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Growing research and development of targeted anticancer drugs in China

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ABSTRACT

Objective: To deliver a comprehensive picture of the landscape and changing trend of trials and approvals on targeted anticancer drugs in China from 2012 to 2021.

Methods: Trials, investigated products, and listed drugs were acquired from national databases. The status quo, changing trend of absolute number, and proportion of targeted trials, products, and drugs, as well as the corresponding difference between domestic and foreign companies were analyzed.

Results: A total of 2,632 trials on 1,167 targeted antitumor drugs were identified, accounting for 81.5% of all registered trials. The number and proportion of trials on targeted drugs increased steadily, with an average growth rate of 36.0% and 6.2%, respectively. A similar growth trend was observed in the number (33.7%) and proportion (13.8%) of targeted drugs. Targeted drugs and trials owned by domestic companies accounted for a higher proportion than that by foreign companies (80.5% vs. 19.5%; 83.2% vs. 16.8%, respectively), and the growing trend for both targeted drugs (13.8% vs. 5.7%) and trials (13.8% vs. 33.7%) owned by domestic companies was faster. The proportion of targeted drug trials (80.5% vs. 85.6%) and multicenter trials (6.0% vs. 69.9%) initiated by domestic companies was lower than that by foreign companies, with the gap gradually narrowing. Among the identified 18 targets of the 126 immune drugs under development, only one globally new target was found.

Conclusions: Research and development of targeted antitumor drugs in China are booming and advancing rapidly, and domestic enterprises have become the pillar. Encouraging genomics activities and establishing incentives and public–private collaboration frameworks are crucial for innovation-oriented drug development in China.

1. Introduction

Tumor is a major disease that seriously threatens human health globally.[1] It is also a complex disease that is closely associated with molecular profiling, phenotypes, and genotypes. Recent scientific and technological progress, as well as the combination of expertise and data from different disciplines, has led to the emergence of the cross-cutting field of personalized medicine, which allows us to identify the best therapeutic approach for each individual patient in cancer control and treatment.[2,3] Traditional evidence-based medicine roughly types tumors according to cancer site without fully recognizing the uniqueness and complexity of individual genetic variation, making it difficult to understand disease causation and achieve targeted treatment with better efficacy and less side effects.[3,4] Undoubtedly, in the last decade, great progress and achievement in targeted cancer therapeutics have shown the world its potential to improve healthcare and sparked the attention of policymakers in their search for more efficient and sustainable health systems.[5,6]

Cancer disease burden in China is heavy, and the survival of cancer patients is relatively poorer compared with the United States.[7,8] The development of and access to personalized medicine are crucial to improve the prognosis of cancer patients. Previous studies have shown that China has made important progress in research and development (R&D) and the availability of anticancer drugs, as well as the R&D ecosystem.[9–12] To our knowledge, evidence on the overall progress in the R&D and availability of personalized anticancer drugs in China is scarce.

Hence, the scope of this study was to deliver a comprehensive view of the wide landscape and changing trend of trials and approvals on

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targeted anticancer drugs in China from the beginning of 2012 to the end of 2021. In addition, this study aimed to identify the key barriers and provide corresponding solutions to facilitating the development of targeted cancer drugs in China, thus providing data basis and reference for related stakeholders.

2. Materials and methods

2.1. Search strategy and selection criteria

Information on anticancer trials and involved drugs from January 1, 2012, to December 31, 2021 was mainly sourced from Registration and Information Disclosure Platform for Clinical Trials, the registration database of the China Food and Drug Administration (CFDA).[13] The database mainly includes three types of information: basic project information, trial management information, and trial scientific information. Search strategy and detailed information were depicted in previously published research.[10,11] The listed anticancer drugs were directly acquired from our work that was published recently.[12]

A total of 15,527 drug clinical trials had been registered and recorded on the platform by December 31, 2021. Data processing was mainly divided into the following three steps (Supplementary Fig. 1): (1) screening the indication to malignant tumor clinical trials using "cancer," "tumor," "chemotherapy," and "leukemia" as the keywords, a total of 3,635 trials on cancer drugs were found; (2) manual rescreening was performed by two chief physicians independently, and if the results were found to be inconsistent, then the final inclusion of tumor clinical trials was determined by a third chief physician; in order to ensure no omission, we randomly selected 20% of the database-excluded data in the initial screening and verified by two chief physicians; and (3) clinical trials on cancer preventive drugs and adjuvant drugs as well as those with a first ethical review time before January 1, 2012, were excluded. Finally, a total of 3,229 antitumor drug trials were included.

2.2. Statistical analysis

The primary indicators are the number and proportion of targeted drug clinical trials as well as targeted investigated drugs, all of which were count data, and the frequency (%) was used for statistical description. Chi-squared test was used for comparison between the number of domestic enterprises trials and foreign enterprises trials, and the different trial drug groups. The time trends from 2012 to 2021 were analyzed using a simple regression model for trend test, and the average tempo was used to calculate an annual average increasing rate. As a measure of the accuracy of the models, the coefficient of determination (R^2) was used. The significance level α was 0.05, and SAS 9.4 software was used for data processing and analysis. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

Among the 3,229 identified anticancer drug trials, a total of 2,632 (81.5%) trials were tested on targeted anticancer drugs, and the annual proportion ranged from 51.3% in 2012 to 88.0% in 2021 (Table 1). The number and proportion of trials on targeted drugs showed a steady growth trend, with the corresponding average growth rate being 36.0% ($R^2 = 0.919$, $P < 0.001$) and 6.2% ($R^2 = 0.897$, $P < 0.001$), respectively.

Overall, registered trials on targeted drugs initiated by domestic companies showed a rapidly growing trend. The average annual growth rate was 41% ($R^2 = 0.934$, $P < 0.001$) and the total number amounted to 2,069 trials, accounting for 80.5% of all trials on targeted anticancer drugs. The number of targeted drugs initiated by foreign companies also steadily increased, with an average annual growth rate of 17.0% ($R^2 = 0.770$, $P < 0.001$). Relatively speaking, the overall proportion of targeted drug trials initiated by foreign companies was higher than that by domestic companies (85.6% vs. 80.5%, $P = 0.003$). In terms of annual proportion of targeted drug trials, the growth rate of domestic enterprises (8.0%, $R^2 = 0.875$, $P < 0.001$) was significantly higher than that of foreign enterprises (3.6%, $R^2 = 0.716$, $P = 0.002$). Thus, the gap in annual proportion of targeted drug trials between domestic companies and foreign companies is gradually narrowing, with the corresponding proportions being 87.4% and 91.0%, respectively, in 2021 (Fig. 1).

Table 1
Trends in the number and proportion of targeted drug trials among all targeted anticancer drug trials, 2012-2021.

Year	No. of all identified trials	Trials on nontargeted drugs		Trials on targeted drugs	
		No.	Proportion (%)	No.	Proportion (%)
2012	78	38	48.7	40	51.3
2013	98	42	42.9	56	57.1
2014	107	33	30.8	74	69.2
2015	113	33	29.2	80	70.8
2016	243	51	21.0	192	79.0
2017	318	75	23.6	243	76.4
2018	363	61	16.8	302	83.2
2019	496	78	15.7	418	84.3
2020	688	99	14.4	589	85.6
2021	725	87	12.0	638	88.0
Total	**3229**	**597**	**18.5**	**2632**	**81.5**

For all the trials on targeted anticancer drugs, 2,294 (87.2%) trials tested on original drugs, 2,069 (78.6%) trials were initiated by domestic companies, and 2,113 (80.3%) trials were single center and conducted only in China. The proportion of phase I trials accounted for the highest (47.1%), followed by phase II trials (20.6%) and phase III trials (22.8%). Compared with trials initiated by foreign companies, the proportion of multicenter trials initiated by domestic companies was significantly lower (69.9% vs. 6.0%, $P < 0.001$), the proportion of early-stage trials was higher (17.5% vs. 55.1%, $P < 0.001$), and no statistical difference was found by drug type (Table 2).

Cumulatively, there were 1,167 different kinds of antitumor-targeted drugs in China tested in clinical trials, of which 971 (83.2%) were initiated by domestic companies (Fig. 2). Both annual number of tested targeted drugs and annual proportion of targeted drug trials by domestic companies demonstrated the tendency of rapid increase, with the annual growth rate being 33.7% ($R^2 = 0.922$, $P < 0.001$) and 13.8% ($R^2 = 0.852$, $P < 0.001$), respectively. Similar increasing trend with relatively lower annual growth rate was also observed for the number of tested targeted drugs (13.8%, $R^2 = 0.660$, $P = 0.004$) and proportion of targeted drug trials (5.7%, $R^2 = 0.440$, $P = 0.037$) by foreign companies.

In terms of the top 10 cancer types by annual incidence rate in China[16], lung cancer was the most common and was involved in the largest number of targeted drugs (255) and related trials (509), followed by breast cancer (134 drugs, 228 trials) and liver cancer (77 drugs, 127 trials). As for the proportion of targeted drugs and related trials, corpus carcinoma was the highest, for which 100% of tested drugs and trials was personalized medicine, followed by cervical cancer (96.2% drugs, 90.6% trials) and lung cancer (88.5% drugs, 92.9% trials), respectively. Prostate cancer (11.8% drugs, 22.6% trials) and breast cancer (65.0% drugs, 71.3% trials) had relatively low proportions of targeted drugs and trials (Table 3).

Among the 87 anticancer new drugs approved in China over the last decade, 74 (85.1%) drugs were targeted medicines. The ratio of targeted medicine was higher for approvals by domestic companies (97.3%, 36/37) than those owned by foreign companies (76.0%, 38/50, $P = 0.006$). The three targets with the largest number of approved drugs were multitargets (11), PD-1 (8), and HER2 (7). Given the full picture of target distribution of approved drugs[12], we took a further look at the targets of the 127 immune drugs under clinical development, with 86 drugs dominated by domestic companies, and 41 by foreign companies.

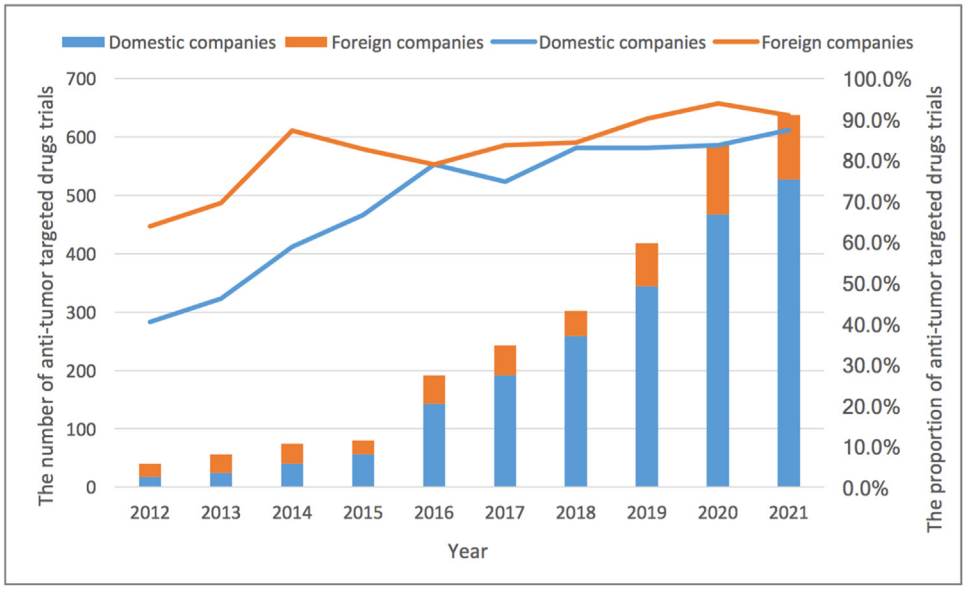

Fig. 1. Ten-year trend analysis of targeted antitumor drug trials by sponsor type in China, 2012-2021.

Table 2
Comparative analysis of the 2,632 trials on targeted anticancer drugs by sponsor type in China, 2012-2021.

Variables	Domestic companies		Foreign companies		Statistics	*P* value
	No. of companies	Proportion (%)	No. of companies	Proportion (%)		
Drug type					3.92	0.14
Generic	214	10.3	3	0.5		
Biosimilar	118	5.7	3	0.5		
Original	1,737	84.0	557	99.0		
Trial scope					1,146.58	< 0.0001
Multicenter	123	6.0	392	70.0		
Single center	1,944	94.0	168	30.0		
Trial phase					590.10	< 0.0001
Phase I	1,140	55.2	98	18.1		
Phase II	415	20.2	126	23.2		
Phase III	285	13.8	315	58.1		
BE	224	10.8	3	0.6		

BE, bioequivalence trials.

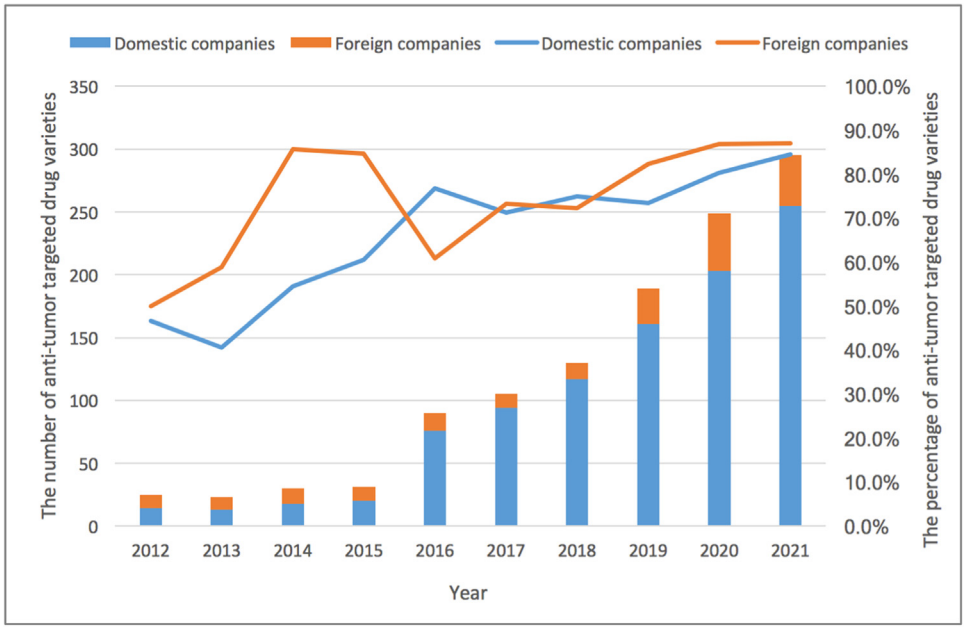

Fig. 2. Ten-year trend analysis of targeted antitumor drug varieties by sponsor type in China, 2012-2021.

Table 3
Overview of involved targeted drug trials and varieties in different tumor types in China, 2020.

Cancer type	Annual incidence rate*, per 100 thousand	No. of all involved trials on anticancer drugs (A)	No. of involved trials on targeted drugs (B)	Proportion of targeted drug trial (C=B/A, %)	No. of all involved anticancer drugs (D)	No. of involved targeted anticancer drugs (E)	Proportion of targeted drugs (F=E/D, %)
Lung cancer	35.9	548	509	92.9	288	255	88.5
Breast cancer	29.6	320	228	71.3	206	134	65.0
Gastric cancer	18.6	112	100	89.3	76	65	85.5
Colorectal cancer	17.8	105	87	82.9	88	71	80.7
Liver cancer	17.4	162	127	78.4	103	77	74.8
Esophageal cancer	11.3	54	42	77.8	30	23	76.7
Cervical cancer	10.9	32	29	90.6	26	25	96.2
Thyroid cancer	10.4	24	19	79.2	20	15	75.0
Corpus carcinoma	6.7	8	8	100.0	7	7	100.0
Prostate cancer	6.5	133	30	22.6	85	10	11.8

* Age-standardized incidence rate by Segi population.

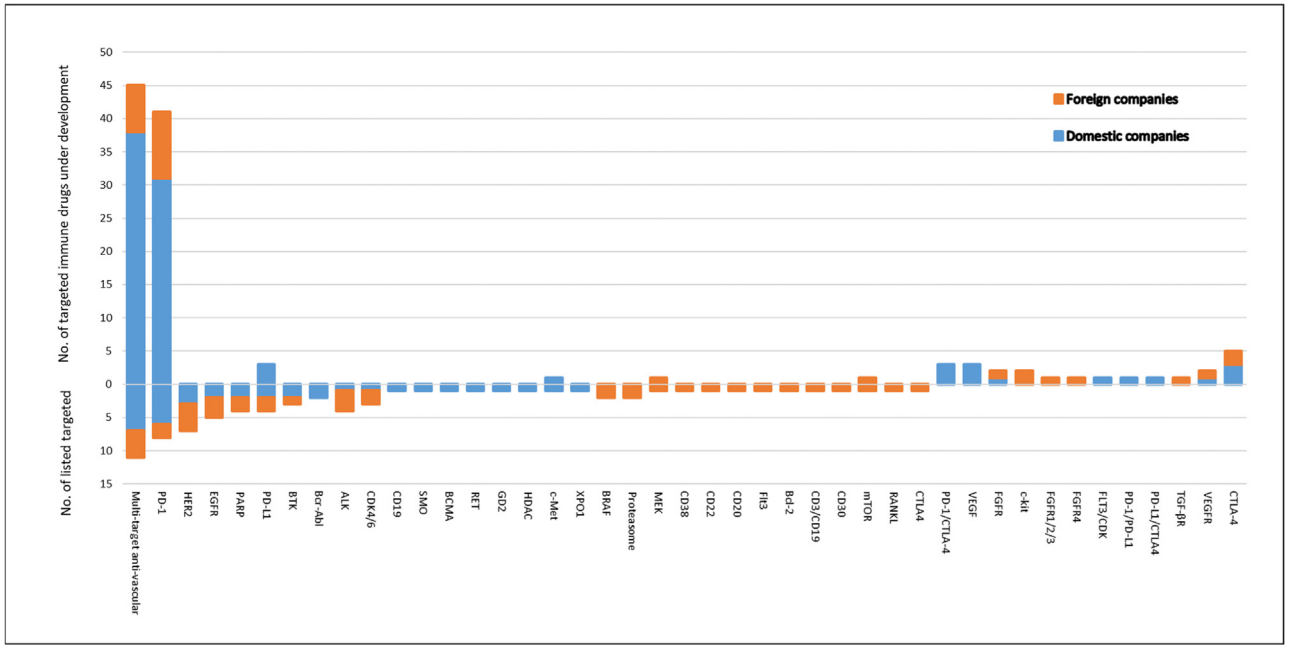

Fig. 3. Target distribution of targeted drugs listed and under development.

The top two targets were also multitargets (45), with PD-1 (41) and PD-L1 (15) getting the third place. Among the 18 targets of immune drugs under development, only TGF-βR was globally first-in-class, and the remaining 17 targets had at least listed drugs approved in China and beyond (Fig. 3).

4. Discussion

On the basis of previous research work, including the 10-year process of oncology drugs clinical trials, the panorama of tumor-immune drugs, and the availability of oncology drugs[10–12,14,15], this study for the first time takes the targeted antitumor drugs research and approvals as the entry point, systematically depicts the overall advances in personalized cancer medicine in China for the past 10 years, and provides macro data support and decision-making basis for the reference by relevant stakeholders. The results show that research and development of antitumor-targeted drug in China are booming, and the number and proportion of trials, test varieties, and listed drugs have increased significantly year by year, which hints that the implementation of personalized medicine in China is appealing for the sustainable development of the pharmaceutical market and healthcare system.

The great progress on antitumor-targeted drugs in China is likely mainly attributed to three aspects, which could form a benign cycle. Firstly, academic and industrial advances in R&D of anticancer drugs globally have driven the development in China and beyond.[17,18] Secondly, the gradually improving ecosystem of drug innovation in China, which is largely correlated with the acceleration due to the series of reforms since 2015[19,20], has attracted more investment from companies at home and abroad and driven their sustainable development. Last but not least, the high potential of personalized medicine to improve healthcare has sparked the attention and input of policymakers for more efficient and sustainable healthcare systems worldwide, including China.[21]

The comparion of domestic and foreign enterprises in this study suggests that, after the R&D of antitumor drugs fully entered the era of precise targeted therapy, domestic enterprises have become the pillar in China, especially since 2016. The gap in the proportion of targeted antitumor drug varieties (84.4% vs. 87.0% in 2021) and trials (87.4% vs. 88.0% in 2021) between domestic companies and foreign companies was gradually narrowed. The absolute number of antitumor drug varieties and trials by domestic companies far exceeded that of foreign companies, as well as the proportion of approved targeted drugs. This finding is consistent with previous research.[14] Taking the high-quality development of domestic enterprises as the starting point to drive

Chinese pharmaceutical R&D forward is the key to targeted antitumor drug development for the next decade, especially for its innovation-oriented drug development.

Based on the fast follow-up model, targeted anticancer drugs in China has achieved remarkabe development, though the listed drugs were not first-in-class.[12] Moreover, this study demonstrated that almost all of the targets under development in China already had products on the market, and the globalization of domestic companies was significantly lower than foreign companies. This means that Chinese enterprises are still unable to contribute first-in-class targeted antitumor new drugs to the world in the short term. In the new era of integration of China into the globalization of R&D[22], the R&D mode in China must be changed from "me-better" to "first-in-class," from the perspective of innovation ability, internal and external force of innovation, as well as innovation ecosystem.

Human genetic resources in China play an indispensable role in sustainable development of precision medicine research. They are especially prominent within oncology research and multicenter research.[23] China has continuously strengthened legislation and ethics, and has initially established a relatively complete legal system and ethical guidelines from collection to export of biological resources.[24] R&D organizations commonly feel that control of human genetic resources is relatively stricter in China compared with the United States. The United States regulates and manages the transfer of human genetic resource materials in scientific research projects by formulating standard biological material transfer agreements.[25] The outward transfer of human genetic resources in China is also under administration of the government; however, the sample export requirement is a little bit strict and the process is a little bit time-consuming.[26] The outward transfer of human genetic resources in China is also under admistration of the government. The sample export shall undergo a strict application process consisting of ethic approval, research approval, administrative authorization, and others. Only legal domestic entities can export the resources.[27,28] The overall layout at the national level should be strengthened to facilitate the development of targeted drugs and personalized medicines.

On the one hand, R&D organizations should advocate for regulations and policies that encourage genomics activities, including internationally, given the fundamental importance of clinical genomics in cancer. On the other hand, we should also work together to establish a national resource strategic preservation platform and standardize safe storage and sharing of samples and data so as to ensure that patient privacy and data security are protected. Additionally, establishing incentives and public–private collaboration frameworks to facilitate access of academia and industry stakeholders to biological samples and data for research purposes is also crucial for sustainable R&D of innovative targeted antitumor drugs in China.

There are three main limitations in this study. First, only registered trials on oncology drugs in China were included due to data availability. Second, only target distribution of identified immune drugs was analyzed while other targets are not fully depicted, which is an important direction in the future. Lastly, the development of targeted anticancer drugs is just one typical aspect of precision medicine in oncology, and markers and algorithms to stratify patients in more detail are also important fields of personalized medicine.

In summary, this study pioneered to show that research and development of targeted antitumor drugs in China are booming and have increased significantly year by year, which hints that the implementation of personalized medicine in China is appealing for the sustainable development of the pharmaceutical market and health system. Encouraging genomics activities, and establishing incentives and public–private collaboration frameworks are crucial for innovation-oriented personalized medicine development in China.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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Author contributions

H.H., J.D., and X.M. contributed to the framework planning and draft writing, as well as data quality control, analysis, and interpretation. N.L. led the overall framework planning and data interpretation. D.W., Y.Y., and S.W. participated in the framework planning and contributed to data interpretation. All the authors reviewed and revised the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2023.02.004.

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