Changes in clinical trials of cancer drugs in mainland China over the decade 2009–18: a systematic review

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As a result of recent, substantial capacity building, a new landscape for cancer drug trials is emerging in China. However, data on the characteristics of cancer drug trials, and how they have changed over time, are scarce. Based on clinical trials published on the China Food and Drug Administration Registration and Information Disclosure Platform for Drug Clinical Studies, we aimed to systematically review changes over time in clinical trials of cancer drugs in mainland China from 2009 to 2018, to provide insight on the effectiveness of the pharmaceutical industry and identify unmet clinical needs of stakeholders. A total of 1493 trials of 751 newly tested cancer drugs were initiated. Increases over time were observed for the annual number of initiated trials, newly tested drugs, and newly added leading clinical trial units, with a sharp increase after 2016. Of the 1385 trials in which cancer types were identified, solid tumours (325 [23%] trials), non-small-cell lung cancer (232 [17%]), and lymphoma (126 [9%]) were the most common. A markedly uneven distribution was also observed in the geography of leading units with the largest number of leading units located in east China (50 [41%]) and the smallest number located in southwest China (4 [3%]). The growth trends we observed illustrate the progress in and increasing capability of cancer drug research and development achieved in mainland China over the decade from 2009. The low number of clinical trials on tumours with epidemiological characteristics unique to the Chinese population and the unbalanced geographical distribution of leading clinical trial units will provide potential targets for policy makers and other stakeholders. Further research efforts should address cancers uniquely relevant to Chinese populations, globally rare cancers, and the balance between equitable drug access, efficiency, and sustainability of cancer drug research and development in mainland China.

Introduction

Annual cancer cases and deaths have been increasing in China since 2000, and in 2018, 24% of estimated new cancer cases and 30% of cancer-related deaths globally occurred in China.[1,2] Improving outcomes of patients with cancer by encouraging biopharmaceutical research and development, as well as through timely delivery of effective and affordable cancer drugs, should be the priorities of governments, including in China.

However, before 2013, the availability of drugs in mainland China had been compromised by the so-called drug lag, caused by a backlog of applications or delays in the approval process.[3] During the past decade, particularly since 2015, a series of measures have been taken to promote the development of cancer drugs and strengthen medical innovations, shifting from strict entry and tolerant exit (ie, it was difficult to get approval for clinical trials but easy to obtain marketing authorisation), to tolerant entry and strict exit.[4,5] Nevertheless, few studies on the overview of research and development for cancer drugs are available for mainland China. Studies published to date have included an annual report of ongoing phase 1 oncology trials,[3] a perspective on innovative cancer drugs,[6] and papers that mainly focused on the number of trials or a specific treatment approach or tumour type.[7–9] The only time-trend analysis of anticancer drug research and development was one that examined the basic and methodological characteristics of anticancer drug studies based on the Chinese Clinical Trial Registry; however, registration in this trial database is not mandatory.[10]

Data on the characteristics of cancer drug trials in China, and how they have changed over time, are scarce. Importantly, the national authoritative database for clinical trials, the China Food and Drug Administration (CFDA) Registration and Information Disclosure Platform for Drug Clinical Studies,[11] established in 2013, has made the deep mining of longitudinal data possible. As such, we did a systematic review to analyse trends over time in the research and development of cancer drugs tested in clinical trials in mainland China from 2009 to 2018, using three indicators: initiated trials, newly tested drugs, and leading clinical trial units. We aimed to provide insight on the effectiveness of the cancer drug pipeline and identify unmet clinical needs, to provide essential supportive data for policy makers and other stakeholders.

Data collection

Search strategy and selection criteria

We did a systematic review of trials on the CFDA Registration and Information Disclosure Platform for Drug Clinical Studies that were registered on the platform between Jan 1, 2013, and Dec 31, 2018. To fulfil the scientific and moral obligations of researchers and regulatory agencies, the CFDA issued a notice in 2013 that all drug clinical trials being done as registration trials must be registered on the CFDA Registration and Information Disclosure Platform for Drug Clinical Studies in China as of 2013, including phase 1–4 drug trials and bioequivalence studies, which evaluate the consistency of pharmacokinetic parameters between generic chemical drugs and reference drugs.[11] For trials initiated before 2013 but for which the related new drug application was unfinished, registration was required to be done retrospectively.

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For the **CFDA Registration and Information Disclosure Platform for Drug Clinical Studies** see http://www.chinadrugtrials.org.cn/

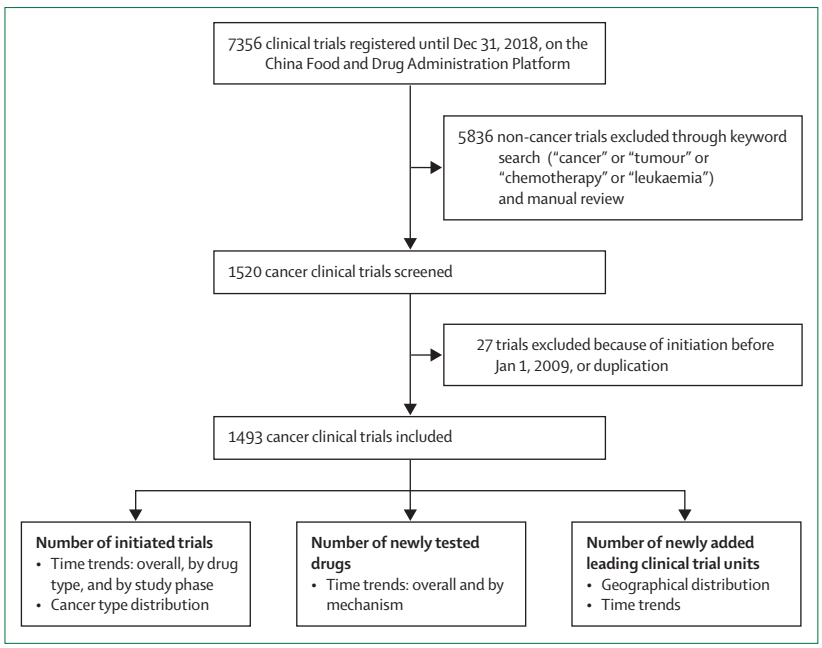

Figure 1: **Data processing and key indicators**

Registration for drug trials must be completed before first patient enrolment to ensure data timeliness. In addition, during drug reviews and inspection—an essential review process done by experts from the CFDA after submission of a new drug application—the CFDA routinely cross-checks the information on the platform with the related data and summary report submitted with a given trial to ensure the validity and integrity of the data.

Publicly accessible information in the CFDA website includes sponsor and registration items, such as sponsor and contact details and date of registration; basic management items of clinical trials, such as funding, leading unit, date of first ethical review, date of first enrolment, and insurance; and scientific information on study design, such as indication, drug (chemical, biological, and others), study phase, study scope, inclusion and exclusion criteria, sample size, and primary and secondary endpoints.

7356 drug trials were registered on the CFDA platform between Jan 1, 2009, and Dec 31, 2018 (figure 1). We included all trials on cancer therapeutic medications (anticancer drugs), adjuvant drugs (ie, drugs for cancer supportive care, including haemopoietic growth factors, antiemesis, and treatment for prevention of skeletal-related events and cancer pain), and preventive medications (human papillomavirus vaccines). Data processing was divided into three steps. The first step was to screen for clinical trials of cancer drugs. We roughly targeted cancer drug trials indicated by keywords ("cancer" or "tumour" or "chemotherapy" or "leukaemia"), and excluded those not for cancer drugs through manual review according to expert opinions from two independent oncologists (S-HW and D-WW). In case of any disagreement, a third oncologist (NL) was invited to arbitrate until the decision was unified. All searches were done by H-YH according to the jointly developed retrieval strategy. There was no need to do data extraction manually since the database from the CFDA platform was electronically available. To make sure we did not omit relevant trials, we selected 20% of the trials by a simple random sampling method from the primarily excluded group (n=5836) and had the same two oncologists independently check if any of the trials were related to cancer drugs (none were found). Thus, 1520 trials of cancer drugs were identified (figure 1).

The earlier the initiation date of a trial, the greater the likelihood that the trial was not registered on the CFDA platform, since it was founded in 2013 and trials initiated before then had to be retrospectively registered. In 2009, the Chinese Major New Drug Innovation Program, for the 11th Five-Year Plan on national economic and social development of the Chinese government,[12] was launched to support the construction of a platform for clinical trials of cancer drugs, marking the beginning of a new era of drug research and development in China. Therefore, as a second step, we chose Jan 1, 2009, as a cutoff, and excluded all trials initiated before this date according to the year of first ethical review. Duplicated trials were preliminarily identified with SAS software on the basis of reporting the same sponsor, drug, and study phase, and were independently confirmed and excluded by the initial two oncologists. 1493 cancer drug trials were included in the final analysis (figure 1).

The third step was data correcting and reassignment, including by cancer type, drug type or mechanism (ie, cytotoxic, immune drugs, and targeted drugs, including small molecule targeted drugs), and geographical location of the leading clinical trial units (north, east, south, central, northeast, northwest, and southwest).

Our analysis looked at three key indicators of cancer drug development (figure 1): the number of initiated trials between 2009 and 2018, overall and by drug type, study phase, and cancer type; the number of newly tested drugs, overall and by drug mechanism; and geographical distribution of all leading clinical trial units and newly added leading clinical trial units over time.

Statistical analysis

We used SAS (version 9.4) for data processing and analysis. For descriptive analyses, number (%) was used for qualitative variables. We analysed the 10-year trends in our selected indicators, including the number of initiated trials, the proportion of phase 1, phase 2, phase 3, and bioequivalence trials, the number of newly tested drugs (in total and by mechanism), and the number of newly added leading clinical trial units, using a simple regression model. The annual rate of change was calculated for each indicator. The year of a trial was

defined by the date of the first ethical review. The χ^2 test was used for subgroup comparisons of leading clinical trial units by geography. A two-tailed p value of less than 0·05 was deemed significant.

Findings

Time trends of initiated trials

1493 cancer drug trials were initiated from 2009 to 2018 in mainland China. 1347 (90%) involved therapeutic medications, 123 (8%) adjuvant drugs, and 23 (2%) preventive medications. The annual number of initiated clinical trials increased over time (p<0·0001), with an average annual growth rate of 33%. A notable increase in the number of clinical trials occurred in 2016, with 255 clinical trials launched, corresponding to an increase of 113% over the number launched in 2015 (figure 2). For molecular drug types, 949 (64%) clinical trials were of chemicals (small molecules), and 510 (34%) of biological drugs (large molecules). The proportion of biological drugs gradually increased year by year (p=0·00040), and amounted to 154 (48%) of all 322 initiated trials in 2018 (appendix). Regarding the phase distribution of all cancer drug trials, phase 1 trials accounted for the largest proportion (619 [41%]), followed by phase 3 trials (403 [27%]), phase 2 trials (256 [17%]), bioequivalence studies (182 [12%]), and phase 4 trials (28 [2%]), with the phase for the remaining five trials unknown. The proportion of phase 1 trials increased annually (p=0·0013), with an average change per year of 15%, whereas the proportions of phase 2 and phase 3 trials decreased annually, with an average change per year of 6% (p=0·0067) and 10% (p<0·0001; figure 2), respectively.

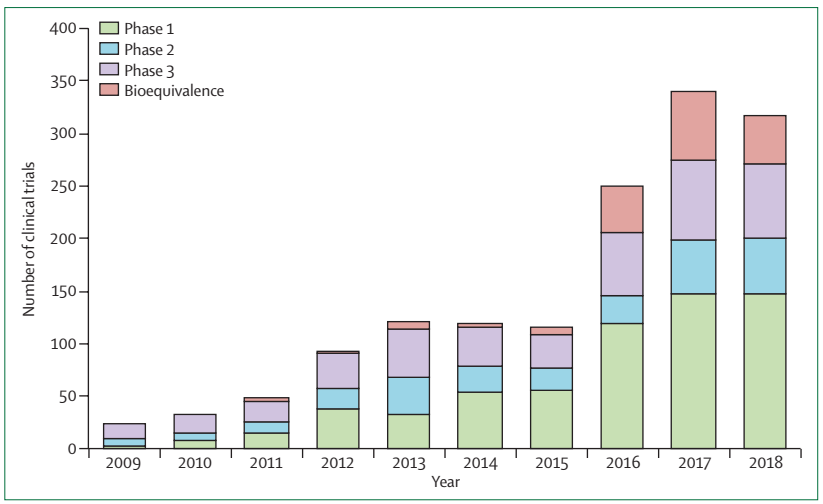

Figure 2: **Annual numbers of initiated cancer drug clinical trials by study phase in mainland China, 2009–18**

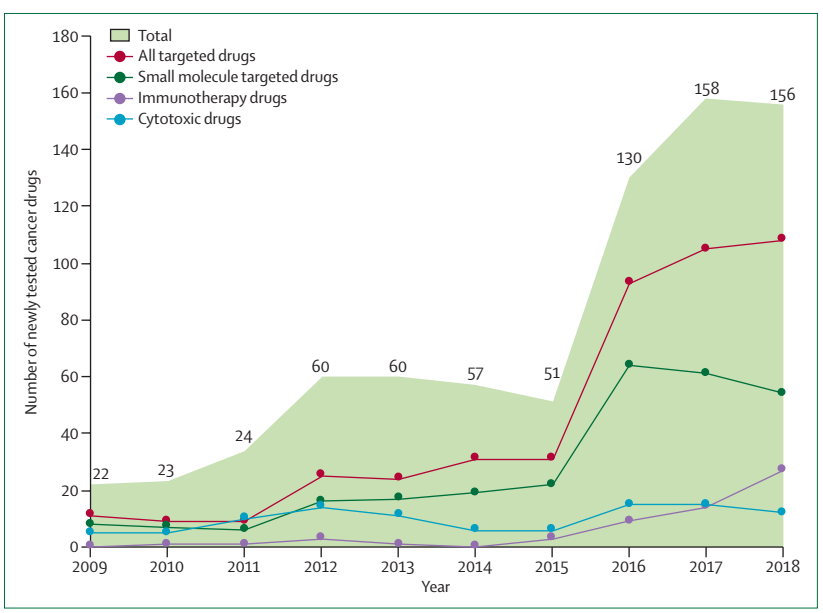

Figure 3: **Annual numbers of newly tested cancer drugs in China, 2009–18**

Total represents 751 cancer drugs tested in clinical trials between 2009 and 2018, including therapeutic drugs, adjuvant drugs, and preventive drugs. Among the 671 therapeutic drugs, targeted, immunotherapy, and cytotoxic drugs were the three most common types (targeted and immunotherapy drugs were not strictly mutually exclusive; 43 drugs were counted in both categories after judgement by two independent coauthors and resolution by a third coauthor). Targeted drugs are generally divided by molecular type into large molecule and small molecule targeted drugs; the data for all targeted drugs and small molecule targeted drugs are shown. 40 out of the 172 large targeted drugs were also counted as immunotherapy drugs.

Time trends of newly tested drugs

751 cancer drugs were tested in clinical trials between 2009 and 2018. Among the 671 drugs that were therapeutic medications, 477 (71%) were innovative drugs, 151 (23%) were generics, and 43 (6%) were biosimilar drugs. 528 (79%) of the therapeutic medications were developed by local industries in mainland China and 143 (21%) were from overseas enterprises. The number of new cancer drugs being developed (ie, tested in trials) increased annually with a significant average annual increase of 24% (p=0·00030).

Among the trialled therapeutic medications, the most common cancer drugs according to mechanism were cytotoxic drugs (99 [15%]), immunotherapy drugs (59 [9%]), and targeted drugs (446 [66%]). 43 drugs belonged to both targeted drugs and immunotherapy drugs. For the remaining 80 non-therapeutic medications, 66 were adjuvant drugs and 14 were preventive medications.

Among the targeted therapeutic drugs, 274 (61%) were small molecules. The number of new immunotherapy drugs, targeted drugs, and small molecule targeted drugs being tested in clinical trials increased over time; the average increase over time was 60% (p=0·011) for immunotherapy drugs, 29% (p=0·00040) for targeted drugs, and 24% (p=0·00080) for small molecule targeted drugs. Notably, the numbers of immunotherapy, targeted, and small molecule targeted drugs dramatically increased in 2016, with increases of 200%, 200%, and 191%, respectively, compared with these numbers in 2015 (figure 3). The numbers of cytotoxic drugs being tested in clinical trials annually showed little change over this period.

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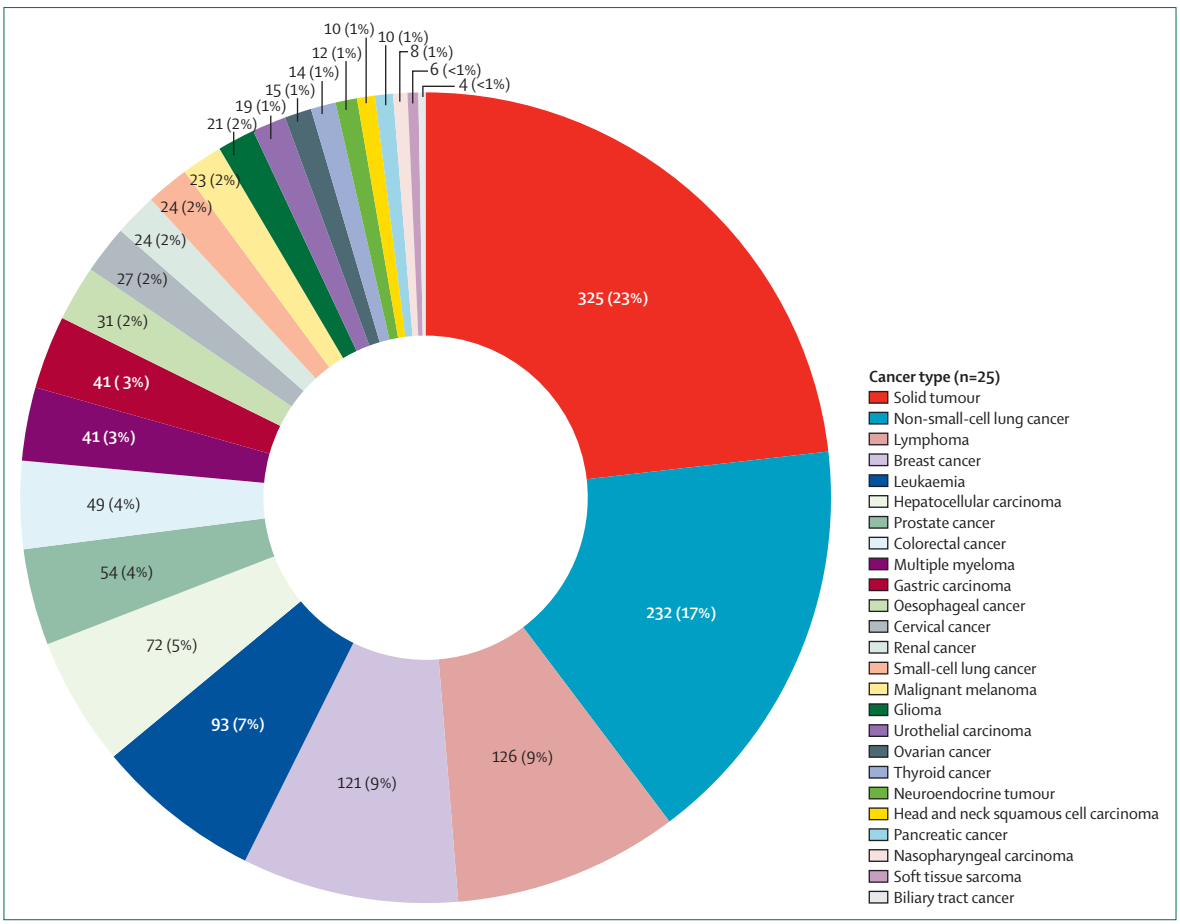


Figure 4: **Cancer type distribution of cancer drug clinical trials in China, 2009–18**
Shown are the total numbers of registered clinical trials in each cancer type and the number as a percentage of the 1385 trials in which a cancer type was identified (with some trials identifying more than one cancer type).

As a representative immunotherapy drug type, we identified 29 monoclonal antibodies against PD-1 or PD-L1 in 180 clinical trials initiated in mainland China by the end of 2018, with 23 of these antibodies developed by local pharmaceutical companies and the rest by overseas companies. Four of 29 were already on the market, and the rest were still under investigation (nine at phase 3, five at phase 2, and 11 at phase 1).

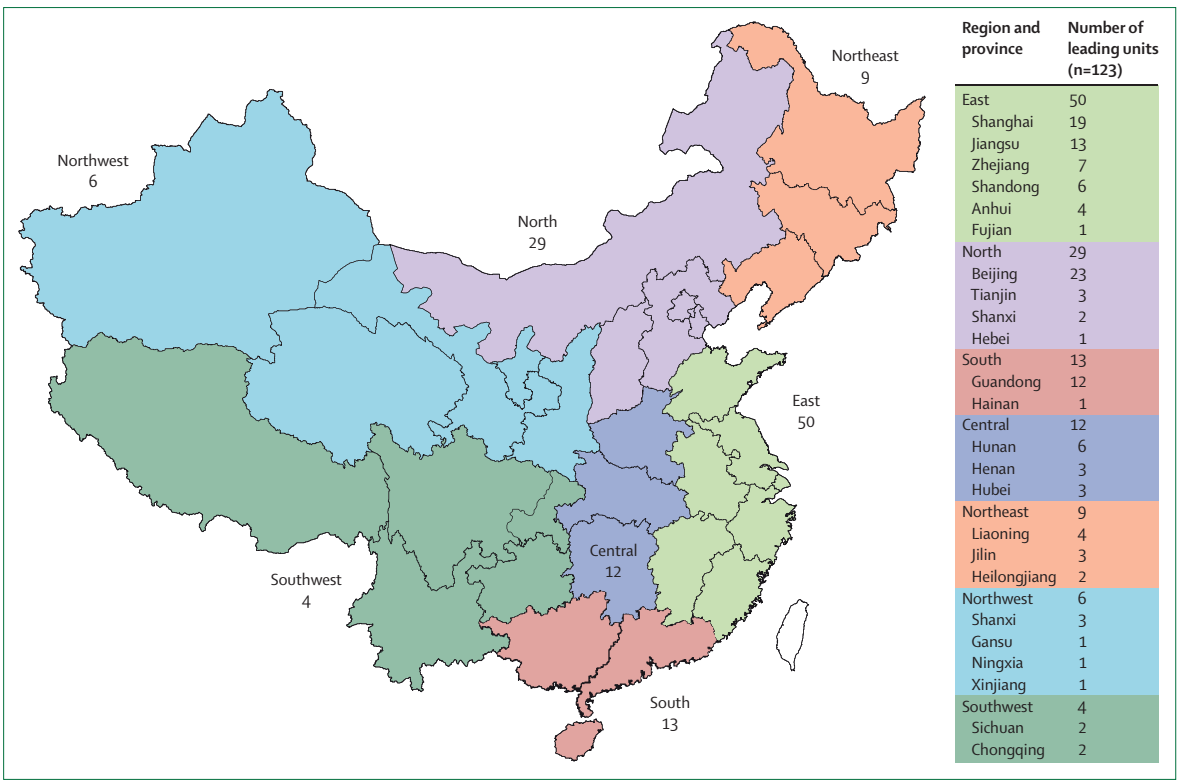
Cancer types in registered clinical trials

In 108 (7%) of 1493 trials we did not identify a cancer type, and 97 of these trials were studies on the prevention or treatment of adverse reactions caused by chemotherapy. 25 different cancer types were identified for the remaining 1385 clinical trials. Solid tumours were the most commonly identified cancer type with 325 (23%) trials, followed by non-small-cell lung cancer (232 [17%]), lymphoma (126 [9%]), and breast cancer (121 [9%]). Several other tumour types had high numbers of clinical trials in the decade from 2009, including leukaemia (93 [7%]), hepatocellular carcinoma (72 [5%]), prostate cancer (54 [4%]), and colorectal cancer (49 [4%]). The distribution of all identified cancer types is shown in figure 4.

Geographical distribution and changes over time of leading clinical trial units

From 2009 to 2018, 123 clinical trial units were involved as the leading site for cancer drug trials in mainland China, with 21 (17%) units participating only in bioequivalence studies. The largest numbers of leading units were located in east China (50 [41%]), followed by north China (29 [24%]), whereas the smallest numbers were in northwest China (6 [5%]) and southwest China (4 [3%]). The geographical distribution of all leading units is shown in figure 5.

We further explored the annual addition of new leading clinical trial units to the CFDA platform, and observed an average annual growth rate of 34% ($p=0·0048$). A surge was identified beginning in 2016, with the number of newly added leading units for the 3 years over 2016–18 amounting to 92, representing three-quarters of all leading units (figure 6).



Region and province	Number of leading units (n=123)
East	50
Shanghai	19
Jiangsu	13
Zhejiang	7
Shandong	6
Anhui	4
Fujian	1
North	29
Beijing	23
Tianjin	3
Shanxi	2
Hebei	1
South	13
Guandong	12
Hainan	1
Central	12
Hunan	6
Henan	3
Hubei	3
Northeast	9
Liaoning	4
Jilin	3
Heilongjiang	2
Northwest	6
Shanxi	3
Gansu	1
Ningxia	1
Xinjiang	1
Southwest	4
Sichuan	2
Chongqing	2

Figure 5: **Geographical distribution of leading clinical trial units of cancer drug clinical trials in mainland China, 2009–18**
Shown are the number of units that were a leading unit of a cancer drug clinical trial at least once in mainland China from 2009 to 2018.

Discussion

This systematic Review provided substantial information on the landscape of cancer drug trials in mainland China. Important increases in the numbers of initiated trials, newly tested drugs, and newly added leading clinical trial units in mainland China illustrate the progress made over the decade 2009–18. These growth patterns are also evidence of the evolving effectiveness of the biopharmaceutical industry in China, and can act as an important guide for directing future cancer drug research and development in mainland China. Importantly, the low number of clinical trials for cancer types of particular relevance for Chinese populations and the uneven geographical distribution of leading clinical trial units will provide potential targets for improvement for policy makers and other stakeholders involved in various apsects of the drug development process.

From 2009 to 2018, the number of cancer drug trials in mainland China showed remarkable growth, with an average annual growth rate of 33%, suggesting the contribution of Chinese biopharmaceutical companies to the global pipeline. As a result, the Chinese pharmaceutical industry has become the second largest pharmaceutical market in the world.[13] This growth in the number of cancer drug trials is likely to be associated with the global growth of the biopharmaceutical industry and important efforts by and support from the Chinese government.

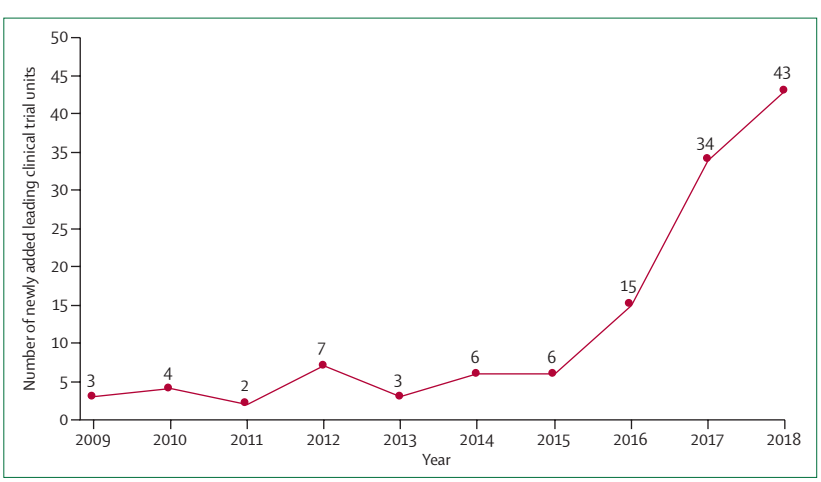


Figure 6: **Annual additions to the China Food and Drug Administration trial platform of leading clinical trial units of cancer drug clinical trials in mainland China, 2009–2018**

Since 2009, the Chinese Major New Drug Innovation Program for the 11th Five-Year Plan,[12] and subsequently the 12th and 13th Five-Year Plans,[6] have continuously supported the construction of a cancer drug clinical trial platform.To overcome the drug lag and cultivate a more innovation-friendly drug research and development

environment in mainland China, the CFDA have implemented a new priority examination and approval process since 2015, which emphasises approval based around clinical value.[4] Additionally, the requirement for a consistent quality and efficacy evaluation for generic drugs has been put forward by the CFDA since 2016.[14]

To further stimulate drug innovation and improve the efficiency of drug clinical trials, the milestone policy of the State Council of the People's Republic of China—"opinions on reforming the examination and approval system for drug and medical devices[15]—was issued in 2015, with several compatible regulatory reforms subsequently being enacted.[14,16–20] In addition, restrictions on imported drug approvals were relaxed in 2017 so that clinical trial data acquired abroad could be accepted,[21] and a 60-day filing system was officially adopted in 2018.[19] In response to these reforms, the numbers of both tested cancer drugs and initiated clinical trials have increased in mainland China since 2016.

Increases were seen in the number of cancer drugs being tested, both overall and by mechanism, including a rapid proliferation of PD-1 and PD-L1 therapies. The proportion of phase 1 trials being initiated increased as well. The typical innovative drug research and development pattern for local pharmaceutical companies in China is intended to avoid risk, giving priority to follow-on drugs with the potential to be best-in-class.[13,22] This follow-on system can effectively address the huge unmet medical needs of the country's general population—resulting from the high incidence of major tumour types and heavy disease burden[1,2]—and benefit citizens by making available affordable drugs in a short amount of time. Since the PD-1 monoclonal antibody nivolumab was first marketed in mainland China in June, 2018, the domestic PD-1 antibodies sintilimab (approved in December, 2018), toripalimab (approved in December, 2018), and camrelizumab have subsequently joined the competition for best-in-class.[23–26] Sintilimab took only 20 months to get final approval after completion of the pivotal trial, resulting in a competitive Chinese market for PD-1 antibodies and a large discount in patient expenditure (currently ¥7838 per 100 mg sintilimab in mainland China) compared with that for nivolumab (currently ¥9268 per 100 mg with a 31-month approval period). As a result of this competitive Chinese market for PD-1 antibodies, the price of nivolumab in mainland China is only about half of that in the USA.[27]

In addition to immunotherapy drugs, small molecule targeted drugs developed by Chinese industries have also showed excellent efficacy in trials. Anticancer drugs with best-in-class potential have priority for examination and approval by the CFDA.[4,19] As a result, in 2018, five Chinese innovative cancer drugs were approved by the CFDA in mainland China, three of which were small molecule targeted drugs (anlotinib, pyrotinib, and fruquintinib) and two PD-1 antibodies (toripalimab and sintilimab). For example, the Chinese pan-HER small molecule inhibitor pyrotinib received conditional approval based on outstanding efficacy in breast cancer.[28] Individuals with cancer globally might benefit from cheap but effective Chinese drugs such as these, and biopharmaceutical companies in China have started to carry out multiregional clinical trials (being both international and multicentre) in recent years according to our systematic search.

Early market success of the first Chinese biopharmaceutical companies provided a model for further industry development but also led to an excess of repetitive clinical trials, compromising the progress of newer companies. Additionally, attempts to simply replicate the success of those drug approvals has hampered pharmaceutical companies in investing in drug innovation, such that Chinese biopharmaceutical firms are still focusing on anti-PD-1 and anti-PD-L1 drugs when the global immuno-oncology pipeline has broadened to novel targets, such as STAT3, IDO1, CD47, and the CSF1 receptor.[22,29] Furthermore, the follow-on method tends to cause excessive duplications of drug research and development; our analysis has shown this to be the case for cancer drug trials in non-small-cell lung cancer, lymphoma, and breast cancer, which together accounted for 479 (35%) of 1385 of all registered cancer drug trials on the CFDA platform over the decade from 2009.

Compared with in developed countries, liver, stomach, and oesophageal cancers are associated with a different set of causes and outcomes in China, and have extremely poor prognoses.[30] But only 144 (10%) out of 1385 trials were in the pipeline in China for these three cancers between 2009–18, which is less than two-thirds of the number of trials for non-small-cell lung cancer. This finding accords with a previous report on challenges for the research and development of innovative cancer drugs in China.[3] Although innovative drugs from China have started to show their full potential in stomach cancers, with apatinib showing potential for metastatic gastric cancer,[31] few breakthroughs have occurred for liver and oesophageal cancers, with no domestic innovative drugs approved since 2009. To encourage drug development for life-threatening cancers with adverse outcomes unique to Chinese populations, as well as for rare diseases that do not have effective treatments yet globally, is not only the current policy orientation,[19] but also an important potential direction of future research and development strategies for medical companies and researchers.

Our Review also identified a surge in newly added leading clinical trial units from 2016. The main cause of this change is likely to be the CFDA's requirement for efficacy consistency evaluation of generic drugs since 2016;[14] as such the requirement to do bioequivalence clinical trials in units with good clinical practice certification has been loosened since 2017.[32] By the end of 2018, 123 different units had served as the leading site of a cancer drug trial, accounting for 36% of all 346 units

with cancer drug trial certification and 15% of all 825 certified drug trial units.[6]

Our Review further showed a markedly uneven geographical distribution of leading clinical trial units across mainland China, consistent with a previous report.[7] 117 (95%) of the 123 leading units are experienced hospitals while the others are centres for disease control. Therefore, we believe that, instead of uneven population or patient distribution, this geographical disparity is the direct manifestation of the uneven distribution of superior medical resources for clinical research across China, which is worrisome for clinicians and should be acted on by the government. It is also likely to be due to the government's demand for Chinese pharmaceuticals to fully play the leading role of major hospitals, with resource priority given to the exemplary role of top leaders. Thus, at the beginning of 2019, the Chinese Major New Drug Innovation Program issued a new notice for major clinical trial units to play this leading role, aiming to facilitate the formation of a highly motivated environment of medical innovation.[33] How to improve the balance between the equitable access to new drugs and the efficiency of pharmaceutical research and development is an important topic worthy of exploration by policy makers.

Based on trials listed on the only mandatory registration platform for clinical trials in mainland China, our systematic Review elucidated the overall landscape of cancer drug research and development in mainland China, and its contribution to the global drug pipeline for the decade 2009–18. However, our Review has some limitations. Although trial registration on the platform is mandatory, time-bound, and cross-checked by CFDA inspections, which ensures the integrity and reliability of the data to a large extent, drug trials that concluded before 2013 might have been omitted. Additionally, the database contains only drug clinical trials for drug registration purposes, and investigator-initiated trials are not included. Furthermore, the initial year of clinical trials for the purpose of our Review was the time of first ethics committee review, instead of the time of online submission or first enrolment, based on the availability and reliability of information, which might hinder comparisons with other reports. International comparisons were also not completed, because no equivalent reports were identified. Further analysis of the annual number of developed or approved drugs in China would be valuable; however, to our knowledge, no official database or report is available to support this analysis.

Conclusion

Over the decade 2009–18, progress in the research and development of cancer drugs was achieved in mainland China. The Chinese follow-on pattern for cancer drug trials appears to have effectively addressed the huge unmet medical needs of the Chinese population, with effective products now available for some common cancers. Given the large patient pool, the rising capability of clinical development, and substantial support from the government, we believe China has become a favourable location for cancer drug research and development, and seems prepared to contribute to the global drug pipeline. Further efforts should now be made for cancers with epidemiologies and outcomes unique to Chinese populations, and rare cancers. How to improve the balance between equitable drug access, efficiency, and sustainability of pharmaceutical research and development, to thus promote medical innovation, is an important issue worthy of exploration by policy makers.

Contributors

NL, H-YH, and D-WW planned and drafted the paper, and contributed to data quality control, analysis, and interpretation. Z-MY, JW, and S-HW contributed to data quality control and interpretation. J-SW provided methodological guidance and support with data interpretation. S-HW, HF, YY, and YB provided administrative, technical, and material support. ZY, YC, MJ, Y-FL, K-YL, B-HX, and YS contributed to planning and data interpretation. JH led the overall planning and data interpretation. All authors reviewed and revised the manuscript.

Declaration of interests

We declare no competing interests.

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