death, following patients' wishes in the last month of life, time spent in place of death before dying, and the patient/surrogate respondent perception of quality of cancer care received, which were obtained from the follow-up surveys. Comorbidities, receipt of chemotherapy treatment, disease stage, histology, presence of brain metastasis, and survival details were collected from medical records. Comorbidity at the time of diagnosis was classified as none, mild, moderate, or severe per the Adult Comorbidity Evaluation 27 Index (ACE-27).[15] Survival data were obtained from medical records and was updated over time from surveys of patients and surrogates and data from participating cancer registries.

Statistical Analysis

Frequencies of categorical variables were calculated according to enrollment in clinical trial. A Monte Carlo approximation to the Fisher exact test and χ^2 tests were used to assess the association between covariates and enrollment in a clinical trial. The Kaplan-Meier curves were used to plot the univariate association between the status of enrolling in a clinical trial and survival. The log rank test was used to compare the 2 Kaplan-Meier curves. Thereafter, a Cox proportional hazard model was used to determine the association between enrollment in a clinical trial and survival adjusting for age, income, PDCR site, comorbidities, self-reported performance status, presence of brain metastasis, stage IIIB versus IV, and cancer histology. The survival analyses had a 90% power to detect a true hazard ratio of 0.645 for the effect of enrolling in a clinical trial on survival as compared with no clinical trial. A Cox proportional hazard model was also used to determine the association between enrollment in a clinical trial and survival only for the patients who received chemotherapy adjusting for the same covariates as in the above model. All analyses were performed in SAS 9.3.

RESULTS

A total of 56 (7%) participants reported having enrolled in clinical trials, which included chemotherapy, 38 (68%); radiation therapy, 8 (14%); or surgery, 1 (2%).

Baseline patient demographics and clinical characteristics for those who enrolled versus did not enroll in a clinical trial are summarized in Table 1. Although patients older than 75 years of age were less likely to receive treatment in a clinical trial (7, 13% vs. 170, 22%), this was not statistically different ($P=0.21$). Patients who received treatment outside a clinical trial were more likely to have lower income ($P=0.02$) and to suffer from brain metastasis ($P=0.02$). There was no significant difference in comorbidities, baseline performance status, PDCR site, cancer stage (IIIB vs. IV), cancer histology, or educational level.

Enrollment in a clinical trial was not associated with improved survival. As shown in the Kaplan-Meier survival curves (Fig. 1), the median survival time for the patients treated within versus outside a clinical trial was 20.5 versus 16.7 months, respectively (Log rank test; $P=0.21$). Assessing survival after adjusting for several covariates using a Cox proportional hazard model (Table 2) also showed no survival benefit for the patients enrolled in clinical trials (hazard Ratio [HR]: 1.05; 95% confidence interval [CI], 0.71-1.55). In the same model, worse survival was noticed in patients with severe comorbidities (HR: 1.54; 95% CI, 1.17-2.02) and stage IV disease (HR: 1.49; 95% CI, 1.23-1.81). The presence of brain metastasis was not associated with worse survival (HR: 1.14; 95% CI, 0.82-1.57). We repeated these analyses after restricting the cohort to the patients who received chemotherapy and still showed no survival advantage for the patients in clinical trials (HR: 1.01; 95% CI, 0.63-1.63) (data in supplementary material, Supplemental Digital Content 1, http://links.lww.com/AJCO/A43).

Table 3 shows the patient-reported symptom management and end-of-life care received according to clinical trial enrollment. There was no significant difference between patients receiving care within versus outside a clinical trial with regard to receiving the needed help for pain ($P=0.93$), mood changes ($P=0.68$), nausea, and/or vomiting ($P=0.98$), cough ($P=0.14$), or breathing ($P=0.21$). Being in a clinical trial did not result in significant differences in the frequency of discussing and receiving hospice care ($P=0.18$ and 0.79, respectively), addressing resuscitation preferences ($P=0.31$), location of death ($P=0.33$), or following patient's wishes in the last month of life ($P=0.87$) (Table 4). However, the patients in clinical trials and their surrogate respondents perceived a superior quality of care compared with the other patients ($P<0.01$) (Table 5).

DISCUSSION

To our knowledge, this is the largest population-based study of stage IIIB and IV NSCLC exploring the survival outcomes and the patients' perception of the care received according to the status of enrollment in a clinical trial. Historically, identifying a comparison group of patients not enrolled in trials has been challenging.[16] However, utilizing the robust CanCORS database, we were able to define stage IIIB and IV NSCLC patients treated within and outside clinical trials with comparable baseline characteristics, and to adjust for important covariates known to be associated with survival in advanced stage NSCLC.

Examining the patients' baseline characteristics (Table 1) showed that those in clinical trials had higher income

TABLE 1. Stage IIIB and IV NSCLC Patient Demographics and Clinical Characteristics

Variables	In Clinical Trial N = 56 N (%)	Not in Clinical Trial N = 759 N (%)	*P*
Sex			0.88
Female	25 (45)	331 (44)	
Male	31 (55)	428 (56)	
Age			0.21
≤64	31 (55)	358 (47)	
65-74	18 (32)	231 (30)	
≥75	7 (13)	170 (22)	
Ethnicity			0.37*
White	38 (68)	543 (72)	
Hispanic	4 (7)	40 (5)	
African American	5 (9)	97 (13)	
Asian	5 (9)	31 (4)	
Other	4 (7)	48 (6)	
Marital status			0.46*
Married	37 (66)	418 (55)	
Living with partner	4 (7)	33 (4)	
Widowed	7 (13)	123 (16)	
Divorced	5 (9)	131 (17)	
Separated	1 (2)	17 (2)	
Never married	2 (4)	33 (4)	
Don't know	0 (0)	1 (<1)	
Missing	0 (0)	3 (<1)	
Region of the country			0.17
Northeast	2 (4)	6 (<1)	
Midwest	14 (25)	154 (20)	
South	11 (20)	164 (22)	
West	29 (52)	435 (57)	
Health insurance			0.20
Yes	53 (95)	677 (89)	
No	3 (5)	82 (11)	
Income ($)			0.02
<20,000	7 (13)	212 (28)	
20,000-<40,000	19 (34)	204 (27)	
40,000-<60,000	6 (11)	121 (16)	
≥60,000	16 (29)	139 (18)	
Missing	8 (14)	83 (11)	
Education level			0.08
Did not finish high school	7 (13)	135 (18)	
High school diploma	19 (34)	241 (32)	
Some college	12 (21)	223 (29)	
College degree	7 (13)	83 (11)	
Grad or professional school	11 (20)	68 (9)	
Missing	0 (0)	9 (1)	
Speaks English at home			0.35*
Yes	53 (95)	730 (96)	
No	3 (5)	22 (3)	
Not applicable	0 (0)	2 (<1)	
Missing	0 (0)	5 (<1)	
PDCR site			0.44
Cancer Research Network	5 (9)	114 (15)	
VA Hospital	7 (13)	97 (13)	
Other	44 (79)	548 (72)	
Comorbidity score at diagnosis			0.58
None	9 (16)	150 (20)	
Mild	17 (30)	244 (32)	
Moderate	8 (14)	116 (15)	
Severe	4 (7)	122 (16)	
Missing	18 (32)	127 (17)	
Recalled performance status			0.17
Not limited at all	28 (50)	302 (40)	
Limited a lot/limited a little	28 (50)	442 (58)	
Missing	0 (0)	15 (2)	
Brain metastasis			
Present	0 (0)	64 (8)	0.02*
Absent	56 (100)	695 (92)	
Stage			0.56
IIIB	18 (32)	273 (36)	
IV	38 (68)	486 (64)	
Histology			0.81
Adenocarcinoma	14 (25)	221 (29)	
Other	24 (43)	411 (54)	
Missing	18 (32)	127 (17)	

*The Fisher Exact Test.
NSCLC indicates non–small cell lung cancer.

($P = 0.02$) and were less likely to have brain metastasis ($P = 0.02$), wherein the latter is mostly due to the common practice of excluding NSCLC patients with brain metastasis from clinical trials. However, other variables associated with survival in NSCLC such as age, performance status, comorbidities, and cancer stage were not statistically different between the patients treated within versus outside trials. This similarity in the baseline characteristics is likely related to our study methods because to achieve comparability we intentionally included only the patients who completed the full baseline survey, who were known to have better baseline performance status, and be more likely candidates for trials. Of note, previous studies showed that selecting healthier patients to enroll in clinical trials has been progressively increasing with time.[17]

In our study, there was no significant difference in the survival of advanced stage NSCLC patients who received care within versus outside a clinical trial even after adjusting for age, income, PDCR site, comorbidities, self-reported performance status, presence of brain metastasis, stage IIIB versus IV, and cancer histology. The only covariates associated with worse survival were cancer stage IV and higher level of comorbidity. The finding that brain metastasis was not associated with worse survival, although exclusively seen in nontrial patients, is consistent with the report by Sperduto et al,[18] which showed that prognosis of NSCLC patients with brain metastasis is variable. Because of the selection process in our study, it is likely that our patient population was fit to receive aggressive treatment for brain metastasis such as surgical resection.

Of interest, survival was not statistically different for the patients according to trial enrollment status after restricting the analysis to those who received chemotherapy. It is noteworthy that most of the recent advances in treating NSCLC have been in the chemotherapy/targeted treatment fields. Of the 56 patients enrolled in clinical trials, 38 (67%) indicated that chemotherapy was involved in the trial. Although this patient-reported item might be limited by the level of the patient's understanding of the research protocol, it does shed a light on the general nature of the clinical trials involved.

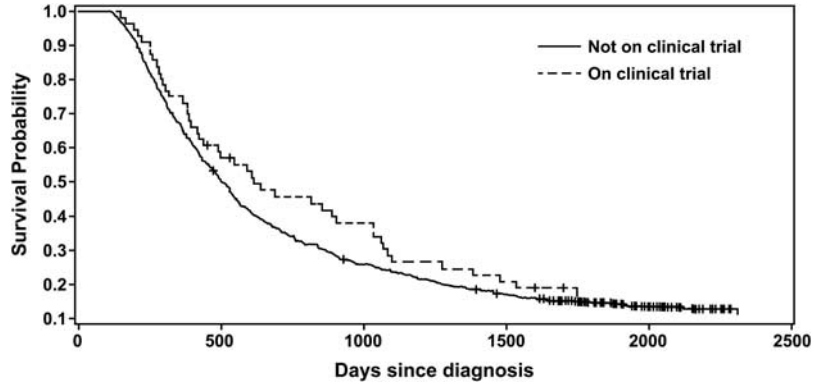

FIGURE 1. Survival analysis for stage IIIB and IV non–small cell lung cancer (NSCLC) patients receiving cancer care within versus outside a clinical trial. Median overall survival after diagnosis of NSCLC was 20.5 versus 16.7 months, respectively (Log rank test: $P = 0.21$).

Various reasons might be put forward to explain the similar survival outcomes. First, advanced stage NSCLC remains a fatal disease, wherein there have been relatively modest improvement in therapy except for a small subset of patients with specific genetic abnormalities lending them candidates for novel targeted therapies.[19,20] Thus, it is crucial not to take our results out of context to discourage patient participation in clinical trials that might potentially introduce new and effective treatments. Second, because of lack of information on the specifics of the trials involved, it is unclear if the trials' outcomes were superior or inferior to standard care. Third, our study might have been underpowered to show a survival difference as the number of patients in trials was relatively small. However, given our results and considering that published studies on the trial effect in advanced stage NSCLC either did not show survival benefit or failed to assign a representative comparison group,[16] it is essential that survival benefit from enrolling in a clinical trial is not implied in efforts to enroll advanced stage NSCLC patients in trials.

The patient-reported cancer care elements including symptom management and end-of-life–related issues were similar, irrespective of the status of enrollment in a clinical

TABLE 2. Cox Proportional Hazard Model of Overall Survival for Stage IIIB and IV NSCLC Patients

Effect	Hazard Ratios (95% CI)	Parameter Estimates (SE)	Wald χ^2 (*df*)	*P*
Enrolled in clinical trial—yes	1.05 (0.71, 1.55)	0.05 (0.20)	0.06 (1)	0.81
Age			2.53 (2)	0.28
≤64	1			
65-74	0.99 (0.80, 1.23)	−0.01 (0.11)	0.01 (1)	0.94
≥75	1.18 (0.94, 1.50)	0.17 (0.12)	1.96 (1)	0.16
Income ($)			4.05 (3)	0.26
<20,000	1			
20,000 - <40,000	0.93 (0.75, 1.16)	−0.07 (0.11)	0.39 (1)	0.53
40,000 - <60,000	0.88 (0.68, 1.15)	−0.12 (0.13)	0.85 (1)	0.36
≥60,000	0.75 (0.56, 1.00)	−0.29 (0.15)	3.92 (1)	0.05
PDCR site			3.10 (2)	0.21
Cancer Research Network	1			
VA Hospital	1.29 (0.92, 1.80)	0.25 (0.17)	2.19 (1)	0.14
Other	1.25 (0.97, 1.63)	0.23 (0.13)	2.91 (1)	0.09
Comorbidity score at diagnosis			12.38 (3)	<0.01
None	1			
Mild	1.03 (0.82, 1.31)	0.03 (0.12)	0.07 (1)	0.79
Moderate	1.12 (0.85, 1.47)	0.11 (0.14)	0.62 (1)	0.43
Severe	1.54 (1.17, 2.02)	0.43 (0.14)	9.44 (1)	<0.01
Recalled performance status			0.36 (1)	0.55
Not limited	0.94 (0.78, 1.14)	−0.06 (0.10)	0.36 (1)	0.55
Limited a lot/a little	1			
Brain metastasis			0.62 (1)	0.43
Absent	1			
Present	1.14 (0.82, 1.57)	0.13 (0.16)	0.62 (1)	0.43
Stage			16.34 (1)	<0.01
IIIB	1			
IV	1.49 (1.23, 1.81)	0.40 (0.10)	16.34 (1)	<0.01
Histology			0.36 (1)	0.55
Adenocarcinoma	0.94 (0.78, 1.14)	−0.06 (0.10)	0.36 (1)	0.55
Others	1			

N = 603.
CI indicates confidence interval; NSCLC, non–small cell lung cancer.

TABLE 3. Symptom Management, Hospice Care, and Revival Status Characteristics of Stage IIIB and IV NSCLC Patients

Variables	In Clinical Trial N = 56 N (%)	Not in Clinical Trial N = 746 N (%)	*P*
Received wanted help for symptom			
Pain			0.93*
Yes	19 (34)	267 (36)	
No	1 (2)	21 (3)	
Not applicable	36 (64)	457 (61)	
Don't know	0 (0)	1 (<1)	
Low energy			0.54
Yes	13 (23)	193 (26)	
No	8 (14)	66 (9)	
Not applicable	34 (61)	479 (64)	
Don't know	1 (2)	8 (1)	
Mood			0.68*
Yes	10 (18)	130 (17)	
No	3 (5)	26 (3)	
Not applicable	43 (77)	588 (79)	
Refused	0 (0)	2 (<1)	
Nausea and/or vomiting			0.98
Yes	14 (25)	190 (25)	
No	1 (2)	11 (1)	
Not applicable	41 (73)	545 (73)	
Cough			0.14*
Yes	11 (20)	209 (28)	
No	0 (0)	35 (5)	
Not applicable	45 (80)	501 (67)	
Don't know	0 (0)	1 (<1)	
Breathing			0.21*
Yes	14 (25)	239 (32)	
No	2 (4)	33 (4)	
Not applicable	39 (70)	472 (63)	
Don't know	1 (2)	2 (<1)	
Hospice was discussed			0.18*
Yes	6 (11)	132 (18)	
No	49 (88)	606 (81)	
Don't know	0 (0)	6 (<1)	
Not applicable	1 (2)	1 (<1)	
Refused	0 (0)	1 (<1)	
Received hospice care			0.79*
Yes	1 (2)	21 (3)	
No	2 (4)	19 (3)	
Not applicable	53 (95)	706 (95)	
Discussed revival or use of life-sustaining machines			0.31*
Yes	18 (32)	258 (35)	
No	37 (66)	472 (63)	
Refused	0 (0)	6 (<1)	
Don't know	0 (0)	8 (1)	
Not applicable	1 (2)	1 (<1)	
Missing	0	1	

*The Fisher Exact Test.
NSCLC indicates non–small cell lung cancer.

TABLE 4. End of Life Care Characteristics for Stage IIIB and IV NSCLC Patients (From Follow-up Surveys)

Variables	In Clinical Trial N = 39 N (%)	Not in Clinical Trial N = 551 N (%)	*P*
Location of patient death			0.33*
Hospital	8 (21)	63 (11)	
Nursing home	0 (0)	8 (1)	
Hospice in patient unit	1 (3)	19 (3)	
Home	3 (8)	91 (17)	
Someplace else	1 (3)	8 (1)	
Not applicable	26 (67)	362 (66)	
Patients' wishes followed during last month of life			0.87*
A great deal	11 (28)	122 (22)	
Somewhat	1 (3)	27 (5)	
Not at all	0 (0)	8 (1)	
Refused	0 (0)	1 (<1)	
Don't know	0 (0)	3 (<1)	
Not applicable	27 (69)	390 (71)	
Time spent in place of death before death			0.78*
<48 h	1 (3)	28 (5)	
48 h-1 wk	2 (5)	49 (9)	
> 1 wk	10 (26)	111 (20)	
Don't know	0 (0)	1 (<1)	
Not applicable	26 (67)	362 (66)	

*The Fisher Exact Test.
NSCLC indicates non–small cell lung cancer.

trial. This suggests, in contrast to published reports, that patients in trials do not receive preferential treatment.[3,21] However, it was noted that the patients treated within a trial perceived a superior quality of care compared with others ($P < 0.01$). Although the basis for this perception is unclear, it is likely to be multifactorial. Patients interested in clinical trials may be inherently more optimistic and likely to hope for successful treatment. Expectations of personal benefit are one reason why patients participate in clinical trials, even if the chances of direct benefit are low.[22] In dose-finding phase I clinical trials, hope for therapeutic benefit was shown to be a strong motivator for participation.[23] Another potential reason for the perceived superior care is that large teams take care of trial patients including physicians, nurses, and research coordinators, which might confer a sense of special care.

Concern about the tendency of research participants to overestimate the benefits of clinical trials has been prominent in discussions of the ethics of cancer trials as well as other studies in which the likelihood of direct benefit is low.[24] Some experts consider this tendency to overestimate the benefits of

TABLE 5. Perceived Quality of Care by Stage IIIB and IV NSCLC Patients or Their Surrogate Respondent (From Follow-up Surveys)

"Would you say That you Received Medical Care That was Better Than, About the Same, or Worse Than Other Patients?"	In Clinical Trial N = 56 N (%)	Not in Clinical Trial N = 759 N (%)	*P*
Better than	17 (30)	106 (14)	<0.01*
About the same	16 (29)	245 (32)	
Worse than	0 (0)	17 (2)	
Refused	0 (0)	3 (<1)	
Don't know	5 (9)	179 (24)	
Not applicable	1 (2)	1 (<1)	
Missing	17 (30)	208 (27)	

*The Fisher Exact Test.
NSCLC indicates non–small cell lung cancer.

clinical trials an example of "therapeutic misconception (TM)" an often-documented failure by research participants to appreciate the differences between research and treatment.[25,26] Despite efforts to fully guard against TM, the risk of TM remains noticeable, particularly in trials for highly serious and fatal disorders.[27,28] Strategies for addressing TM have included efforts to separate the investigators or researchers from control of the clinical care of research patients, clear communication about the differences between on and off trial treatment before and during the informed consent process, and decision monitoring following the consent process.[28] Efforts to address perceived inclusion benefit need not eliminate participants' hope for a positive outcome but, rather, seek to contextualize this hope.

Some limitations should be pointed out when interpreting our results. The number of patients enrolled in trials was relatively small. The trials involved were heterogenous, and included chemotherapy, radiation therapy, and surgery trials without information about the therapeutic agents used or the number of treatments delivered. Only participants who were healthy enough to complete the full baseline interview were included. Finally, the trial type and participation were patient-reported. Despite these limitations, the population-based nature and the large geographic area represented by CanCORS, the ability to adjust for important covariates, and the medical abstraction of clinical variables are unique features that add to the strength of our study.

CONCLUSIONS

This study advances the knowledge on the association between receiving treatment within versus outside a clinical trial, survival outcomes, and patients' perception of quality of care in advanced stage NSCLC. Our findings are insightful for researchers conducting clinical trials as well as for patients. This study supports the notion that survival benefit in NSCLC trials is unlikely related to the ancillary care delivered in trials. In contrast, our study highlights the potential for misperceptions among patients participating in NSCLC trials with respect to the benefits that may confer on them.

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