



Current clinical trials and patent update on lung cancer: a retrospective review

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Practice Points

- Lung cancer is the leading cause of cancer deaths.
- There are nearly 2250 active registered lung cancer clinical trials at [ClinicalTrials.gov](https://clinicaltrials.gov).
- Trials information, for example, trials characteristics, timeline & intervention type are discussed.
- Analysis and trials issues discussed will pave the path for future clinical research.

Several clinical trials using different interventions are currently being sponsored to combat lung cancer at its different stages. The purpose of this study was to provide a portfolio of those trials. All active, open and recruiting clinical trials registered at [ClinicalTrials.gov](https://clinicaltrials.gov) up to March 2018 were included. Information related to 6092 registered lung cancer trials was downloaded. Phase II trials were in the majority, comprising nearly 48.7% of total clinical trials with industry the major sponsor (41.3%) followed by NIH (12.3%). Multicenter studies were the norm accounting for 47.9% and the main study location was the USA (50.9%). Common interventions were radiation (26%), surgery (22%) and EGFR inhibitors (17%). Patent information includes major patent filing office and sponsors. The data analysis provides a comprehensive description of lung cancer trials.

First draft submitted: 5 October 2020; Accepted for publication: 20 January 2021; Published online: 15 February 2021

Keywords: chemotherapy • clinical trials • clinicaltrials.gov • lung cancer • lung cancer patents

Lung cancer is the second common cancer in the USA with nearly 228,820 new cases and 135,720 deaths in 2020 [1]. Active or passive smoking is one of the significant risk factors for lung cancer. Smoking prevalence has decreased in recent years, but still approximately 37% of US adults are former or current smokers [2]. With age, the incidence of lung cancer increases and is most common in adults aged 55 years or older, and the average 5-year survival rate for lung cancer is among the lowest (17%) of all types of cancer, with only 15% of lung cancer cases diagnosed at an early stage [1–4].

Screening for lung cancer is the earliest measure that was implemented in its treatment. In 2004, there had been inadequate evidence to recommend for or against screening for lung cancer with sputum cytologic evaluation, chest radiography (sensitivity of 73.5% and specificity of 91.3% for chest radiography) or a combination of these tests [5]. The most common technique for treating lung cancer is surgery, where for most stage I and stage II NSCLC tumor removal can be managed [5]. The second best option is chemotherapy and radiation, used for people with NSCLC tumors, and the evidence suggests that chemotherapy after surgery, known as ‘adjuvant chemotherapy’, may help prevent cancer from returning especially in stage II and IIIA disease [6]. For people, with stage III lung cancers that are unable to be removed surgically, doctors typically recommend chemotherapy in combination with definitive (high-dose) radiation treatments. Chemotherapy is usually the primary treatment in stage IV lung cancer [7,8].

Receptors such as EGFR also act as doorways by allowing substances in that can encourage a cancer cell to grow and spread [9,10]. EGFR-mutated lung cancer patients respond better to erlotinib than other chemotherapeutic agents [11,12]. An essential upcoming option is immunotherapy; the US FDA approved the immunotherapy nivolumab (Opdivo) for the treatment of metastatic squamous lung cancer unsuccessfully treated with chemother-

apy [13]. Additional approaches to immunotherapy for lung cancer have shown promise in early clinical trials and are now in late-phase development. They fall into four main categories: monoclonal antibodies, checkpoint inhibitors, therapeutic vaccines and adoptive T-cell transfer [14–19]. Various clinical trials have been reported to study the effectiveness of lung cancer screening. The most extensive testing showed a reduction in lung cancer mortality of 16% (95% CI: 5.0–25.0%) and a reduction in all-cause mortality of 6.7% [20]. This trial included 50,000 adults aged 55–74 years with at least 30 pack-year smoking history. When a similar test was combined with a meta-analysis, the relative risk for lung cancer mortality was 0.81 [1]. One European trial, the Multicentric Italian Lung Detection (MILD) study, is an example of such a meta-analysis [21]. Screening trials have been found to be effective yet a few have reported nonbeneficial results. The PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial evaluated more than 150,000 participants from the general population. It found no benefits of screening in this group or in a subgroup that had tobacco smoke exposure, where no benefits were associated with chest radiography screening [22].

Randomized clinical trials are performed to reduce uncertainty over the efficacy and safety of an intervention and should be designed to result in an unbiased information; however, analysis of trial documentation has revealed that some industry-funded drug trials may be done more for marketing purposes than science. We wanted to define characteristics of drug trials and estimate their prevalence. Trials can have varied interests with competing products. The characteristics which we sought to classify are design, intervention type and treatment settings, biomarker analysis, enrollment timeline and patent information. We provide a global overview of the clinical trial statistics in lung cancer. We briefly describe different characteristics for trial design and type of interventional studies used for lung cancer. Finally, we provide a timeline of patient enrollment and registered patents for lung cancer and discuss advantages, challenges and perspectives for the betterment of clinical trial design for lung cancer studies.

Materials & methods

The methods were performed as in [23].

Data source

On 1 March 2018, a dataset of 6092 clinical studies related to lung cancer was downloaded from ClinicalTrials.gov. The dataset was analyzed using various parameters in Microsoft Excel. Information regarding terminologies can be obtained from Clinical Trials Transformation Initiative website [24].

Study parameters

The data were restricted to active recruiting studies. In advanced search the following parameters were selected ‘open/recruiting/active’ studies for recruitment status, ‘all groups’ for study and age groups. The data extracted comprised both interventional and observational studies. We wanted to keep this review current, so we excluded all completed/terminated/not recruiting clinical trials from our search. Further clinical trials with no intervention information were excluded. The information contains all active clinical trials on lung cancer until March 2018 available on ClinicalTrials.gov. Each study was manually reviewed by the authors (title, interventions, outcome measures, recruiting status, MeSH terms and the full ClinicalTrials.gov record if necessary) to certain relevance to lung cancer study. After initial screening, 2250 studies were selected for final data extraction for analysis (Figure 1).

Data collection & analysis

The following information was extracted from the website: clinical trial phase (early Phase I, I/II, II, II/III, III, IV); recruiting status; location of clinical center; study design; type of study (interventional, observational or others); the number of trial centers; primary sponsor; primary outcome; treatment setting; treatment classes; time relation with phases. Along with that, we also compiled information about patents related to lung cancer from the lens.org website using lung cancer treatment, lung cancer therapeutic, lung cancer diagnostic and ‘lung cancer biomarkers.’ The information extracted was: number of patents published; patent office location; primary applicant name and; biologicals.

Results

Trial characteristic & design

Our parameters identified 2385 trials involving lung cancer. One hundred and thirty five had no treatment information or missing information regarding a location of clinical trials and were excluded from the total clinical

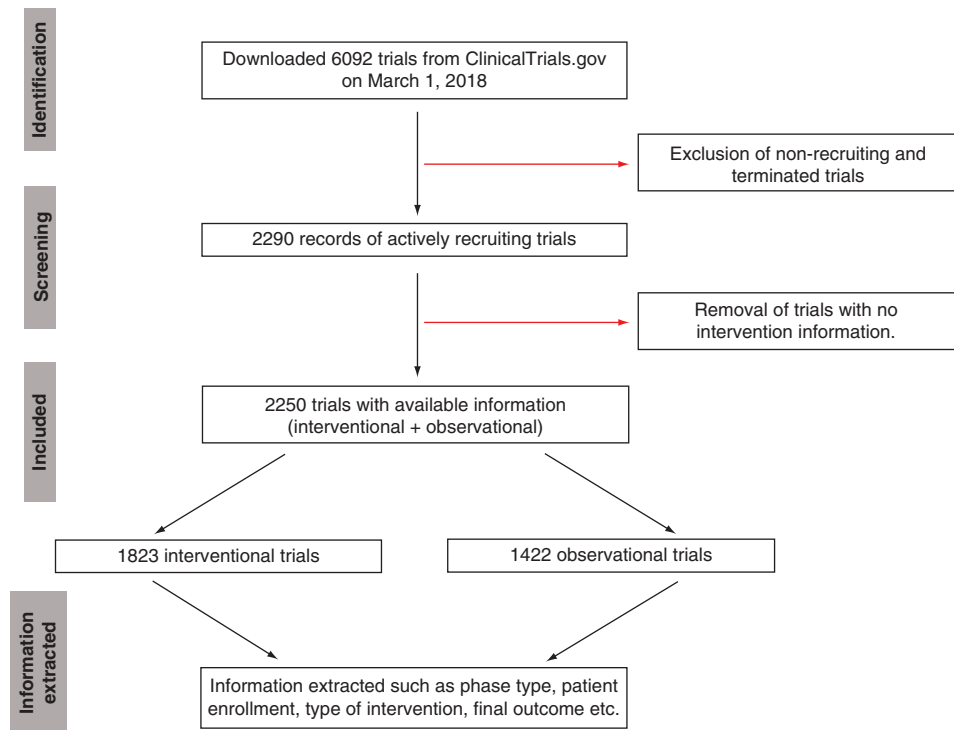


Figure 1. Flowchart of study selection.

trials identified. Overall, 1393 (61.9%) were actively recruiting, 803 (35.7%) were not yet recruiting and 42 (1.9%) were enrolling by invitation only. For 12 trials (0.5%) no information regarding the recruiting status was available, but we included them in our data analysis studies as these clinical trials showed up in our advanced search option when we selected for open and active studies. Of the 2250 clinical trials, Phase II (including Phase I/II) trials were in the majority (810, 48.7%), followed by Phase I (372, 18.7%), Phase III (including II/III) (258, 15.6%) and Phase IV trials (27, 12.4%). Phase was unspecified for 793 (34%) clinical trials. The major sponsor for clinical trials was industry, accounting for 41.3% of trials. For the US federal agency, the NIH was the leading sponsor comprising nearly 276 (12.3%) clinical trials. Nearly half of the total clinical trials (1146, 50.9%) were conducted in the US. A major portion of trials was interventional (1820, 80.9%), indicative of proper treatment/drug provided to one or more group to test for its effects. Moreover, as clinical trials are elaborate in cost, workload and recruitment, more than half of the clinical trials were conducted at multiple locations (Table 1).

The majority of the Phase II (Phase I + Phase I/II) trials were randomized (30.9%) or openlabel (92.6%). For all phases (Phase I, 99.2%; Phase II, 94.4%; Phase III, 81.8%; Phase IV, 96.3%) the standard care or active control was the major arm (Table 2). Overall survival was the major primary outcome in all phases of trials (Phase I, 64%; Phase II, 61.5%; Phase III, 76%; Phase IV, 44.4%) followed by progression-free survival (Phase I, 17%; Phase II, 8.5%; Phase III, 6.2%; Phase IV, 11.1%), tumor response rate (Phase I, 15.9%; Phase II, 16.5%; Phase III, 5.2%; Phase IV, 3.7%) and quality of life (Phase I, 7.8%; Phase II, 11.5%; Phase III, 10.5%; Phase IV, 18.5%) (Table 2).

Intervention type & treatment settings

Lung cancer treatment involves several types of therapeutic methods as seen in Figure 2. Chemotherapy was the most used intervention with EGFR inhibitors being the major class of intervention accounting for nearly 17% of clinical trials. This was followed by microtubule inhibitors (12%) followed by radiation therapy and surgery comprising 26 and 22% of clinical trials, respectively. A recent boom in using immunotherapy as an intervention was also seen in clinical trials (10%). Next, we extracted information regarding the treatment lines for Phase II and Phase III trials. For the advanced stage of disease: first-line therapy was the most common intervention with 177 (22.3%) clinical trials followed by the second-line of therapy with 92 (11.6%). For large datasets, nearly 318 (40.1%) clinical trials no information was provided regarding the line of therapy (Table 3 & Figure 2A).

Table 1. All open clinical trial characteristics.

	Trials, n (%)
Type of clinical trials	
Phase I	372 (16.5%)
Phase I/II	242 (10.7%)
Phase II	568 (25.2%)
Phase II/III	34 (1.5%)
Phase III	224 (9.9%)
Phase IV	27 (1.2%)
Unspecified	
Primary sponsor	783 (34.8%)
Industry	930 (41.3%)
Nonprofit	294 (13.35%)
Others	1042 (46.3%)
Recruiting status	
Actively recruiting	1393 (61.9%)
Not yet recruiting	248 (11%)
Active, not recruiting	555 (24.7%)
Enrolling by invitation	42 (1.9%)
Unknown	12 (0.5%)
Study locations	
Single	969 (43%)
Multiple	1119 (49.7%)
Unspecified	162 (7.2%)
Location of trial centers	
Within the US	1146 (50.9%)
Outside the US	1104 (49%)
Type of study	
Interventional	1820 (80.9%)
Observational	429 (19%)
Others	1 (0.1%)
Data generated from Clinicaltrials.gov	

Table 2. Characteristics of Phase II and III clinical trials.

Study design	Phase I trials, n (%)	Phase II trials, n (%)	Phase III trials, n (%)	Phase IV trials, n (%)
Randomization				
Randomized	26 (6.9%)	251 (30.9%)	236 (91.4%)	18 (66.7%)
Nonrandomized trials	128 (34.4%)	148 (18.3%)	8 (2.1%)	
Unknown	218 (58.6%)	411 (50.8%)	14 (5.4%)	9 (33.3%)
Openlabel	363 (97.5%)	750 (92.6%)	182 (70.5%)	19 (70.4%)
Unknown	9 (2.5%)	60 (7.4%)	76 (29.5%)	8 (29.6%)
Type of control arm				
Placebo	3 (0.8%)	45 (5.6%)	43 (16.7%)	1 (3.7%)
Standard care or active control	369 (99.2%)	765 (94.4%)	211 (81.8%)	26 (96.3%)
Uncontrolled			4 (1.5%)	
Primary outcome				
Overall survival	238 (64%)	498 (61.5%)	196 (76%)	12 (44.4%)
Progression-free survival	46 (17%)	69 (8.5%)	16 (6.2%)	3 (11.1%)
Tumor response rate	59 (15.9%)	134 (16.5%)	14 (5.2%)	1 (3.7%)
Quality of life	29 (7.8%)	93 (11.5%)	27 (10.5%)	5 (18.5%)
Others or unspecified		16 (2%)	5 (1.9%)	6 (22.2%)

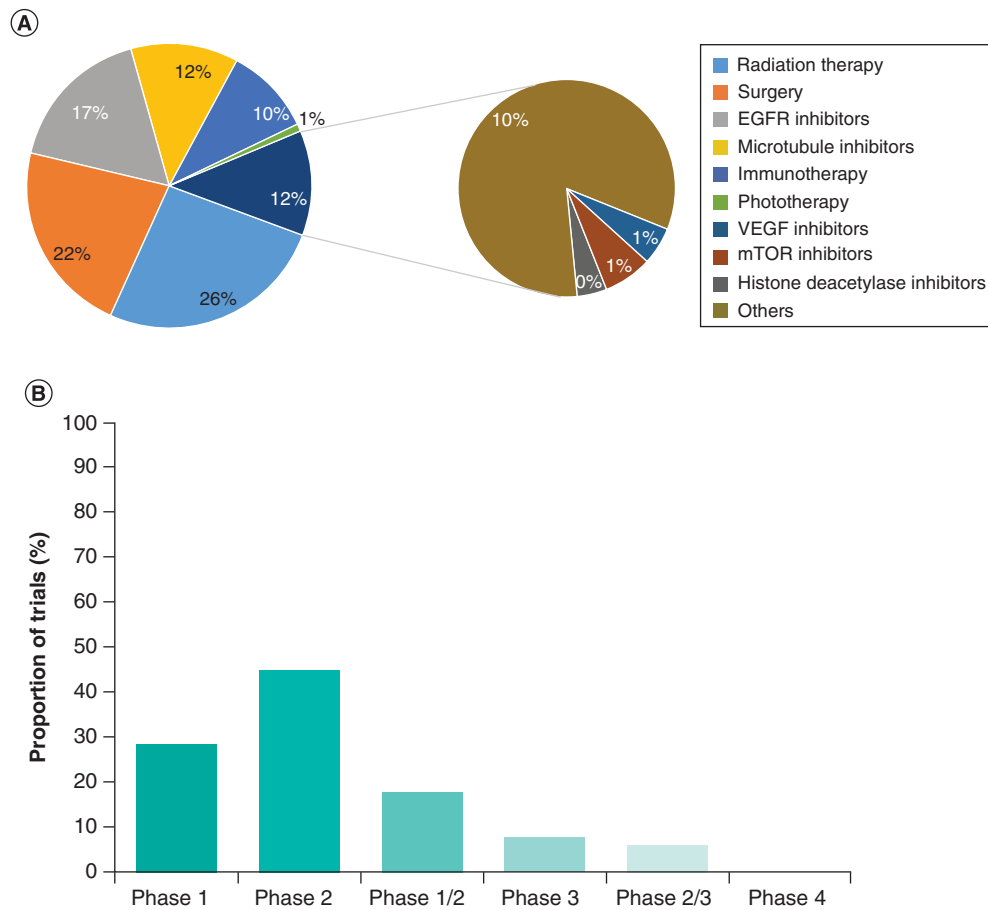


Figure 2. Types of treatment for lung cancer in clinical trials Phase I-IV. (A) Types therapy for treating lung cancer. (B) Biomarker analysis studies in clinical trials.

Table 3. Chemotherapy treatment settings for clinical trials.

Treatment setting	Trials, n (%)
Chemoprevention	4 (0.5%)
Adjuvant therapy	33 (4.2%)
Neoadjuvant therapy	48 (6%)
Adjuvant/neoadjuvant therapy	17 (2.1%)
Concurrent chemoradiotherapy	30 (3.8%)
Advanced-stage disease:	
First line	177 (22.3%)
First or second line	2 (0.2%)
Second line	92 (11.6%)
Maintenance	71 (9%)
Others or unspecified	318 (40.1%)

Biomarker analysis

Early detection of cancer plays a key role in successful treatment. Recently, several research studies have focused on identifying and detecting specific biomarkers in cancers. We also analyzed data from all phases and found out that for 108 clinical trials as a study objectives biomarker was included. In Phase II clinical trials biomarker information was provided for 48 (44.4%) trials, followed by Phase I (30, 27.8%), Phase I/II (16, 17.6%), III (8, 7.4%) and II/III (6, 5.5%) (Figure 2B).

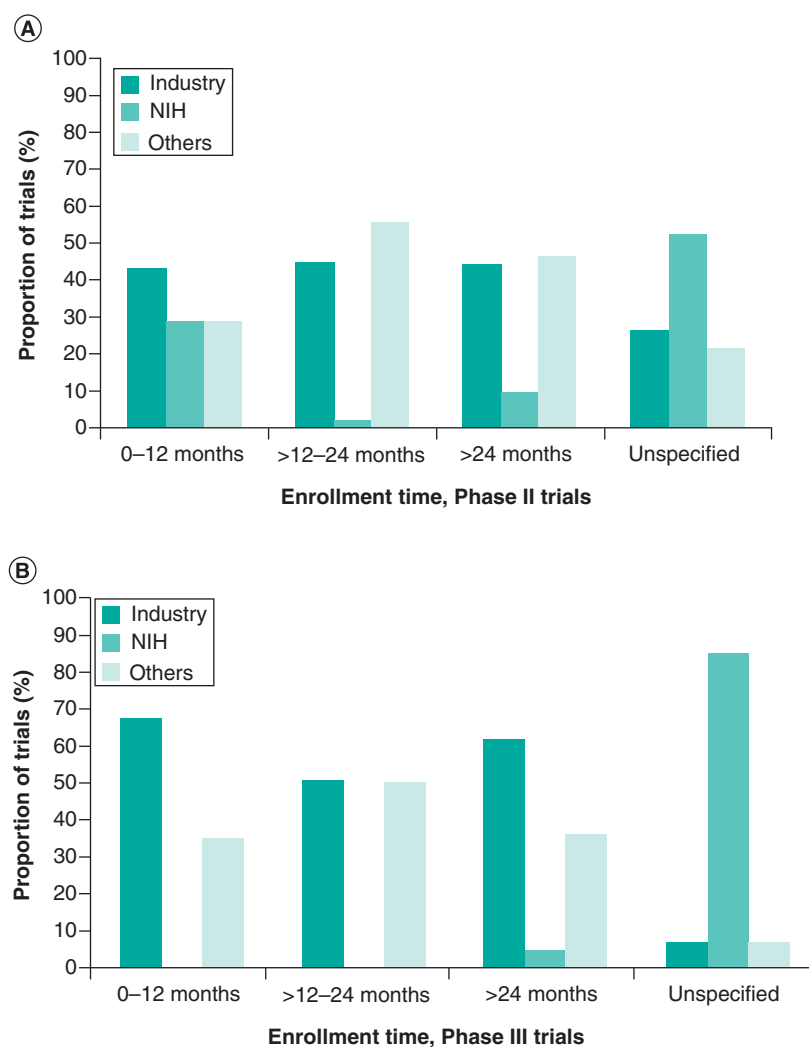


Figure 3. Clinical trials time line for patient enrollment. (A) Phase II and (B) Phase III.

Patient enrollment timeline

Phase II and III clinical trials were considered for patient enrollment data. Number and time of patient enrollment are important variables to determine accuracy of trial interpretation. Industry-sponsored Phase II clinical trials was the largest group when compared (44.9 vs 2%) to NIH sponsored clinical trials. Approximately 52.4% of clinical trials were NIH sponsored, and no patient enrollment information was provided for them. Phase III clinical trials had a similar trend with the industry-sponsored trial taking the lead (61.3%), when compared with NIH sponsored clinical trials. Again, patient enrollment timeline was not provided for a large number of NIH sponsored Phase III clinical trials (Figure 3).

Lung cancer patents information

Our search concluded with nearly 34,760 patents registered for lung cancer as of 1 March 2018. The USA was found to be the significant location for filing patents accounting for 21,543 (62%) patents, followed by Europe 7808 (22.5%) and Australia 5069 (14.6%). Merck registered the highest number of patents on clinical trials (632, 1.8%), followed by Novartis (573, 1.6%) and Genentech (503, 1.4%) (Table 4).

Discussion

Our contemporary study provides lung cancer clinical trial including interventional and observational examinations. Different qualities of preliminaries, for example, design, location, type of intervention, patient enrolment and

Table 4. Recent patents related to lung cancer.

Patents	Patents, n (%)
All	34,740
Patent office location	
USA	21,543 (62%)
Europe	7808 (22.5%)
Australia	5069 (14.6%)
China	57 (0.2%)
South Korea	40 (0.1%)
Hong Kong	34 (0.1%)
Japan	32 (0.1%)
Russia	32 (0.1%)
Spain	27 (0.09%)
Canada	23 (0.09%)
Others	–
Top ten applicants	
Merck	632 (1.8%)
Novartis	573 (1.6%)
Genentech	503 (1.4%)
University of California	441 (1.3%)
Johns Hopkins University	261 (0.7%)
US Health	261 (0.7%)
Covidien	254 (0.7%)
AbbVie	242 (0.7%)
Boehringer Ingelheim	221 (0.6%)
University of Texas	221 (0.6%)
Top ten biologicals	
<i>Homo sapiens</i>	5823 (16.8%)
<i>Mus musculus</i>	1310 (3.8%)
<i>Rattus norvegicus</i>	398 (1.4%)
<i>Bos taurus</i>	225 (0.6%)
<i>Macaca fascicularis</i>	185 (0.5%)
<i>Macaca mulata</i>	144 (0.4%)
<i>Oryctolagus cuniculus</i>	138 (0.4%)
<i>Sus scrofa</i>	131 (0.4%)
<i>Gallus gallus</i>	125 (0.3%)

sponsors are discussed. The study demonstrated significant preliminaries on the ClinicalTrials.gov site for stage 2 lung cancer. As setting up clinical preliminaries requires serious use of assets, cash and publicized patient enrolment, lung cancer trials were in the majority multicentered and sponsored by industry, the NIH and universities. In our investigation, a few information focuses were unknown as the preliminary came up short on the data for that particular column. Industry-supported stage 2 clinical preliminaries were open for a more extended time in contrast with college or US government office-supported preliminaries. However, the pattern was reversed for Phase III clinical trials.

One of the serious issues with all these clinical trials was the absence of biomarkers in stage 2 lung cancer trials, and a comparable example is followed at stage 3 lung cancer trials. Biomarker examination data was accessible for just 10% of complete clinical trials. In the future, the beginning phase clinical trials focusing on the better comprehension of pathways and atomic level examinations should be embedded prior to pushing ahead. In addition, biomarker investigation is an important step in advancement of precision medicine. In advanced stages of lung cancer tissue biomarker analysis is difficult as tissue is degraded for collection. Thus, selecting more patients for beginning phase clinical trials in the lungs would be a good method to beat this constraint. Almost 49% of clinical preliminaries were performed on the patients with lung cancer at stage I or II, which is a decent advance given

the tissues are as yet unblemished for biomarker improvement and examination. Moreover, significant amounts of lung cancer patients undergo relapse at early-stage even after surgery or postoperative therapy [25–27]. The novel biomarkers utilizing the examinations performed on tissues could drastically improve the success rates in beginning phases of lung cancer. All these previously mentioned steps would forestall significant stage 3 clinical preliminary disappointments and would assist with conquering the study design issues.

Another important information discussed in this paper regards currently published patents in lung cancer. In comparison with the clinical trials data, the information provided in patents lacks several major elements. In recent years ClinicalTrials.org has become a prime website to extract clinical trials information, whereas google patents provide the information for patents, but lacks a basic divisional structure like that for clinical trials. So, we utilized lens.org for our patent data analysis as it was better structured and provided the information required for the data analysis. At the country-level finding, the USA was found to be the significant location for filing patents followed by Europe and Australia. Although, we used ClinicalTrials.gov as the primary data source and non-USA trials are registered on EU or Japanese sites, the USA did show a significant patent filling number. Data discrepancy in the analysis due to human error is one of the major issues with such an analysis. We reviewed the data multiple times and blindly among all other authors to overcome this issue.

Other than that, there are several limitations to clinical trial data analysis from ClinicalTrials.gov which needs to be considered as we move forward with such data analysis reviews in future. The ClinicalTrials.gov websites consist of information for all trials in the US or sponsored by multinational organizations (e.g., pharmaceutical companies). However, it lacks information for outside US and trials funded by small organizations. Information and links for other clinical trials registries are provided at the US Department of Health and Human Services, Office for Human Research Protections portal. This includes links of nearly 32 registries from different countries and 11 registries from major pharmaceutical companies. The second issue is related to the information provided in the clinical trials. Moreover, most of the Phase II clinical trials had limited patient enrollment (100 or fewer) which leads to an inappropriate conclusion about the therapy due to failing to reject the null hypothesis and high risk of a type II error [28]. At last, as stated before some data were missing for major characteristics such as intervention, primary sponsor, phases and so on. This might be due to the fact we also selected observational studies for our analysis. Moreover, result information regarding the completed clinical trials was not updated (data not shown), and this is in parallel with the previous observation regarding the low compliance result reporting issue at ClinicalTrials.gov [29]. According to the NIH and FDA CFR 11.44(b) guidelines, some regulations provide for the delayed submission of results information under certain conditions, and also some institutions are not under regulation to submit certain types of information, so a future scope of our present study would be to compare studies covered and not covered by regulatory registration. The NIH further states that the trial has one or more sites in the USA, the trial is conducted under an FDA investigational new drug application or investigational device exemption and the trial involves a drug, biological or device product that is manufactured in the USA or its territories and is exported for research. However, some studies listed as outside the USA could enroll both within and without registration and thus requires a clause to distinguish them and classify separately under regulatory registrations. To overcome a missing data elements issue and improve the quality of lung cancer trial protocols, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement with a 33-item checklist should be followed [30].

Conclusion

Based on the data collected from ClinicalTrials.gov, our analysis reveals that the major clinical trials comprised Phase II with industry-sponsored trials lasting for more than 2 years of enrollment and radiation, surgery and chemotherapy being the major intervention. Most of them were randomized-trials with the primary outcome focused on patient survival. Our comprehensive analysis provides useful information regarding lung cancer which may be helpful to industry and investigators for future decisions.

Future perspective

With rapid changing dynamics of clinical trials and with ongoing vaccine efforts for the COVID-19 pandemic, the importance and awareness of trials has increased. Clinical trials are extremely important in understanding robustness of the trialed agent; however, it is possible for certain private companies to attempt to gain advantage by cutting corners. This review illustrates an increasing number of trials in various for profit and nonprofit institutions, highlighting that a strong regulatory compliance needs to be in place not just in the USA but worldwide to make sure efficacies of trial agents are not compromised in the future.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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References

1. Key Statistics for Lung Cancer. American Cancer Society. (2021). <https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html>
2. Sateia HF, Choi Y, Stewart RW *et al*. Screening for lung cancer. *Semin. Oncol.* 44(1), 74–82 (2017).
3. Furrkh M. Tobacco smoking and lung cancer: perception-changing facts. *Sultan Qaboos Univ. Med. J.* 13(3), 345–358 (2013).
4. Cancer Research UK. Cancer statistics reports for the UK. (2018). <http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>
5. Aberle D, Berg C. National lung screening trial research team. The national lung screening trial: overview and study design. *Radiology* 258(1), 243–253 (2011).
6. Non-small-Cell Lung Cancer Collaborative Group. Chemotherapy in non-small-cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 311(7010), 899–909 (1995).
7. Zappa C, Mousa SA. Non-small-cell lung cancer: current treatment and future advances. *Transl. Lung Cancer Res.* 5(3), 288–300 (2016).
8. Hanna Nasser *et al*. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update summary. *J. Oncol. Pract.* 13(12), 832–837 (2017).
9. Lynch TJ, Bell DW, Sordella R *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* 350(21), 2129–2139 (2004).
10. Paez JG, Jänne PA, Lee JC *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 304(5676), 1497–1500 (2004).
11. Pao W, Miller V, Zakowski M *et al*. Mardis E. EGF receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc. Natl Acad. USA* 101(36), 13306–13311 (2004).
12. Solomon BJ, Mok T, Kim DW *et al*. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* 371(23), 2167–2177 (2014).
13. Kazandjian D, Suzman DL, Blumenthal G *et al*. FDA approval summary: nivolumab for the treatment of metastatic non-small-cell lung cancer with progression on or after platinum-based chemotherapy. *Oncologist* 21(5), 634–642 (2016).
14. Hodi FS, O’day SJ, McDermott DF *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. *N. Engl. J. Med.* 363(8), 711–723 (2010).
15. Lynch TJ, Bondarenko I, Luft A *et al*. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter Phase II study. *J. Clin. Oncol.* 30(17), 2046–2054 (2012).
16. Kazandjian D, Suzman DL, Blumenthal G *et al*. FDA approval summary: nivolumab for the treatment of metastatic non-small-cell lung cancer with progression on or after platinum-based chemotherapy. *Oncologist* 21(5), 634–642 (2016).
17. Borghaei H, Paz-Ares L, Horn L *et al*. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N. Engl. J. Med.* 373(17), 1627–1639 (2015).
18. Topalian SL, Sznol M, McDermott DF *et al*. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J. Clin. Oncol.* 32(10), 1020 (2014).
19. Balmanoukian AS, Rizvi NA, Garon EB *et al*. Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small-cell lung cancer (NSCLC): novel therapies/experimental therapies. *J. Radiat. Oncol.* 90(5), S1–S2 (2014).
20. Pinsky PF, Church TR, Izmirlian G *et al*. The National Lung Screening trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer* 119(22), 3976–3983 (2013).
21. Pastorino U, Rossi M, Rosato V *et al*. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur. J. Cancer Prev.* 21(3), 308–315 (2012).
22. Oken MM, Hocking WG, Kvale PA *et al*. Screening by chest radiograph and lung cancer mortality: the prostate, lung, colorectal, and ovarian (PLCO) randomized trial. *JAMA* 306(17), 1865–1873 (2011).

23. Batra H, Pawar S. Current clinical trials update on HIV/AIDS: a systematic review. *HIV & AIDS review. Int. J. HIV-Rel. Prob.* 18(2), 79–84 (2019).
24. Kreutz D, Ramos FM, Verissimo PE *et al.* Software-defined networking: a comprehensive survey. *Proc. IEEE* 103(1), 14–76 (2015).
25. Ravdin PM, Davis G. Prognosis of patients with resected non-small-cell lung cancer: impact of clinical and pathologic variables. *Lung Cancer* 52(2), 207–212 (2006).
26. Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 111(6), 1710–1717 (1997).
27. Goldstraw P, Crowley J, Chansky K *et al.* International Association for the Study of Lung Cancer International Staging Committee. The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. *J. Thorac. Oncol.* 2(8), 706–714 (2007).
28. Akobeng AK. Understanding type I and type II errors, statistical power and sample size. *Acta Paediatr.* 105(6), 605–609 (2016).
29. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 344, d7373 (2012).
30. Chan AW, Tetzlaff JM, Altman DG *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann. Intern. Med.* 158(3), 200–207 (2013).