

Review of Ongoing Clinical Trials in Non–Small-Cell Lung Cancer

A Status Report for 2012 from the ClinicalTrials.gov Web Site

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Introduction: Clinical research in non–small-cell lung cancer (NSCLC) is a rapidly evolving field. In an effort to identify the current trends in lung cancer clinical research, we reviewed ongoing clinical trials in NSCLC listed in the ClinicalTrials.gov registry in 2012, and we also compared this data to a similar survey conducted by us in 2009.

Methods: The Web site's advanced search function was used to search for the term "non-small cell lung cancer." The search was further refined by using the following options from the search page drop-down menu, "open studies" and "interventional." Studies with non-NSCLC tumor histologies and pediatric studies were excluded.

Results: Of the 477 trials included in the analysis, 105 (22.0%) were phase I, 223 phase II (46.8%), and 63 phase III trials (13.2%). When compared with data from 2009, university-sponsored trials decreased in number (45.4%–34.2%; $p < 0.001$) whereas industry-sponsored trials remained almost the same. There was a significant increase in trials conducted exclusively outside of the United States (35.9%–48.8%; $p = 0.001$). The number of studies with locations in China (61, 12.8%) was second only to that in the United States (244, 51.2%). Studies reporting biomarker analysis increased significantly from 37.5% to 49.1% in 2012 ($p < 0.001$). Biomarker-based patient selection also increased significantly from 7.9% to 25.8% ($p < 0.001$). Targeted therapies were evaluated in 70.6% of phase I/II and II trials, and the most common class of targeted agent studied was epidermal growth factor receptor tyrosine kinase inhibitors (38.0%). Prespecified accrual times were observed to increase when compared with data reported in 2009, especially among industry-sponsored studies.

Conclusions: Our survey identified major changes in lung cancer clinical research since 2009. Almost half of all studies registered at the ClinicalTrials.gov Web site are being conducted outside the United States, and several novel molecularly targeted agents are being evaluated in the treatment of patients with NSCLC. More importantly, we identified a threefold increase in the number of studies that perform biomarker testing to determine patient selection over the last 3 years.

Key Words: Non–small-cell lung cancer, ClinicalTrials.gov, Lung cancer, Ongoing studies.

(*J Thorac Oncol.* 2013;8: 860-865)

Lung cancer is the leading cause of cancer related death in both men and women.¹ In 2012, it was estimated that there would be 226,160 new cases of lung cancer and 160,340 related deaths in the United States. Despite some major advances in our understanding of cancer biology and the development of molecularly targeted drugs, there has been only an incremental improvement for patients with lung cancer. Further progress depends upon clinical trials that evaluate new diagnostic and treatment modalities for patients with lung cancer. Clinical trials evaluating anticancer drugs require significant resources, and the vast majority of them do not meet their stated endpoints.^{3,4} We need a better understanding of the composition and characteristics of these trials to improve trial design, identify neglected areas of research, and promote diverse lung cancer research.

Three years ago, we surveyed⁵ ongoing therapeutic clinical trials for patients with non–small-cell lung cancer (NSCLC), registered with ClinicalTrials.gov Web site and the goal of that study was to shed light on trends in clinical trials research, the impact of new developments, such as the use of targeted therapies for the treatment of lung cancer, and the development of novel clinical trial designs to improve the efficiency of clinical trial research. For the first time, the study described ongoing clinical trials evaluating treatments for lung cancer and also identified that only 8% of the trials used a biomarker-based patient selection method. Given the need for better and more efficient clinical trials, we planned on repeating the survey every few years to identify new developments and to keep the information current to guide future trial design.

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/13/0807-0860

The ClinicalTrials.gov Web site was established by the Department of Health and Human Services based on the 1997 Food and Drug Administration Modernization Act and is maintained by the National Library of Medicine at the National Institute of Health.⁶ It is a publicly accessible resource, where all studies in the United States are required to register under federal penalty.⁷ The International Committee of Medical Journal Editors (ICMJE) requires that all clinical trials be enrolled in a freely accessible registry before patient enrollment.⁸ The ClinicalTrials.gov Web site provides a vehicle that allows international organizations to comply with this requirement. This study is a follow-up on our 2009 survey and identifies the progress made in clinical trial design and implementation in the last 3 years.

MATERIALS AND METHODS

The data for this study were collected from the ClinicalTrials.gov, which is an open-access Web site. The advanced search option was used with the search term, “non-small cell lung cancer.” The search was refined by selecting “open studies” for recruitment status, “interventional studies” for study type and selection to adult (18–65 years) and senior (66 years and above) age groups. We used the same search criteria as used in our previous study published in 2010. Trials were excluded from analysis if they did not involve patients diagnosed with NSCLC or did not list medical therapy as an intervention. Our search was executed on March 8, 2012, and the results were saved to a database file. We extracted the following information: (1) clinical trial phase; (2) recruitment status; (3) staging per American Joint Committee on Cancer guidelines; (4) study design including randomization, control group, and number of arms; (5) site location; (6) sponsor; (7) subject accrual time; (8) histology; (9) treatment setting and modality; (10) biomarker analysis; and (11) biomarkers. Study data accuracy was ensured by independent verification of the entire data by three investigators. Statistical analysis was performed to compare data collected in 2012, with previously published data from 2009. Contingency tables were created for comparison and Fisher’s exact test was used to determine whether significant difference existed between these two groups. Data groups analyzed by this method included: (1) study characteristics, including phase, sponsor, recruitment status, study location, randomization, and number of treatment arms, (2) biomarker analysis, including whether biomarker testing was used for patient selection or as inclusion criteria treatment regimen among studies with biomarker analysis, and type of trials analyzing biomarkers. Statistical analysis was not used to compare the type of study outcomes because many trials listed multiple primary outcomes or did not clearly list the primary endpoint. Similarly, we did not calculate statistical significance for differences in the distribution of drug types because the earlier 2009 survey reported only percentages, and also, we did not do a statistical comparison of projected accrual time because some studies did not report this data.

RESULTS

Our search identified a total of 704 trials, of which 227 were excluded from analysis because they included patients

with tumor histologies other than NSCLC or they did not include medical therapy for patients with lung cancer. Of the 477 trials selected for analysis, 440 (92.2%) were actively recruiting, 31 (6.5%) were not yet recruiting, and six had either completed recruitment, or had an unlisted recruitment status but were present in the search result. These six studies were included in the final analysis based on an intention-to-treat principle.

Phase II studies (223, 46.8%) were the most common study type, followed by phase I (105, 22.0%), and phase III (63, 13.2%). The distribution of studies was similar to what we had reported in our 2009 survey ($p = 0.59$; Table 1). In 2012, fewer studies listed universities as the primary sponsor compared with data from 2009 (45.4% versus 34.2%; $p < 0.001$). Phase I/II and II trials were sponsored more often by universities (36.6%) than industry sponsors (27.2%) and other organizations (22.6%), whereas more number of phase III trials were sponsored by industry (46.0%) compared with 11.1% sponsored by universities and 17.4% by other organizations.

More than half (55.8%) of all clinical trials had multiple study locations, which was similar (56.8%) to that reported in the 2009 survey ($p = 0.8$). In 2012, the United States was

TABLE 1. Characteristics of All Clinical Trials Included in Analysis

	2009 (%)	2012 (%)	<i>p</i>
N	493	477	
Type of clinical trial			0.59
Phase I	92 (18.7)	105 (22.0)	
Phase I/II	61 (12.4)	56 (11.7)	
Phase II	240 (48.7)	223 (46.8)	
Phase II/III	3 (0.6)	7 (1.5)	
Phase III	77 (15.6)	63 (13.2)	
Phase IV	8 (1.6)	9 (1.9)	
Unspecified	12 (2.4)	8 (1.7)	
Pilot studies	Not reported	6 (1.2)	
Primary sponsor			<0.001
Industry	166 (33.7)	158 (33.1)	
University	224 (45.4)	163 (34.2)	
Cooperative group	43 (8.7)	46 (9.6)	
National Cancer Institute	18 (3.7)	21 (4.4)	
Others	42 (8.5)	89 (18.7)	
Recruitment status			0.079
Actively recruiting	472 (95.7)	440 (92.2)	
Not yet open for recruitment	19 (3.9)	31 (6.5)	
Closed to recruitment	2 (0.4)	4 (0.8)	
Number of study locations			0.08
Single-study location	213 (43.2)	211 (44.2)	
Multiple-study locations	280 (56.8)	266 (55.8)	
Location			<0.001
United States only	253 (51.3)	189 (39.6)	
International only	177 (35.9)	233 (48.8)	
Located in United States and elsewhere	63 (12.8)	55 (11.5)	

the most common study location (244, 51.1%), followed by the People's Republic of China (61, 12.8%), the Republic of Korea (56, 11.7%), and then the European countries, including France (46, 9.6%), Germany (44, 9.2%), Italy (41, 8.6%), and the United Kingdom (34, 7.1%). Another notable finding in our 2012 data was that when compared with 2009, fewer studies were listed as taking place solely in the United States (39.6% versus 51.3%; $p < 0.001$), whereas there was an increase in studies that listed only locations outside the United States (48.8% versus 35.9%; $p < 0.001$). The percentage of trials occurring in both international locations and in United States was 12.8% in 2009 and 11.5% in 2012. International trials without locations in the United States accounted for a significant proportion of the phase III trials (40, 63.5%) and approximately half of phase I/II and phase II trials (145, 52.0%). Of the 40 phase III trials with locations exclusively outside of the United States, 17 studies (42.5%) had locations in Europe, 18 in Asia, and four additional studies (1.0%) listed locations in both regions.

Among phase I/II and II trials, 59.9% were nonrandomized, the majority were open label (92.8%), and had single-arm design (58.1%; Table 2). In contrast, phase III trials were all randomized, more than half were open-label studies (66.7%) and most of them (93.7%) had at least two treatment arms. There did not seem to be any significant change in the distribution of the most common outcome measures between the two surveys. In phase II trials the most frequent primary outcome measure was progression-free survival, followed by response rate, and then overall survival (Table 3). Similarly, in phase III trials the most common outcomes continued to be overall survival followed by progression-free survival. The majority of phases I/II, II, II/III, and III studies evaluated treatment in patients with advanced stage NSCLC (267, 76.5%). Overall, these findings were not significantly different from the 2009 data ($p = 0.6$; Table 4).

TABLE 2. Selected Characteristics of Phase II and III Trial

Study Design	Number of Phase I/II and II Trials (%) N = 279	Number of Phase II/III Trials (%) N = 7	Number of Phase III Trials (%) N = 63
Randomization			
Randomized	111 (39.8)	7 (100)	63 (100)
Nonrandomized	167 (59.9)	0 (0.0)	0 (0.0)
Open label	259 (92.8)	4 (57.1)	42 (66.7)
Single blinded	2 (0.7)	0 (0.0)	1 (1.6)
Double blinded	18 (6.5)	3 (42.9)	20 (31.7)
Number of treatment arms			
1	162 (58.1)	0 (0.0)	0 (0.0)
2	102 (36.5)	7 (100)	59 (93.7)
≥3	15 (5.4)	0 (0.0)	4 (6.3)
Type of control arm			
Placebo only ^a	0 (0.0)	2 (28.6)	3 (4.8)
Standard care/active control	94 (33.7)	5 (71.4)	49 (77.8)
Uncontrolled	185 (66.3)	0 (0.0)	11 (17.4)

^a Placebo only and excludes studies with placebo in conjunction with best standard of care/active control.

Most studies included some form of targeted therapeutic agent in their treatment arms (Table 5). Many studies involved a combination of standard-of-care treatment with molecularly targeted agents. In phase I/II, II, II/III, and III trials, combined targeted and cytotoxic drugs accounted for 36.1% of all trials compared with 30.1% in 2009, targeted agents alone or in combination with radiation or alternative therapies accounted for 32.1% as compared with 29.1% in 2009, and finally cytotoxic drugs alone or in combination with radiation or alternative therapies accounted for 30.1% compared with 26.8% in the previous study. In clinical trials examining targeted drugs, 38.0% used first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) (Table 6). This was followed by multireceptor TKI (which includes vascular endothelial growth factor receptor TKIs), EGFR antibodies, and second-generation EGFR TKI.

There were significant differences in the number of studies with biomarker analysis between 2009 and 2012 (Table 7). The total number of studies, including biomarker analysis, increased from 37.5% to 49.1% in 2012 ($p < 0.001$). In 2012, almost all (97.0%) studies analyzing biomarkers specified the biomarker being tested, as opposed to only 78.4% of the trials specifying the biomarker ($p < 0.001$) in

TABLE 3. Primary Outcomes of Phase II and III Trials

Outcome	Phase II ^a		Phase III	
	2009	2012 ^b	2009	2012 ^c
OS ^d	32 (10.6)	28 (10.0)	50 (64.9)	37 (58.7)
PFS	106 (35.2)	96 (34.4)	21 (27.3)	19 (30.2)
RR	111 (36.9)	87 (31.2)	1 (1.3)	2 (3.2)
DFS	1 (0.33)	3 (1.1)	1 (1.3)	2 (3.2)
Feasibility	10 (3.3)	10 (3.6)	1 (1.3)	0 (0.0)

^a Includes phase I/II and II trials.

^b Many studies listed up to 4 primary outcomes, thus the total sum will be different than total number of phase I/II and II trials analyzed.

^c Three studies listed 2 primary outcomes.

^d Includes OS, mean survival, survival, and time-specified survival.

OS, overall survival; PFS, progression-free survival; RR, response rate; DFS, disease-free survival.

TABLE 4. Treatment Setting in Phase II and III Trials^a

Treatment Setting	Year and Number of Trials		<i>p</i>
	2009 (N = 381)	2012 (N = 349)	
Adjuvant	22 (5.8)	15 (4.3)	<i>p</i> = 0.6
Neoadjuvant	18 (4.7)	20 (5.7)	
Neoadjuvant/adjuvant	7 (1.8)	4 (1.1)	
Concurrent	38 (10.0)	43 (12.3)	
Palliative total	294 (77.2)	267 (76.5)	
First-line (palliative)	130 (34.1)	115 (33.0)	
First- or second-line (palliative)	7 (1.8)	6 (1.7)	
Second-line or more (palliative)	132 (34.7)	113 (32.4)	
Any line (palliative)	11 (2.9)	7 (2.0)	
Unspecified palliative line	14 (3.7)	26 (7.4)	

^a Includes phases I/II, II, II/III, and III.

TABLE 5. Type of Medical Therapy Being Evaluated in Patients with NSCLC

	Phase I (%) N = 105	Phase I/II, II (%) N = 279	Phase II/III (%) N = 7	Phase III (%) N = 63
Targeted therapy	70 (66.7)	197 (70.6)	5 (71.4)	36 (57.1)
Chemotherapy	48 (45.7)	175 (62.7)	5 (71.4)	51 (81.0)
Immunotherapy	20 (19.0)	13 (4.7)	2 (28.6)	6 (9.5)
Other	7 (6.7)	11 (3.9)	0 (0.0)	0 (0.0)

Total exceeds 100% of studies included in this analysis because of multiple modalities used in some studies.

TABLE 6. Targeted Therapies Being Evaluated in Lung Cancer

Targeted Therapy	Number of Studies ^a (N = 308)(%)
EGFR TKI (first generation)	117 (38.0)
Multitargeted TKI ^b	37 (12.0)
EGFR antibodies	21 (6.8)
Second-generation EGFR inhibitors ^c	20 (6.5)
HDAC inhibitor	20 (6.5)
MTOR inhibitor	14 (4.5)
PI3K inhibitor	11 (3.6)
CMET inhibitor	11 (3.6)
Hsp 90 inhibitors	7 (2.3)
Other	49 (15.9)

^a Phase I, I/II, II, II/III, and III with targeted agents.

^b Multitargeted TKI includes VEGF TKI.

^c Second-generation EGFR inhibitors include: Her2/EGFR, PanHER inhibitor, HER3 Ab.

2009. When compared with clinical trials registered in 2009, which included biomarker analysis, the proportion of such studies with molecularly targeted therapy increased from 42.7% to 47.9% in 2012 ($p = 0.02$). Importantly, there was a significant increase in the number of studies using biomarkers to select patients, either for inclusion in the study, or directing them to specific treatment arms (7.9%–25.8%; $p < 0.001$). The most common biomarker was *EGFR* (62.6%) followed by *KRAS* (11.4%). *ALK* rearrangements were used for patient selection in six trials (4.9%). Among the 16 phase III trials with biomarker-directed patient selection, 10 trials (62.5%) used *EGFR* status. Similarly, in the 80 phase II trials with biomarker-directed patient selection, 54 trials (67.5%) included *EGFR*.

Studies that are registered on the ClinicalTrials.gov Web site also have to provide the time duration over which they plan to accrue all of their patients. Because the timeline for patient enrolment is significantly different between phase II and phase III trials, we analyzed them separately (Supplemental Tables 1 and 2, Supplemental Digital Content 1, <http://links.lww.com/JTO/A402>). The prespecified accrual data were not reported for all studies. Of all phase II and III studies in 2012, 27 studies (9.4%) did not report their accrual time. Overall, clinical trials in 2012 had longer projected accrual times compared with those in 2009. Among phase II trials, the number of studies with projected accrual times less than a year dropped from 93 (38.8%) in 2009, to 19 (8.5%) in

TABLE 7. Characteristics of Clinical trials with Biomarker Analysis

	2009 N (%)	2012 N (%)	<i>p</i>
Studies with biomarker analysis	185 (37.5)	234 (49.1)	<0.001
Biomarker(s) specified			<0.001
Yes	145 (78.4)	226 (96.6)	
No	40 (21.6)	8 (3.4)	
Biomarker-based patient selection	39 (7.9)	123 (25.8)	<0.001
Biomarker used in patient selection			0.08 ^a
EGFR-based selection	17 (43.6)	77 (62.6)	
KRAS-based selection	5 (12.8)	14 (11.4)	
BRAF-based selection ^a	Unreported	8 (6.5)	
Treatment regimen in studies with biomarker analysis ^b			0.02
Targeted therapy	79 (42.7)	112 (47.9)	
Chemotherapy with targeted agent	46 (24.9)	67 (28.6)	
Chemotherapy	24 (13.0)	37 (15.8)	
Immune	23 (12.4)	24 (10.3)	
Alternative	2 (1.1)	0 (0.0)	
Others	11 (5.9)	11 (4.7)	

^a BRAF excluded from statistical analysis.

^b Total exceeds 100% because of overlap in treatment modalities in 2012.

BRAF, v-raf murine sarcoma viral oncogene homolog B1.

2012. Industry-sponsored studies had the greatest reduction in the number of phase II trials with less than 1 year projected accrual time (62.1%–8.0%) and a similar trend was seen in all sponsor groups. As a result, there was an increase in the proportion of phase II clinical trials with projected accrual times of 12 to 24 months and greater than 24 months in 2012 (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/JTO/A402>). This increase was primarily seen in industry-sponsored trials, with the proportion of studies with accrual time of 12 to 24 months increasing from 21.2% in 2009 to 34.0% in 2012. A similar trend was seen for studies with greater than 24 months' projected accrual time by the increase from 16.7% to 58.0%. Projected accrual time for phase III studies in 2012 had a similar trend with a significant decline in the proportion of trials with accrual times less than 12 months from 27.2% to 3.2%. Notably, there were 13 industry trials (39.4%) with accrual times less than 12 months in 2009, and in 2012 there were no industry trials listing their projected accrual time as less than 12 months. In contrast to phase II trials, the 12- to 24-month accrual time also decreased for phase III trials. There were more studies in the greater-than-24-month time frame, and notably, industry trials with accrual times over 36 months increased from 18.2% in 2009 to 62.1% in 2012.

DISCUSSION

Our follow-up survey of ongoing trials in NSCLC registered with ClinicalTrials.gov yielded several interesting findings. The basic study characteristics have remained largely unchanged from our 2009 survey; the majority of the studies were multicenter phase II clinical trials. As expected, the

vast majority of trials were focused on treating patients with advanced stage disease.

We find that globalization has had a major impact on lung cancer clinical trials, with nearly half of all clinical trials (irrespective of the phase of the studies) now being conducted outside the United States, primarily in Asia, followed closely by Europe. This is different from 2009 because only a third of the clinical trials at that time were conducted exclusively outside the United States. A new finding was that 63.5% of phase III trials were located outside of the United States with a similar distribution between Europe and Asia. In fact, the number of clinical trials conducted outside the United States is likely to be even higher because international trials are not required to register with ClinicalTrials.gov, though, the ICMJE does require registration in a publicly accessible register.⁸ The smaller international registries tend to be regional, and in our preliminary research, we observed overlap between these registries and ClinicalTrials.gov, suggesting that this is the preferred registry (data not shown).

Not surprisingly, industry sponsorship is significantly higher for phase III trials, given the expenses and the complexities associated with conducting large studies.⁹ Despite the majority of phase II trials taking place in academic institutions, they remain predominantly nonrandomized, open-label studies with single-arm design, consistent with the data from our earlier publication.⁵ Furthermore, response rate continues to be used frequently as a primary outcome, despite evidence that it may not be an optimal predictor for successful phase III outcomes.^{10,11}

One of the key findings in this study was that the number of clinical trials with biomarker-based treatment selection for lung cancer has significantly increased over the last 3 years. In 2009, biomarkers received limited attention in lung cancer clinical trials, especially with regard to patient selection. Over the last few years, there has been ongoing discussion on the need for biomarker-based patient selection, particularly for clinical trials involving molecularly targeted therapies.^{12–14} This discussion seems to have had a definite impact, and the number of clinical trials with biomarker-based patient selection has tripled in 2012. However, there is still significant room for improvement because nearly 80% of all clinical trials include targeted therapies and this is very likely to increase. Most of the clinical trials involving molecularly targeted drugs for lung cancer are focused on targeting *EGFR*. In comparison, only a few studies include testing for *ALK* rearrangement as inclusion criteria or to direct therapy. There are several new trials focusing on novel targets such as the *Pi3K/MTOR* pathway, *MET*, and heat-shock proteins. Overall, the increasing trend to incorporate biomarker-based patient selection is a welcome development.

Achieving patient accrual targets is essential for successful completion of any clinical trial.¹⁵ In the United States, only 3% to 14% of adults with cancer participate in clinical trials.^{16,17} In our study, we observed that the prespecified accrual times for both phase II and phase III trials have increased when compared with data from 2009. This increase has been uniform across the board for all study sponsors and especially, among industry-sponsored studies. The addition of biomarker-based patient selection, where only a smaller

number of patients are potentially eligible for trial participation, might have led to a realistic projection of timelines.

There are several limitations to our study. The accuracy of the data relies on the study sponsor, and data entry is not uniform across studies, with some studies having a wealth of information and some others providing the bare minimum details. Because the registry is based in the United States, it is not a comprehensive database for all lung cancer trials. Many international trials and even some trials in the United States also may not have been registered on the Web site. The requirements by ICMJE that clinical trials should have been registered on the Web site before publication of the Food and Drug Administration Amendments Act of 2007, which has established penalties for failing to register, are powerful incentives to ensure that the vast majority of clinical trials in the United States, and many other international trials as well, are registered on the ClinicalTrials.gov Web site. Human error in data collection is another potential source of inaccuracy. To avoid such inaccuracies, we implemented multiple layers of data verification, including an initial complete review of the entire data to ensure data accuracy. The strength of this study is our ability to compare the study data with data from 2009, and the comprehensive nature of ClinicalTrials.gov database, which, since 2009, requires sponsors to provide even more detailed information regarding their studies.

Overall, our new survey shows that there has been some significant progress in the design and implementation of lung cancer clinical trials, particularly in the use of biomarker-based patient selection. Given the molecular heterogeneity of lung cancer and the narrow spectrum of activity with molecularly targeted agents, rational drug development is critical to improve the outcomes of patients with lung cancer.

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