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journal homepage: www.elsevier.com/locate/lanwpcThe changing landscape of anti-lung cancer drug clinical trials in mainland China from 2005 to 2020[☆]Qiaofeng Zhong^{a,1}, Yunxia Tao^{a,1}, Haizhu Chen^a, Yu Zhou^a, Liling Huang^a, Xiaohong Han^{b,*}, Yuankai Shi^{a,*}

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ABSTRACT

Background: In recent years, new drug development on lung cancer is in full swing in China. The aim of this study was to overview the changing landscape of anti-lung cancer drug clinical trials in mainland China from 2005 to 2020.

Methods: We analysed anti-lung cancer drug clinical trials registered on three websites including the China National Medical Products Administration Centre for Drug Evaluation platform, the Chinese Clinical Trial Registry and ClinicalTrials.gov.

Findings: A total of 1595 anti-lung cancer drug clinical trials from Jan 1st, 2005 to Dec 31st, 2020 were extracted, which included 630 (39.5%) investigator-initiated trials (IITs), 698 (43.8%) domestic industry-sponsored trials (ISTs), and 267 (16.7%) international ISTs. During the past 16 years, the number of anti-lung cancer clinical trials including IITs and domestic ISTs had a remarkable growth, however, the number of international ISTs increased slowly. The number of principal clinical trial units also increased significantly over time. Of the 1595 trials, the largest growth was observed in phase I trials during 2013–2020, with an average annual growth rate of 38.6%. 278 trials were led by principal investigators (PI) from Guangdong, followed by Beijing ($n=273$) and Shanghai ($n=257$). Among the 965 ISTs, clinical trials involving targeted drugs (588, 60.9%) accounted for the largest proportion, followed by immunotherapeutic drugs (284, 29.4%), cytotoxic drugs (75, 7.8%), and traditional Chinese medicine (18, 1.9%). In terms of targeted drugs, EGFR-TKIs remained the most studied drugs (225/588, 38.27%). As for immunotherapy, 125 out of 284 (44.01%) trials involved PD-1 inhibitors, 60 (21.13%) trials involved PD-L1 inhibitors, and seven (2.46%) trials involved CTLA-4 inhibitors.

Interpretation: In the past 16 years, the development of anti-lung cancer drug clinical trials has achieved much progress in mainland China. The most progress lied in targeted therapy and immunotherapy.

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Research in context

Evidence before this study

We searched PubMed website using “lung cancer”, “clinical trials”, and “China” as keywords to identify eligible published articles. One study depicted the whole changing landscape of registered clinical trials for all cancer types and one study for breast cancer in mainland China, and several studies described clinical trials involving specific treatment strategy for lung cancer, such as tyrosine kinase inhibitors (TKIs) and programmed cell death-1(PD-1)/PD-1-ligand 1 (PD-L1) inhibitors. However, no previous study has provided overall landscape in the research and development (R&D) on anti-lung cancer drug clinical trials in mainland China to date.

Added value of this study

This study provides a comprehensive analysis of anti-lung cancer drug clinical trials during 2005–2020 in mainland China. During the past 16 years, the number of anti-lung cancer clinical trials displayed a continued increase, irrespective of investigator-initiated trials and industry-sponsored trials. The number of principal clinical trial units increased over time as well. The largest growth was observed in phase I trials, with an average annual growth rate of 38.6%. For newly tested drugs, the most obvious growth was seen in clinical trials involving targeted and immunotherapeutic drugs. For targeted drugs, epidermal growth factor receptor was the most studied target. PD-1/PD-L1 inhibitors represented the most studied immunotherapeutic drugs. To the best of our knowledge, this is the first study to comprehensively depict the changing landscape of anti-lung cancer drug clinical trials in mainland China (2005–2020).

Implications of all the available evidence

This study demonstrated the substantial progress of the R&D on anti-lung cancer drugs and clinical trials during the past 16 years (2005–2020) in mainland China. The prosperous development of clinical trials has provided more therapeutic options for Chinese patients with lung cancer and contributed to the global drug pipeline. Meanwhile, this study pointed out several shortcomings requiring improvement such as the severe uneven geographical distribution of principal clinical units across mainland China and excessive duplications of “me-too” drugs. Therefore, this study could provide useful information and direction of efforts for investigators, pharmaceutical enterprises, policy makers and other stakeholders.

1. Introduction

Lung cancer is the most common cancer worldwide, with about 2.2 million new cases and 1.8 million deaths in 2020 [1]. There were about 733, 300 newly diagnosed lung cancer cases, accounting for 17.1% of all cancer diagnoses, and 610, 200 lung cancer deaths, representing 21.7% of overall cancer mortality in China in 2015 [2].

Lung cancer is generally divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for approximately 85% of all lung cancer cases [3]. The median overall survival (OS) was only about four months for metastatic NSCLC with the best supportive care [4], and platinum-based chemotherapy yielded a response rate of 20–30% with a median OS less than one year [5]. The substantial improvement in survival, resulting from dissemination of targeted therapies, contributed most to a rapid decline in mortality from NSCLC [6]. In recent years, immunotherapy, mainly programmed cell death-1 (PD-1) and PD-1-ligand 1 (PD-L1) inhibitors have dramatically improved patients' survival and quality of life, and shifted treatment paradigm of NSCLC [7–12]. While for SCLC, no obvious improvement in survival was observed before the approval of PD-L1

inhibitors as first-line treatment options [13,14]. Therefore, the development of new anti-cancer drugs plays a remarkable role in improving the survival of lung cancer patients.

In recent years, the Chinese government has issued a series of regulatory policies for promoting the development of innovative drugs and clinical trials since 2015, and the research and development (R&D) on anti-lung cancer drugs is in full swing [15–18]. Therefore, we analysed registered clinical trials from three websites to depict the changing landscape of anti-lung cancer drug clinical trials in mainland China between 2005 and 2020. We hope that this analysis could provide useful information for investigators, pharmaceutical enterprises, policy makers and other stakeholders.

2. Methods

2.1. Data sources

We retrieved registered trials regarding anti-lung cancer drugs on the China National Medical Products Administration (NMPA) Centre for Drug Evaluation (CDE) website (<http://www.cde.org.cn/>), Chinese Clinical Trial Registry (ChiCTR) (<http://www.chictr.org.cn>), and ClinicalTrials.gov (<https://clinicaltrials.gov/>).

On Sept 6th, 2013, NMPA (formerly named China Food and Drug Administration, CFDA) required that all on-going clinical trials for drug registration in China must be registered on the NMPA CDE website, and trials initiated before 2013 but for which the related new drug application (NDA) was not completed were required to be registered retrospectively. ChiCTR has the largest number of registered clinical trials in China. The first clinical trial registered on this platform was on Sept 26th, 2005. Clinical studies involving humans were required to be registered on ChiCTR since 2007. It also accepts retrospective registration. Therefore, Jan 1st, 2005 was identified as the start date in this study.

2.2. Search strategy and selection criteria

We searched NMPA CDE and ChiCTR websites using “lung cancer” as keyword. We retrieved the ClinicalTrials.gov website using the keyword “lung cancer” in the “Condition or disease” field, restricted the country to China, and the first posted time span between Jan 1st, 2005 and Dec 31st, 2020.

We included trials that met the following criteria: (1) the trial must be intended for lung cancer. (2) Trials were registered between Jan 1st, 2005 and Dec 31st, 2020. (3) Only trials involving anti-cancer drug were deemed eligible. It was noteworthy that cell therapy and cancer vaccine were also regarded as anti-cancer drugs in this study. (4) Study sites of trials were located in mainland China.

We excluded trials concerning adjuvant drugs, which were used to relieve cancer-related symptoms and adverse reactions caused by anti-cancer therapy, such as haemopoietic growth factors, painkillers, drugs for prevention of skeletal-related events and chemotherapy-induced vomiting and fatigue. Retrospectively registered trials which were initiated before January 1st, 2005 were excluded. In addition, trials on predictive or prognostic biomarkers or resistance mechanism of anti-cancer drugs were also ineligible.

The following information were collected for analysis: trial identifier, trial title, registered date, trial status, primary tested drug, type and mechanism of tested drug, trial objective, trial phase, pathological subtype, sponsor, sponsor type, number of participating centres, geographical location of the principal clinical trial units, key inclusion criteria and exclusion criteria.

Three investigators (QFZ, YXT, and LLH) independently extracted data study by study and excluded trials which did not meet the

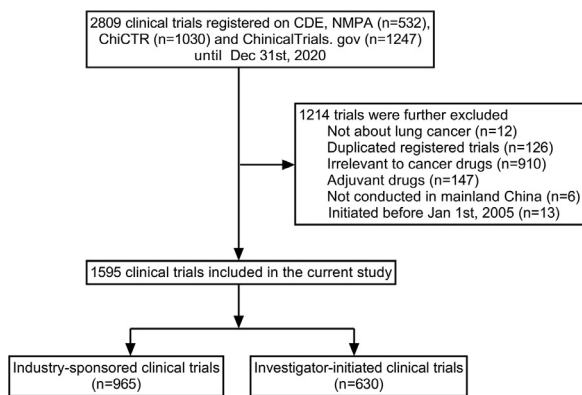


Fig. 1. Process of determining the final clinical trial dataset.

criteria above. Then two other investigators (HZC and YZ) identified duplicated trials. When consensus was not reached by discussion, all investigators were consulted for final decision. Finally, a total of 1595 clinical trials were included in this study. The data retrieval process is illustrated in Fig. 1.

2.3. Data analysis

Newly tested drugs were defined as drugs assessed in industry-sponsored trials (ISTs). We classified drugs into four types according to drug mechanism: cytotoxic drugs, targeted drugs, immunotherapeutic drugs, and traditional Chinese medicine (TCM). According to anti-cancer mechanism, immunotherapeutic drug was divided into six classes: first, T cell-targeted immunomodulators (for example, monoclonal antibodies against PD-1, PD-L1, or cytotoxic T lymphocyte associate protein-4 [CTLA-4]); second, other immunomodulators (for example, agonists against toll-like receptors [TLR] or interferon- α/β receptor 1 [IFNAR1]); third, cancer vaccines; fourth, cell therapies; fifth, oncolytic viruses; and sixth, bispecific monoclonal antibodies (BsAbs). The topology diagram of anti-cancer drugs categorisation is illustrated in Fig. S1.

We used GraphPad Prism (version 8.0) and R software (version 3.6.2) for data processing and analysis. For descriptive analyses, the number and percentage were used for categorical variable. We further analysed the time trends for the selected indicators including the number of registered trials, the proportion of trials in each phase, the number of principal clinical trial units, the number of trials by sponsorship, and the number of trials involving newly tested drugs by drug type and mechanism. It was noteworthy that, the analysis of indicator for clinical trials stratified by drug type and mechanism only conducted in ISTs because newly tested drugs were routinely investigated in ISTs. The annual rate of change was calculated for the specific indicator. The chi-square test was used for subgroup comparisons of anti-lung cancer drug clinical trials stratified by sponsorship. A two-tailed *P* value of less than 0.05 was deemed significance.

2.4. Role of the funding source

The funding source of this study did not involve in the study design, collection, analysis, interpretation of data, writing of the report, and the decision to submit the paper for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication.

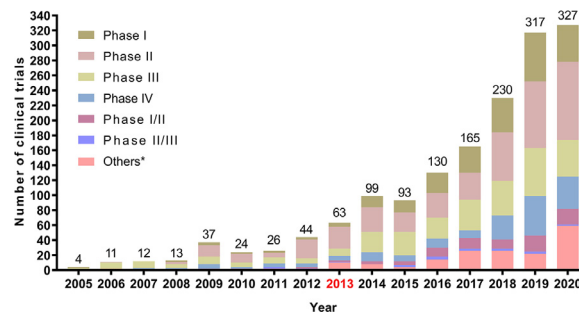


Fig. 2. Annual number of all anti-lung cancer drug clinical trials including IITs and ISTs by study phase in mainland China during 2005–2020.

Abbreviation: IITs, investigator initiated trials, ISTs, industry-sponsored trials.

* Others included 174 trials for which the information of phase was unknown on the registered websites.

The red colour of “2013” at the horizontal axis is to demonstrate the difference of clinical trials number before and after this date.

3. Results

3.1. Basic characteristics

A total of 1595 anti-lung cancer drug clinical trials registered on the three websites from Jan 1st 2005 to Dec 31st 2020 in mainland China were eligible for analysis in this study. Among the 1595 registered trials, 630 (39.5%) were IITs, 698 (43.8%) were domestic ISTs, and 267 (16.7%) were international ISTs. The basic characteristics of IITs, domestic ISTs and international ISTs for lung cancer in mainland China are showed in Table 1.

3.2. Time trends of registered anti-lung cancer drug clinical trials by study phase

The annual number of all anti-lung cancer clinical trials by study phase in mainland China between 2005 and 2020 is illustrated in Fig. 2. During 2005–2013, the number of anti-lung cancer drug clinical trials was extremely small, though it increased slowly over time. However, an increasingly large number of clinical trials were registered between 2013 and 2020, with an average annual growth rate of 26.5%.

Among the four different phases (phase I–IV), the largest growth was observed in phase I, followed by phase IV, phase III, and phase II during 2013–2020, with average annual growth rate of 38.6%, 32.5%, 25.5%, and 20.2%, respectively. The annual number of IITs, domestic ISTs and international ISTs by study phase in mainland China between 2005 and 2020 is illustrated in Fig. S2, Fig. S3, and Fig. S4, respectively.

3.3. Time trends of principal clinical trial units

Consistent with the increase in the number of clinical trials, the number of principal clinical trial units for lung cancer in mainland China increased significantly over time. The number of principal units increased from 1 in 2005 to 110 in 2020, with an average annual growth rate of 36.8%, greatly expanding the scale of clinical trial units for lung cancer across mainland China. The time trend of principal clinical trial units is illustrated in Fig. 3.

3.4. Distribution and time trends of clinical trials by sponsorship

For clinical trials sponsorship on lung cancer in mainland China, the number of IITs displayed a continued increase during 2017–2020, with an average annual growth rate of 47.2%. The number of domestic ISTs increased gradually during 2005–2013, whereas it increased rapidly during 2013–2020, with an average annual

Table 1
Basic characteristics of clinical trials for anti-lung cancer drugs in mainland China during 2005–2020 (N=1965).

Characteristics	IITs, n (%)	ISTs Total, n (%)	Domestic ISTs, n (%)	International ISTs, n (%)	P value P1†	P2‡
Total number	680	965	698	267		
Pathological subtypes					<0.001	<0.001
NSCLC	523 (83.0)	731 (75.8)	502 (71.9)	229 (85.8)		
SCLC	74 (11.7)	81 (8.4)	57 (8.2)	24 (9.0)		
Others*	33 (5.2)	153 (15.9)	139 (19.9)	14 (5.3)		
Treatment strategy					<0.001	<0.001
Neoadjuvant therapy	57 (9.0)	19 (2.0)	15 (2.1)	4 (1.5)		
Adjuvant therapy	34 (5.4)	30 (3.1)	17 (2.4)	13 (4.9)		
Neoadjuvant + adjuvant therapy	1 (0.2)	4 (0.4)	2 (0.3)	2 (0.7)		
Salvage therapy	507 (80.5)	767 (79.5)	539 (77.2)	228 (85.4)		
Others or unknown**	31 (5.0)	145 (15.0)	125 (17.9)	20 (7.5)		
Multicentre study					<0.001	<0.001
No	442 (70.2)	303 (31.4)	303 (43.4)	0 (0)		
Yes	188 (29.8)	662 (68.6)	395 (56.6)	267 (100)		
Study phase					<0.001	<0.001
Phase I	37 (5.9)	236 (24.5)	221 (31.7)	15 (5.6)		
Phase I/II	28 (4.4)	68 (7.0)	56 (8.0)	12 (4.5)		
Phase II	282 (44.8)	196 (20.3)	154 (22.1)	42 (15.7)		
Phase II/III	13 (2.1)	10 (1.0)	8 (1.1)	2 (0.7)		
Phase III	42 (6.7)	310 (32.1)	131 (18.8)	179 (67.0)		
Phase IV	130 (20.6)	69 (7.2)	56 (8.0)	13 (4.9)		
Others***	98 (15.6)	76 (7.9)	72 (10.3)	4 (1.5)		

Abbreviation: NSCLC, non-small cell lung cancer, SCLC, small cell lung cancer, IITs, investigator-initiated trials, ISTs, industry-sponsored trials. *Others included 68 trials for health volunteers, 65 trials with phase I, 46 trials for lung cancer (without distinction between NSCLC and SCLC), four trials for pulmonary neuroendocrine tumours, two trials for pulmonary sarcomatoid carcinoma, and one trial for lymphoepithelioma-like carcinoma.

**Others included 54 trials for locally advanced lung cancer and 122 trials for which the information of treatment strategy was unknown on the registered websites.

***Others included 174 trials for which the information of phase was unknown on the registered websites.

P1† represents chi-square test for comparing the differences of numbers between IITs and ISTs.

P2‡ represents chi-square test for comparing the differences of numbers between domestic ISTs and international ISTs.

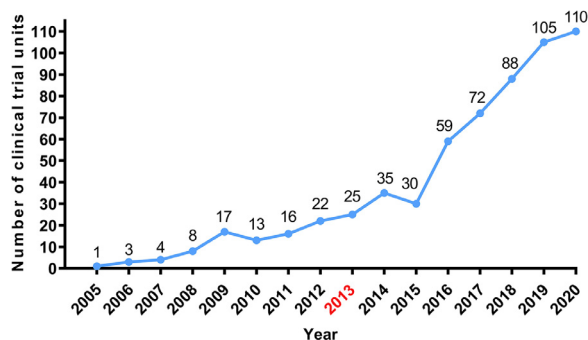


Fig. 3. Annual number of anti-lung cancer clinical trials principal clinical trial units in mainland China during 2005–2020. The red colour of “2013” at the horizontal axis is to demonstrate the difference of clinical trials number before and after this date.

growth rate of 49.0%. However, the number of international ISTs increased slowly over the past 16 years (Fig. 4).

3.5. Geographical distribution of clinical trials

Overall, 1595 trials were conducted at 31 provinces, municipalities and autonomous regions across mainland China. 278 trials were led by principal investigators (PI) from Guangdong, followed by Beijing ($n=273$), and Shanghai ($n=257$). By contrast, the number of trials led by PI from several provinces, such as Gansu ($n=2$), Hainan ($n=2$), Jiangxi ($n=2$) and Ningxia ($n=1$) were rare, reflecting a severe uneven geographical distribution of PIs across mainland China. Detailed geographical distribution of clinical trials for IITs and ISTs is demonstrated in Fig. 5.

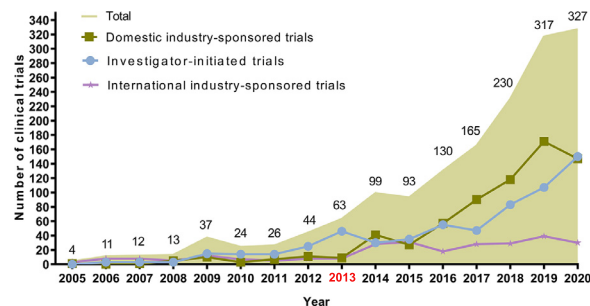


Fig. 4. Annual number of anti-lung cancer drug clinical trials by sponsorship in mainland China during 2005–2020. The red colour of “2013” at the horizontal axis is to demonstrate the difference of clinical trials number before and after this date.

3.6. Distribution and time trends of clinical trials by drug type and mechanism

Among the 965 ISTs, clinical trials involving targeted drugs (588, 60.9%) accounted for the largest proportion, followed by immunotherapeutic drugs (284, 29.4%), cytotoxic drugs (75, 7.8%), and TCM (18, 1.9%). We analysed the time trends of anti-lung cancer drug clinical trials by drug type in mainland China (Fig. 6). Since 2013, the number of trials involving targeted drugs had continued to increase, with an average growth of 34.6%. The number of trials involving immunotherapeutic drugs remained scarce before 2013, and increased notably during 2013–2020, with an average growth of 64.1%. However, the number of cytotoxic drugs and TCM were rare, and there was no remarkable change over the past 16 years.

In terms of targeted drug clinical trials for lung cancer in mainland China, epidermal growth factor receptor (EGFR) was the most studied target. Among the 588 trials on targeted drugs,

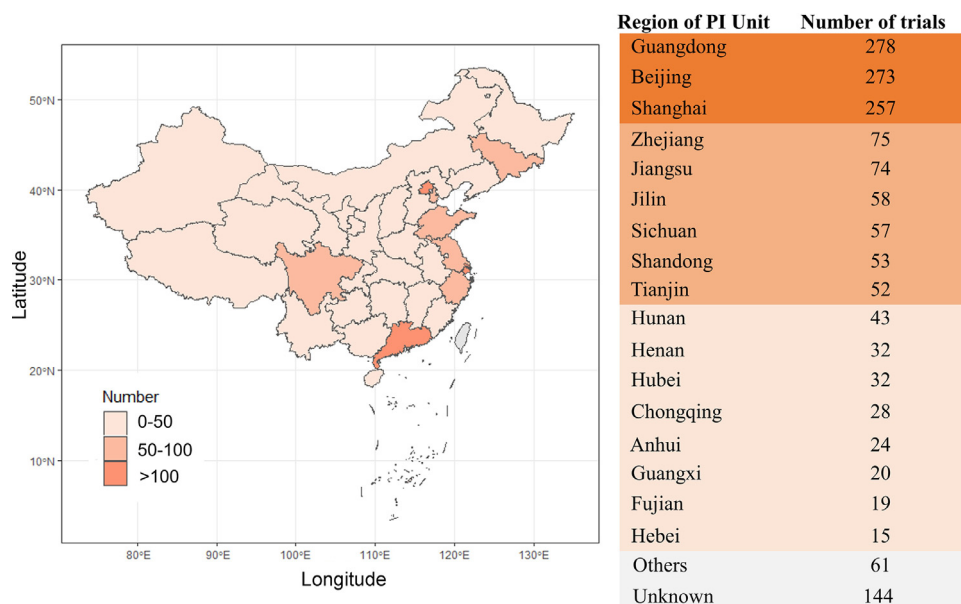


Fig. 5. Distribution of anti-lung cancer clinical trials according to provinces, municipalities and autonomous regions of principal clinical trial units during 2005–2020. Note: There were 144 trials with unknown information of principal clinical trial units, 38 trials with more than one principal investigator unit.

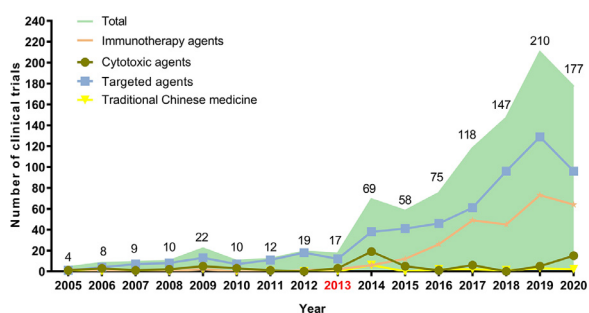


Fig. 6. Annual number of clinical trials involving newly tested anti-lung cancer drugs by drug types in mainland China during 2005–2020. The red colour of “2013” at the horizontal axis is to demonstrate the difference of clinical trials number before and after this date. Note: This analysis was done based on industry-sponsored trials.

225 (38.27%) investigated EGFR-tyrosine kinase inhibitor (TKI), and 100 (17.01%) involved multitarget VEGFR-TKI. In addition, 96 (16.33%) trials involved anaplastic lymphoma kinase (ALK)/ROS proto-oncogene 1 (ROS1)/mesenchymal-epithelial transition factor (MET)-TKI, 49 (8.33%) involved endothelial growth factor (VEGF) antibody, 22 (3.74%) involved recombinant human endostatin, ten (1.70%) involved EGFR antibody, six (1.02%) involved poly ADP-ribose polymerase (PARP) inhibitor, five (0.85%) involved other multitarget TKI, and four (0.68%) involved rearranged during transfection (RET) inhibitor. In addition, there were 19 (3.23%) trials on EGFR/human epidermal growth factor receptor-2 (HER-2)-TKI. The distribution of anti-lung cancer clinical trials on targeted drugs is illustrated in Fig. 7a.

As for immunotherapy, PD-1/PD-L1/CTLA-4 inhibitors represented the hottest strategy. Among 284 trials involving immunotherapeutic drugs, 125 (44.01%) trials were on PD-1 inhibitor, 60 (21.13%) on PD-L1 inhibitor, and seven (2.46%) on CTLA-4 inhibitor. 15 (5.28%) trials involved chimeric antigen receptor-T (CAR-T) cell therapy. Additionally, BsAbs have also emerged as a promising therapeutic strategy in cancer immunotherapy in recent years. There were 17 (5.99%) trials involving BsAbs, with six on CTLA-4/PD-L1, five on CTLA-4/PD-1 and three on transforming growth factor-β (TGF-β)/PD-L1. Other clinical trials regarding immunother-

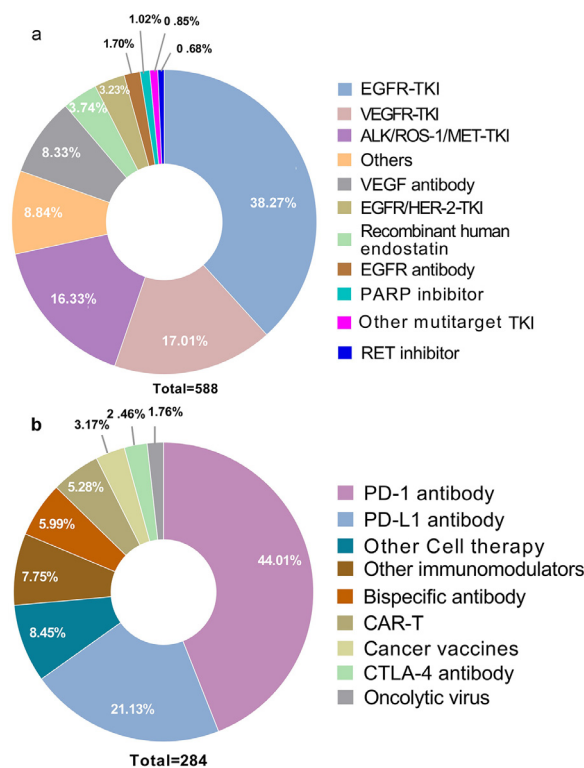


Fig. 7. Distribution of clinical trials involving newly tested anti-lung cancer drugs by drug mechanism in mainland China during 2005–2020. a. Distribution of trials involving targeted drugs; b. Distribution of trials involving immunotherapy. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; MET, mesenchymal-epithelial transition factor; VEGF, vascular endothelial growth factor; HER-2, human epidermal growth factor receptor-2; PARP, poly ADP-ribose polymerase; RET, rearranged during transfection; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; CAR-T, chimeric antigen receptor T cell; CTLA-4, cytotoxic T lymphocyte associate protein-4. Note: This analysis was done based on industry-sponsored trials.

apy included other cell therapy (24, 8.45%), other immunomodulators (22, 7.75%), cancer vaccines (9, 3.17%) and oncolytic virus (5, 1.76%). The distribution of anti-lung cancer drug clinical trials on immunotherapeutic drugs is illustrated in Fig. 7b.

4. Discussion

Over the past two decades, the constantly evolving treatment paradigm, which has been primarily driven by the development of anti-angiogenic therapy, targeted therapy, and immunotherapy, has substantially improved treatment outcomes for advanced NSCLC. The treatment advances were largely attributed to the biopharmaceutical R&D and the rapid development of anti-lung cancer drug clinical trials. Lung cancer was the most commonly identified cancer type in registered anti-cancer drug clinical trials during 2009–2018 in mainland China [19]. However, no previous study has provided landscape about trends over time in the R&D of anti-lung cancer drug clinical trials in mainland China to date. To the best of our knowledge, this is the first study to comprehensively depict the changing landscape of anti-lung cancer drug clinical trials in mainland China.

For a long time, generic drugs have been the main products of Chinese pharmaceutical companies. Undoubtedly, developing generic drugs enhances patient access to anti-cancer drugs, and introduces price competition, reducing the financial burden on patients and society. However, patients have less access to new therapies. To promote the R&D of innovative drugs, great efforts have been made by the Chinese government. Chinese government has established national major project for new drug innovation since 2008. To accelerate drug review and approval process, the Chinese government has issued several key reform policies since 2015 [15–18]. NMPA became a member of the International Council for Harmonization (ICH) on June 1st, 2017. All of these efforts stimulated the development of new anti-cancer drugs and clinical trials for various types of cancer, especially for lung cancer. Fig. S5 illustrates the domestic innovative drugs and biosimilars for lung cancer approved by NMPA up to Dec 31st, 2020.

For newly tested drugs, the most obvious growth was seen in targeted and immunotherapeutic drugs. The top hotspot for targeted drugs was EGFR. The discovery of sensitizing EGFR gene mutations opened the prelude of precision medicine for NSCLC. Sensitizing EGFR mutations occur in 17.3% of Caucasian NSCLC patients [20] and 46.3% of Asian patients with advanced lung adenocarcinoma [21]. Stimulated by favourable efficacy of EGFR-TKIs, many industries participated in the development of EGFR-TKIs. Up to Dec 31st, 2020, there have been 225 trials on EGFR-TKIs in mainland China. Icotinib, a first-generation EGFR-TKI, was considered as a milestone in the development of new anti-cancer drugs in mainland China [22]. Based on ICOGEN study (NCT01040780) [23], in which icotinib was non-inferior to gefitinib for advanced NSCLC patients after failure of at least one prior chemotherapy regimen in terms of PFS, icotinib was approved by NMPA on June 7th, 2011, six years after gefitinib marketing in China. CONVINCe study (NCT01719536) demonstrated the superiority of icotinib over conventional chemotherapy in efficacy and safety for advanced EGFR-sensitizing mutation-positive NSCLC in the first-line setting [24]. Besides, icotinib demonstrated better intracranial progression-free survival (PFS) than whole-brain irradiation plus chemotherapy for patients with EGFR-sensitizing mutation-positive NSCLC and multiple brain metastases (NCT01724801) [25]. Third-generation EGFR-TKI almonertinib (HS-10296, NCT02981108), resulting in an objective rate (ORR) of 68.9% in patients with previously treated EGFR T790M-positive NSCLC in a phase II study, was approved by NMPA on Mar 18th, 2020, three years after osimertinib marketing in China [26]. Furmonertinib (AST2818, NCT03452592) showed an ORR of 73.6% in EGFR T790M mutated NSCLC in a phase IIb

trial, and gained its approval on Mar 3rd, 2021 [27]. Additionally, gefitinib (NCT01405079), erlotinib (NCT01683175), and osimertinib (NCT02511106) improved disease-free survival in adjuvant setting in Chinese NSCLC patients with EGFR-sensitizing mutations [28–30]. These clinical trials provided more treatment options and optimized treatment paradigm for Chinese lung cancer patients [31–33].

The subsequent hotspots of targeted drugs for lung cancer were echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion, ROS1 fusion and MET alterations. In this study, 96 registered clinical trials for targeted drugs on ALK/ROS1/MET were identified. To date, four ALK-TKIs (crizotinib, alectinib, ceritinib and ensartinib) and one ROS1-TKI (crizotinib) have been approved by NMPA. Ensartinib, achieving an ORR of 52% for ALK-positive NSCLC patients who had failed to crizotinib therapy in a phase II trial (NCT03215693) [34] was approved by NMPA on Nov 19th, 2020. Other second-generation ALK-TKIs including WX-0593 (NCT03389815) [35] and CT-707 (NCT02695550) [36] showed preliminary anti-tumour activity and their phase III studies were ongoing (NCT04632758 and CTR20200770). Savolitinib revealed promising anti-tumour activity for NSCLC with MET exon 14 skipping mutation (NCT02897479) [37], and received a priority review from NMPA on Jul 29th, 2020. Only a limited number of trials investigated targeted drugs against RET fusion ($n=4$), neuro trophin receptor kinase (NTRK) fusion ($n=1$), and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) V600E mutation ($n=1$). Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation was found in 9.8% of Chinese NSCLC patients [38]. Therefore, the R&D of new drugs targeting KRAS is an urgent need.

Anti-angiogenic therapy, comprising monoclonal antibodies (mAbs) binding VEGF or VEGFR, recombinant human endostatin, and small molecule VEGFR-TKIs is an important treatment strategy for NSCLC. Recombinant human endostatin (Endostar) plus irinotecan and cisplatin was approved by NMPA as a first-line therapeutic option for advanced NSCLC on July 23rd, 2006 based on a phase III study (CTR20131255) [39]. As for mAbs, bevacizumab (Avastin) received its approval for advanced non-squamous lung cancer in the first-line setting in mainland China on Aug 1st, 2015. Since NMPA launched “Guidelines for the research, development and technique assessment of biosimilar drugs (Trial)” in 2015 [15], 49 trials involving bevacizumab biosimilars have emerged. QL1101 (ChiCTR1900022767) [40] and IBI305 (NCT02954172) [41] were approved by NMPA on Dec 18th, 2019 and June 19th, 2020, respectively.

In this study, among the 588 trials on targeted drugs, 100 (17.01%) trials involved multitarget VEGFR-TKIs. Anlotinib, a novel multitarget VEGFR-TKI, has shown survival benefit compared to placebo in lung cancer patients after failure of two or more previous lines of chemotherapy and was approved for both NSCLC (NCT02388919) [42] and SCLC (NCT03059797) [43] by NMPA on May 9th, 2018 and Aug 30th, 2019, respectively.

Immunotherapy has also been one of the break-through therapies in lung cancer during the last decade. Immune checkpoint inhibitors (ICIs) have dramatically changed the landscape for the treatment of NSCLC and SCLC. The apparent clinical benefits of ICIs in NSCLC and SCLC have drawn great attention from Chinese pharmaceutical companies. Check-Mate 078 was the first phase III study conducted predominantly in Chinese patients with previously treated advanced NSCLC (NCT02613507) [44]. Due to a superior OS over docetaxel, nivolumab was approved by NMPA on June 15th, 2018. PD-1 inhibitors camrelizumab and sintilimab were approved for non-squamous NSCLC in the first-line setting on June 19th, 2020 and Feb 3rd, 2021 based on Camel study (NCT03134872) [45], and ORIENT-11 study (NCT03607539) [46]. According to RATIONALE 307 study (NCT03663205), in which the addition of tislelizumab to chemotherapy resulted in an improved

PFS than chemotherapy alone for previously untreated squamous NSCLC [47], tislelizumab was approved on Jan 14th, 2021 by NMPA.

BsAbs, designed to bind two distinct antigens simultaneously, can directly target immune cells to tumour cells [48]. Among the 284 trials on immunotherapy, 17 (5.99%) trials involved BsAbs, with six on CTLA-4/PD-L1, five on CTLA-4/PD-1, and three on TGF- β /PD-L1. However, most of these trials were phase I/II.

The landscape of sponsors for of anti-lung cancer drug clinical trials in mainland China have changed. On the one hand, the number of IITs increased substantially during 2005–2020. IITs are incredibly important for developing new treatments for patients with cancer, allowing doctors and researchers to do exploratory study that may offer meaningful results. Additionally, IITs are generally faster to obtain proof-of-concept data or evidence that shows whether or not the trial is producing the expected results, which means that new drugs and therapies can be available to patients more quickly. On the other hand, although not as expanding as domestic ISTs, the international ISTs remain an important component of anti-cancer clinical trials on lung cancer in mainland China. International clinical trials conducted in mainland China increase Chinese patients' availability to new therapies, provide data on drug efficacy and safety in Chinese patients and provide data for NDA in mainland China.

Despite that the substantial progress has been made over the past 16 years, there remain shortcomings requiring improvement. First, this study showed a severe uneven geographical distribution of principal clinical units across mainland China, reflecting that more resources of clinical trials were allocated to leading hospitals. To improve the unbalanced situation, more medical facilities that meet the requirements to conduct clinical trials should be fostered. In this aspect, the government plays a crucial role in cultivating a highly motivated environment for clinical trials in more regions. Second, Chinese doctors are consumed with clinical work, which hinders them from conducting clinical trials. To resolve this problem, hospital managers should carry promotion policy to increase doctors' enthusiasm in participating in clinical trials. Third, Chinese pharmaceutical enterprises have flocked to the development of "me-too" drugs due to its lower risk. However, excessive duplication is a waste of resources and hinders the R&D on original innovative drugs.

Several limitations of this study need to be acknowledged. One limitation is that a potential selection bias may exist when searching all the drug clinical trials for lung cancer manually. Meanwhile, although clinical study involving humans were required to be registered retrospectively on the ChiCTR since 2007, the clinical trials that completed before 2007 but not registered retrospectively might have been omitted. However, these limited number of trials might not influence the overall analysis results and conclusion of this study. Another limitation lies in that some data, such as the principal clinical trial units and drug type for a small number of trials, were not provided by the registration platforms. Although this would not influence the overall findings and conclusion of this study, cautions should be addressed on making interpretation from this study. Despite these limitations, this study was the first study to provide a comprehensive landscape of anti-lung cancer drug clinical trials in mainland China from 2005 to 2020.

5. Conclusion

This study provides a comprehensive analysis of anti-lung cancer drug clinical trial landscape during 2005–2020 in mainland China. In the past 16 years, the anti-cancer drug clinical trials for lung cancer and new drug R&D capabilities have witnessed a rapid development and scored remarkable achievements. The most considerable progress lied in targeted therapy and immunotherapy. The prosperous development of clinical trials has provided more

therapeutic options, thus enabling more benefit for Chinese patients with lung cancer. A concerted effort among biopharmaceutical companies, academic organisations and policy makers is required to further improve the innovative drug R&D for lung cancer in mainland China.

Author contributions

YKS and XHH contributed to the study concept and design. QFZ, YXT, HZC and YZ contributed to data quality control and data interpretation. QFZ, YXT, and LLH performed the systematic search, data extraction and data analysis. YYS, XHH, QFZ and YXT drafted and revised the manuscript. All authors approved the final version of the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Declaration of Interests

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.lanwpc.2021.100151](https://doi.org/10.1016/j.lanwpc.2021.100151).

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