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REVIEW ARTICLE

Characteristics of clinical trials of new oncology drugs approved in China

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Abstract

Background: Since reforms were introduced to incentivize drug innovation in 2015, the Chinese pharmaceutical market has experienced unprecedented prosperity, with more new drugs than ever before, especially anticancer treatments. In 2021, Chinese regulatory agencies issued the new guideline for clinical research and development of antitumor drugs, triggering a series of responses on the drug market. Limited research has outlined the nature of the original new drugs in China to understand the dynamic response of the market.

Methods: The objective of this article was to map the clinical development of approved new oncology drugs in China from 2015 to 2021 and differed from previous studies by focusing on original new drugs, using the United States as a benchmark, and elaborating the endogenous features of clinical trials.

Results: Clinical trials conducted in China have risen to a level similar to that of the United States in many aspects of trial design, but there is still distance between the implementation and operational details of clinical trials. In the meantime, China has made significant breakthroughs in drug approval. Greater than 60% of novel anticancer drugs in China received accelerated approved for their first listing. Approximately 90% of the pivotal clinical trials supporting initial drug approval used surrogate measures as end points, and one half were nonrandomized or did not have a control group. However, duplicate development without evidence of a clinical advantage compared with current therapies was widely observed.

Conclusions: By presenting a multidimensional landscape of clinical trials and approvals in the real world, this review allows interested researchers, developers, and even regulators to understand what has been done and what should be done next in anticancer drug development in China.

KEYWORDS

clinical evidence, drug lag, novel anticancer drugs, pivotal clinical trials, programmed death-1 (PD-1) inhibitors, programmed death-ligand 1 (PD-L1) inhibitors

INTRODUCTION

China is the world's most populous country and second largest economy, with huge unmet medical needs for oncology drugs. It has been reported that 55% of novel drug candidates in pipelines in China are for oncology use.[1] China's rapidly emerging local research and development (R&D) power has become a force in global innovation, leading the world in R&D spending, the number of scientific publications, and the number of patents, with global shares of 22%, 23%, and 49%, respectively.[2] As the most critical part of drug

innovation, clinical trials involving original new drugs (i.e., new drugs in category 1 based on the Chinese definition of *global new* for new drugs) are an informative window to understanding this huge market and the R&D power behind it.

Since 2015, when China launched groundbreaking registration reform,[3–5] there has been a significant increase in the number of clinical trials for cancer treatments in China.[6,7] How to launch drugs in China earlier and faster is a concern for pharmaceutical companies around the world. In this rich but competitive race, the rules are dynamic. The Chinese National Medical Products Administration (NMPA) released a new guideline in 2021, named the *Clinical Value-Oriented Guideline for Clinical Development of Antineoplastic Drugs*[8] (hereinafter referred to as *the 2021 Guideline*), which requires the use of the best current standard of care (SOC) in comparative arms of clinical trials, immediately sending shock waves throughout the capital market in the biotech and pharmaceutical industry in China.[9]

In this context, comprehensively characterizing the clinical trials of new oncology drugs approved in China can inform players in the field, including researchers, investors, and even regulators, of what has been done and what should be done next. This article maps the clinical development of approved new oncology drugs in China from 2015 to 2021 and differs from previous studies by focusing on original new drugs, using the United States as a benchmark, and elaborating the endogenous features of clinical trials.

MATERIALS AND METHODS

Collection of new oncology therapeutic drugs

In this study, we identify the new drugs as *new molecular entities* or new *therapeutic biologic products*. Accordingly, we retrieved the defined novel anticancer drugs approved in China and the United States by using the Chinese NMPAs and Center for Drug Evaluation (CDE) official websites (https://www.nmpa.gov.cn/ and https://www.cde.org.cn/; accessed April 12, 2023) and the US Food and Drug Administration's (FDA's) official website (https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products; accessed April 12, 2023) from 2000 to 2021. We also used a third-party database, pharmacodia (https://pharmacodia.com; accessed September 30, 2021), to collect the historic approval information because of limited publicity. It is worth noting that the definition of *novel drug* is different in the two countries. Novel drugs, as defined by the FDA, are those *never before approved or marketed in the United States*.[10] In China, novel drugs are defined as the *globally new drugs, which have never been approved or marketed globally and registered as class 1 type*.[11,12] Drugs never approved in China but launched in other countries are classified as type 5.1 for small-molecule entities and type 3.1 for biologic products, respectively.[12] The type 1 new drugs in China are identified in an extra column in Table S1.

Collection of clinical trial data

To compare the characteristics of the new drugs approved in the two countries, this research adopts the local definitions of novel drugs in each country and limits the first approval year from 2015 to 2021. We retrieved 29 type 1 new drugs and 90 new oncology therapeutic drugs in China and the United States, respectively. We then obtained and reviewed the summary reports, approval letters, and drug labels of the investigated anticancer drugs from the Drugs@FDA and CDE databases. Data for expedited program designations and pivotal clinical trials supporting initial approval were also extracted from these documents (see Table S2 and S3).

We further developed a data set of clinical trials investigating the drugs listed by the US government registry of clinical trials (ClinicalTrials.gov). Searches were limited to interventional clinical trials initiated between the years 2000 and 2021, and duplicate trials were removed (Figure 1). Pivotal trials previously identified for the listed drugs were included and labelled in this clinical trial data set.

Extraction of clinical trial features

For all clinical trials, we extracted various key data, such as: the numbers of investigated indications, trial groups, end point measures, enrollment, and countries as well as trial starting and completion dates. For multiple trials of a drug, we took an averaging approach to counting the data related to indications, trial groups, end point measures, and enrollments. Trials were marked as international (more than one country) or noninternational, and trial duration was calculated according to the number of months from the start date of a trial to the actual or estimated completion date. For pivotal clinical trials, we collected more detailed information, including the exact trial design and the end point measures.

Case study

To further explore the type 1 innovative drugs approved in China, we conducted a case study by reviewing the clinical trial end point results of eight inhibitors targeting programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) and compared them with the data of two pioneer PD-1/PD-L1 products (nivolumab and pembrolizumab). The trials supporting drug indication approval before the year 2022 were collected from summary reports, approval letters, and drug labels. According to the approval timeline, nivolumab and pembrolizumab were approved for the first time in 2014 in Japan and the United States, respectively. Both entered drugs China in 2018 registered as type 3 drugs, whereas the eight PD-1/PD-L1 inhibitors included in our case study were approved only in China one after another since December 2018 as type 1 new drugs. Nivolumab and pembrolizumab was launched for more indications in the United States than in other countries, so the corresponding clinical evidence for approval in the United States was gathered as a benchmark. The

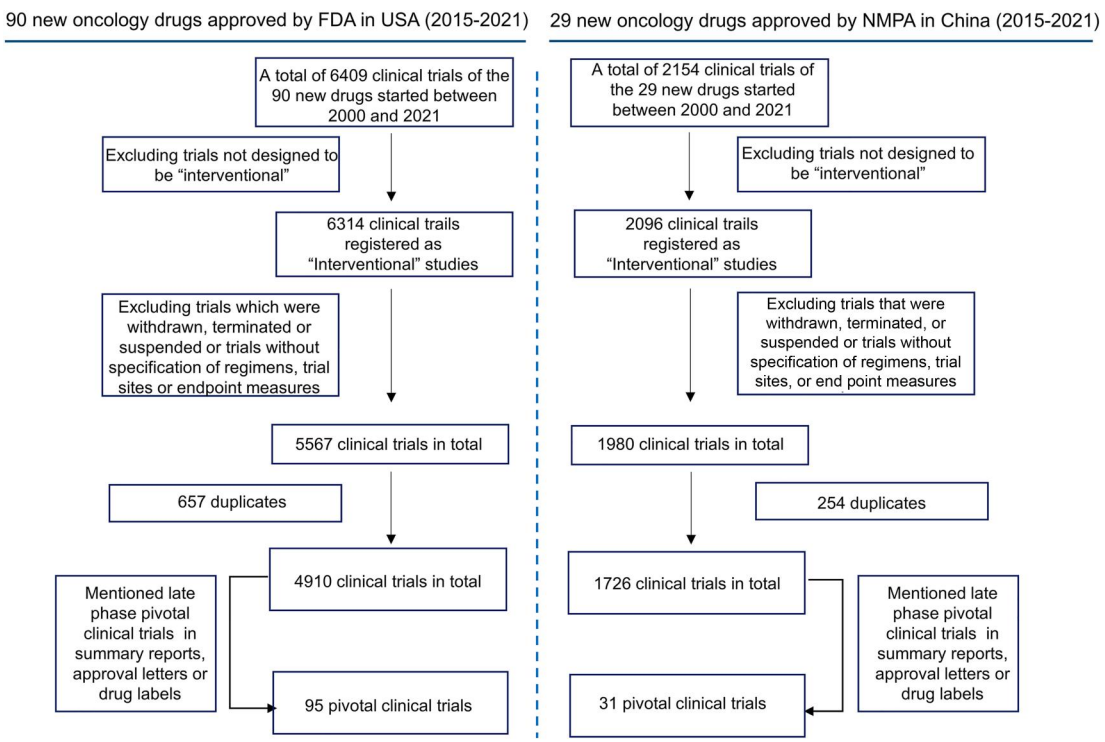

FIGURE 1 Data-processing diagram of clinical trials. FDA indicates US Food and Drug Administration.

objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) data were collected from trials in the first-line setting. For second-line or later lines of treatment, only ORR results were included.

Statistical analysis

We used Microsoft Excel 2016 (Microsoft Corporation) and SPSS version 22 (SPSS Inc./IBM Corporation) for data analysis. Descriptive statistics were calculated as the number and percentage of clinical trials in each category. Spearman correlation analysis was used to describe the associations between the number of studied new drugs and cancer incidence (evaluated by new cases in China in 2020[13]) or disease burden (evaluated using the World Health Organization WHO disability-adjusted life-years [DALYs] data from 2019[14] by calculating the DALY rate per 100,000, setting the American population as 328.3 million and the Chinese population as 1398 million[15]).

RESULTS

Availability of oncology drugs in China

The 2015 registration reform resulted in a large number of oncology drugs launched in China market, especially after the year 2017. Although there is a lag >5 years after the first approval in the United States for many drugs, we witnessed that a large proportion of drugs were available in China with a drug lag <4 years in recent years (Figure 2).

Novel anticancer drugs from 2015 to 2021

Except to make up for the drug lag, China also incentivizes the launch of globally new drugs. China did not approve of any new oncology drugs from 2015 to 2017, had a breakthrough in 2018, and then increased rapidly to a peak of 13 approvals in 2021 (Table 1). In contrast, the United States steadily maintained a level of >10 approvals per year from 2015 to 2021, with the exception of 2016. Also, an analysis of sponsor nationality indicates that 90% of new anticancer drugs approved in China are developed by domestic organizations; whereas, in the United States, 51% of new anticancer drugs are from foreign applicants. Furthermore, 86% of the drugs approved in China were being approved for the first time globally, and all were domestically developed, in contrast to 84% in the United States. The four new drugs not first approved in China were zanubrutinib from BeiGene, dacomitinib from Pfizer, niraparib from GSK, and pralsetinib from Blueprint Medicines, all of which were first launched to market in the United States.

When investigating the drug types approved, China and the United States are identical, with 69% small-molecule products and 31% biologic products. Among the 29 approved new drugs in China, there are no global first-in-class drugs, although many first-in-class drugs are in the pipeline.[16] In the United States, 29 of the 90 novel anticancer drugs (32%), were first-in-class drugs.

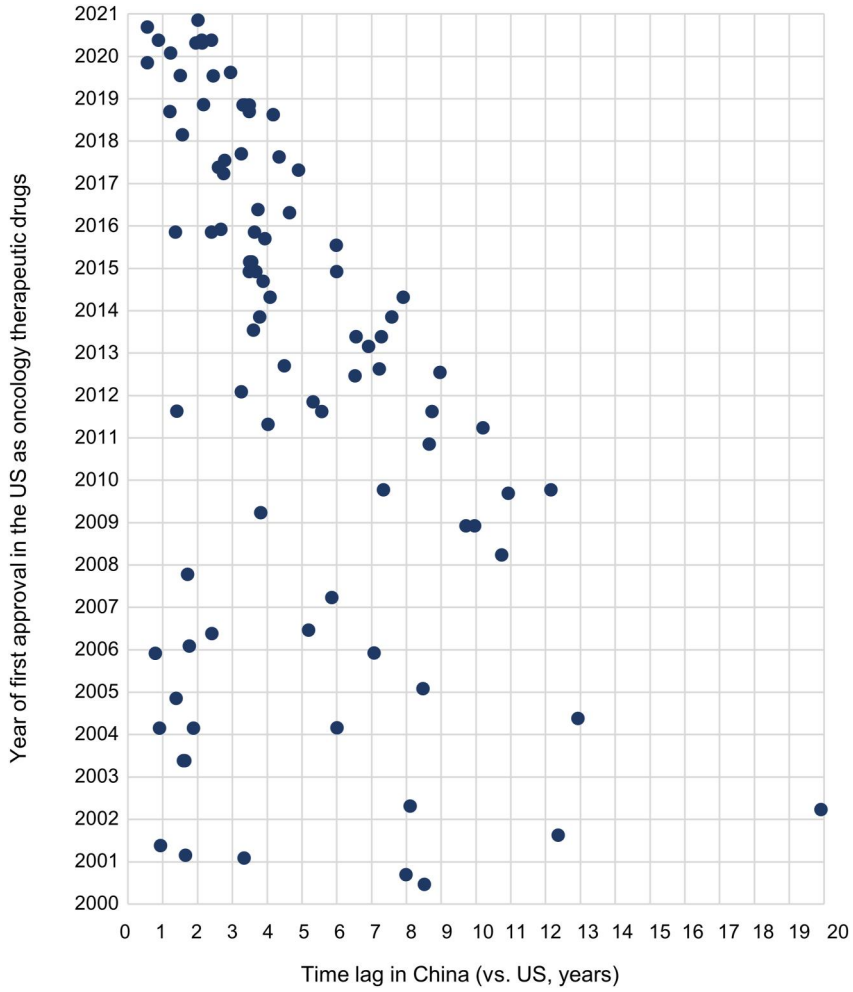

FIGURE 2 Drug lag of oncology drugs in China compared with drug approval in the United States.

Expedited approval programs are commonly used, and most approved drugs receive priority reviews. These programs were introduced to speed up drug availability and were available in the United States substantially sooner than in China. The FDA started priority review and accelerated approval in 1992, fast-track designation in 1997, and breakthrough therapy designation in 2012. China introduced priority review in 2015, conditional approval (similar to accelerated approval) in 2017, and breakthrough therapy in 2020. In the United States, 44 of 90 drugs (49%) received accelerated approval by the FDA; whereas, in China, 18 of 29 drugs (62%) were under conditional approval. Orphan drug position is not designated in approved new drugs in China.

Cancer types

The left column in Figure 3 lists the most concentrated cancer types of new oncology drugs in China. Lung cancer, as the most burdensome cancer type, accounted for the largest set of new drug approvals in China. Conversely, drugs for classical Hodgkin lymphoma had five initial approvals, only second to lung cancer, despite having a much lower disease burden (less than 1% of the DALY value of lung cancer). In general, the rationales supporting the Chinese cancer indications are reflected in the positive associations between the number of new drugs and the incidence and DALY rates, with significant Spearman correlation coefficients of 0.667 ($p < .01$) and 0.714 ($p < .001$), respectively. Moreover, the number of new drugs can be categorized by initially approved cancer types and expanded indications. The high proportion of expanded indications shows a rather frequent development of new clinical uses. For instance, many PD1 antibodies followed the *two-step strategy*[17] of the expanding oncology market in China: first launching for a *rare* cancer type (Hodgkin lymphoma) to gain fast access the market, and then extending to a more prevalent cancer. Features like the dominance of lung cancer, the consistency of clinical development efforts to assess the diseases' natural profiles, and the wide expansion of cancer indications can also be observed in the United States despite the slight differences between the two countries' cancer profiles and clinical developments.

TABLE 1 The characteristics of approved new anticancer drugs, 2015–2021.

Characteristics		No. (%)	
		China, *n* = 29	United States, *n* = 90
Approval year	2015	0	14
	2016	0	4
	2017	0	12
	2018	5	18
	2019	5	11
	2020	6	17
	2021	13	14
Domestic sponsor	Yes	26 (90)	44 (49)
	No	3 (10)	46 (51)
Globally first approval	Yes	25 (86)	76 (84)
	No	4 (14)	14 (16)
Approval type	Biological product	9 (31)	29 (32)
	Small molecule	20 (69)	61 (68)
First-in-class	Yes	0 (0)	29 (32)
	No	29 (100)	61 (68)
Expedited program	Priority review	26 (90)	79 (88)
	Accelerated approval[a]	18 (62)	44 (49)
	Fast track	–	32 (36)
	Breakthrough therapy	10 (34)	49 (54)
	None	1 (3)	7 (8)
Orphan drug designation	Yes	–	67 (74)
	No	–	23 (26)

[a]Conditional approval in China is identical to accelerated approval in the United States.

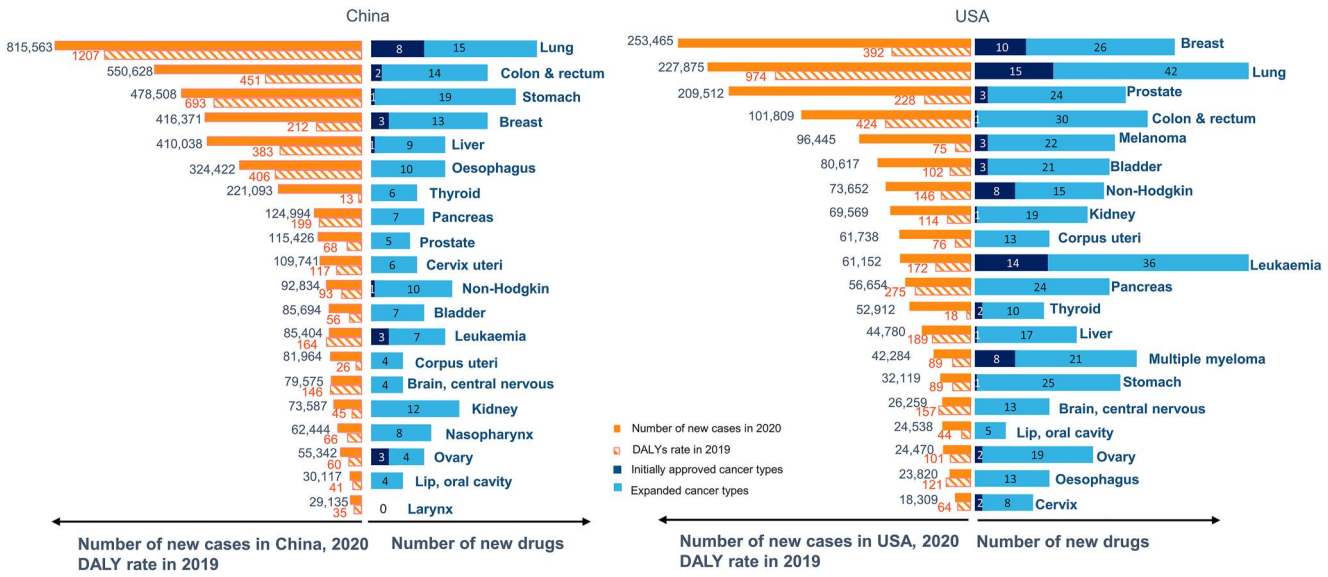

FIGURE 3 The number of new drugs targeting the top 20 cancer types in the United States and China and the corresponding number of new cases and DALY rate. Spearman correlation analysis demonstrated that the number of drugs investigated is correlated with cancer incidence and the DALY rate. DALYs indicates disability-adjusted life-years.

Targets

Unsurprisingly, biologic products showed different target mappings compared with small-molecule drugs (Figure 4). Biologic products targeting PD-1/PD-L1 showed high productivity in both countries. In China, eight PD-1/PD-L1 reagents were approved one after the other, when the first got conditional approval in 2018. Except for PD-1/PD-L1 and HER2, new biologic products in the United States successfully demonstrated clinical profit compared with many different targets. Small-molecule drugs targeting EGFR, *KDR*, PARP, PDGFR, *FLT1/FLT4*, FGFR, BTK, and BCR-ABL generated the most approvals in both counties. Moreover, China showed a highly overlapped target distribution with the United States, although the United States produced more new approvals for drugs with different targets. One of the *new molecular entities*, named *utidelone*, a nontaxane anticancer drug targeted to the tubulin beta-1 chain, was approved in China in 2021. The most recent novel drug with the same target in the United States was the taxane reagent named *cabazitaxel*, which was approved by the FDA in 2010. This indicates overlapped/me-too and crowded outputs for certain targets in China. The Chinese agencies also noted this trend and issued the 2021 Guideline, requiring that clinical development show comparative advances over the SOC. That is to say, the future approval of me-too drugs must be evidenced by head-to-head studies with superior benefits over the best approved drugs. Therefore, the oncology pipeline in China will be more competitive not only for candidates with the same target but also for different targets with the same indication.

Overall clinical trials

In total, there were 1726 clinical trials related to new oncology drugs approved in China from 2015 to 2021. A box plot of clinical trials by phase in China and in the United States shown in Figure 5 includes the number of indications, trial groups, end point measurements, patients enrolled, international trials, and duration. Using the United States as an international benchmark, China exhibits lower values and less variation in the six aspects mentioned above, with a lower center in the box plots, smaller range, and closer mean and median values. However, in terms of averages, the differences between

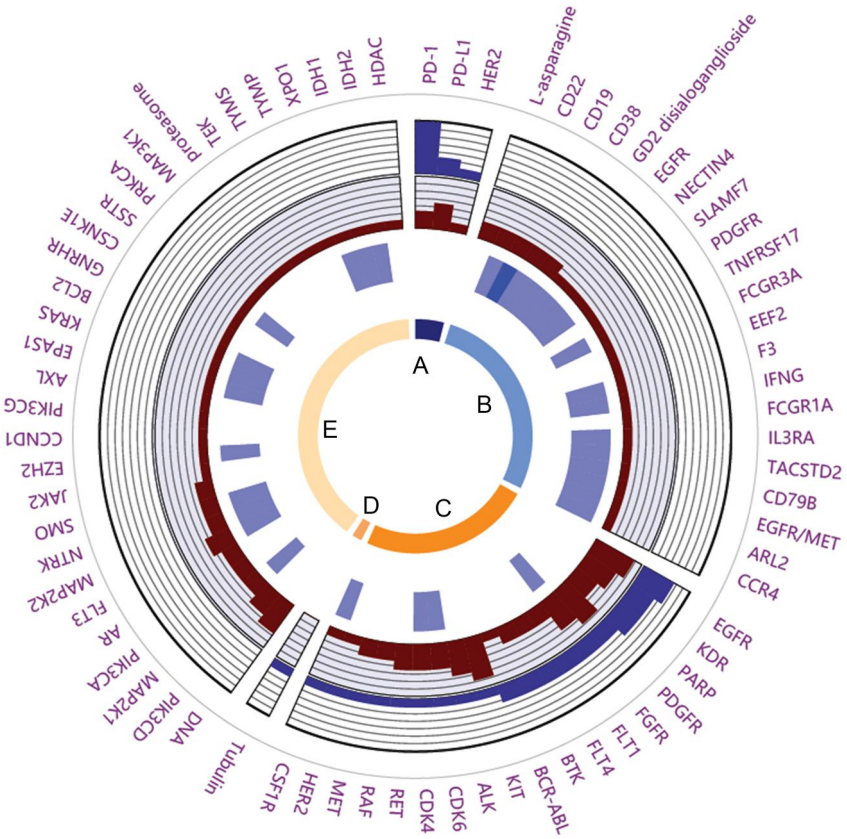

FIGURE 4 Circos plot displaying targets of the approved novel anticancer drugs divided into five sectors: (A) targets of new biologic products that overlapped in China and the United States; (B) targets of new biologic products unique in the United States; (C) targets of new molecular entities that overlapped in China and the United States; (D) targets of new molecular entities unique in China; and (E) targets of new molecular entities unique in the United States. The outer ring shows all targets by category. The next two rings illustrate the number of approvals in China (in blue) and the United States (in red) using histogram plot. One more inside circle shows the targets of novel anticancer drugs designated as first-in-class by the US Food and Drug Administration from 2015 to 2021.

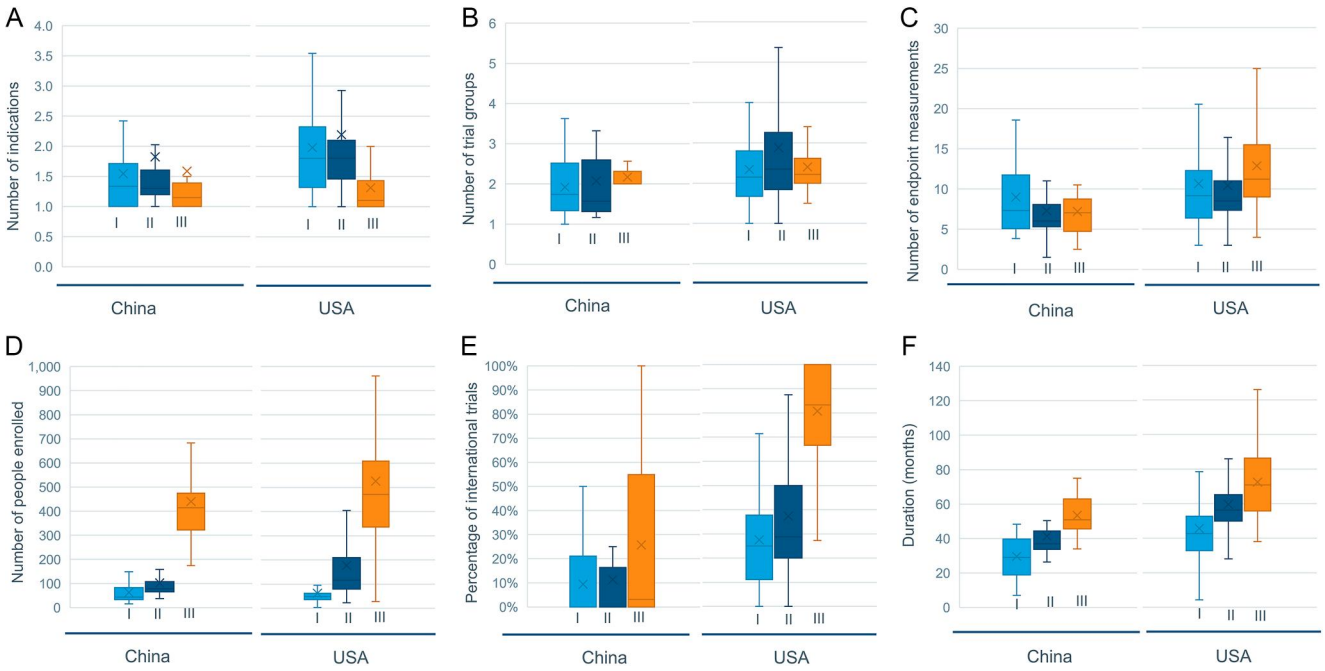

FIGURE 5 (A–F) Box plots of all clinical trials of new oncology drugs from 2015 to 2021. The variables were calculated on an average basis for drug levels. Box plots indicate the dispersion of the listed metrics with the outliers removed. The interquartile ranges shape the box body, and the ends mark the minimum and maximum values.

China and the United States are not large except in the percentage of international trials. In phase 3 studies, <30% of the trials for drugs approved in China are international and multicentric, much lower than the approximately 80% of such trials in the United States.

Chinese clinical trials have slightly fewer indications than those in the United States, and most trials in China first claim one indication for the higher chance of approval and then gradually expand to other areas, following the *two-step strategy*[17] mentioned above. Like clinical trials in the in the United States, most phase 3 clinical trials in China involve two trial groups, with the wide adoption of a control-group design. On average, phase 3 trials in China use about seven end point measurements, whereas more indicators (>10) are used in the United States. In terms of enrollment, there was less variation in China than in the United States regardless of clinical stage, although the average numbers were very close. With fewer multiregion clinical trials (MRCTs), China showed faster completion of clinical trials than the United States, averaging 30 months for phase 1, 40 months for phase 2, and 50 months for phase 3 trials. In addition, our data show that the percentage of clinical trials involving pediatric investigations is significantly lower in China than in the United States (see Figure S1).

Pivotal clinical trials

Of the clinical trials overall, 1.8% are pivotal clinical trials directly supporting initial approvals recorded in the official documents of the drug authorities in China, and the remaining 98.2% are investigator-initiated clinical trials or are related to support expanded therapeutic areas. Table 2 shows the characteristics of these pivotal clinical trials with their comparable standards in the United States.

Sixty-eight percent of pivotal trials are in phase 2 because of the urgent clinical needs of patients who have cancer; this is like the United States, where 57% of trials are in phase 2, and 4% of trials are even in phase 1. With the potential concern over trial quality, 58% of China's pivotal trials were single-group trials without a control group, compared with 37% of pivotal trials in the United States. Similarly, in both countries, almost one half of trials were not randomized, and 80% of trials were open-label.

As observed in the clinical trials overall, the pivotal data set demonstrates a large lag in China versus the United States with regard to international trials. The percentage of international studies in pivotal Chinese clinical trials was <10%, which was much lower than the 95% in US clinical trials. In 2017, the International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued Guidance E17 to reinforce the use of MRCTs in global drug development. In the same year, China was accepted as a new member of the ICH. On the basis of the 2015 reform, the new Chinese system is much more open to international clinical evidence than ever before. For example, niraparib was granted conditional approval with pharmacokinetic data on Chinese patients, whereas the clinical benefit was evidenced in international phase 3 studies without China's engagement. With an increasing domestic force for drug innovation, Chinese enterprises are seeking to go abroad to expand their international markets. However, the low proportion of MRCTs and, more importantly, the neglect of international trials as a mindset may be key bottlenecks for Chinese innovative enterprises to register overseas.

TABLE 2 The characteristics of pivotal clinical trials of new oncology drugs, 2015–2021.

Characteristics of pivotal clinical trials		No. (%)	
		China, $n = 31$	United States, $n = 95$
Phase	Phase 1	0 (0)	4 (4)
	Phase 2	21 (68)	54 (57)
	Phase 3	10 (32)	37 (39)
Allocation	Nonrandomized	18 (58)	49 (52)
	Randomized	13 (42)	46 (48)
Intervention model	Crossover	0	3 (3)
	Sequential	0	5 (5)
	Parallel	13 (42)	52 (55)
	Single group	18 (58)	35 (37)
Masking	Open label	25 (81)	77 (81)
	Double	0	5 (5)
	Triple	0	3 (3)
	Quadruple	6 (19)	10 (11)
International	Yes	3 (10)	90 (95)
	No	28 (90)	5 (5)
Primary outcome measures	OS	3 (10)	6 (6)
	PFS	7 (23)	22 (23)
	ORR/DOR/CR	17 (54)	57 (60)
	Others	4 (13)	10 (11)

Abbreviations: CR, complete response; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ORR.

Moreover, on primary outcome measures, surrogate end points are widely used in late-phase pivotal clinical trials in China, like in the United States. Compared with regular approval, which requires adequate evidence of clinical efficacy based on well controlled trials, drugs that receive accelerated approval designations are allowed to use surrogate end points to predict clinical efficacy. In both countries, only about 10% of the studies used the primary outcome metric of OS. Instead, other measures, such as PFS, the ORR, the duration of response, and the complete response rate, were often used. Both countries showed a high tolerance for surrogate end points in new anticancer drug approval.

According to the pivotal clinical trials summarized in this research, the Chinese drug authority NMPA shares evaluation standards similar to those used in the United States. Policy flexibilities widely used in the registration of oncologic new drugs, such as single-arm studies and surrogate end points, are highly accepted for approval in both countries. As mentioned above, the 2021 Guideline requires use of the SOC in the comparative arms of clinical trials rather than already replaced therapies. However, definitions of the SOC are not clear in the 2021 Guideline, especially if identification of the SOC depends on regular approval, or is listed in clinical treatment guidelines, or is widely accepted by clinical practitioners or others because policy flexibility exists to some extent in practical operation. Nevertheless, a pragmatic solution to avoid risking control design would be involving the registration administrator at the beginning of the trial-design process. Meanwhile, it is expected that single-arm trials as approval evidence will decrease in the future, not only in China but also in the United States.

Case study of PD-1/PD-L1 inhibitors

China initiated its breakthrough reform in the year 2015, which was only 2 years after the breakthrough year for oncology immunotherapy.[18] With remarkable clinical benefits across multiple cancer types, the first two PD-1/PD-L1 inhibitors, nivolumab and pembrolizumab, are now the leading immune checkpoint treatments. Adding to this global flood of development, Chinese biopharma delivered eight new PD-1/PD-L1 inhibitors during our investigational period, and there are many more waiting in the pipeline.[16]

The clinical results (Figure 6) showed that the eight PD-1/PD-L1 inhibitors approved in China are mainly concentrated in lung cancer,[19–25] Hodgkin lymphoma,[26–30] nasopharyngeal cancer,[31–34] bladder cancer,[35] liver cancer,[36,37] and esophageal cancer.[38,39] However, nivolumab and pembrolizumab have been approved for use across most cancer types. The number of approvals for lung cancer

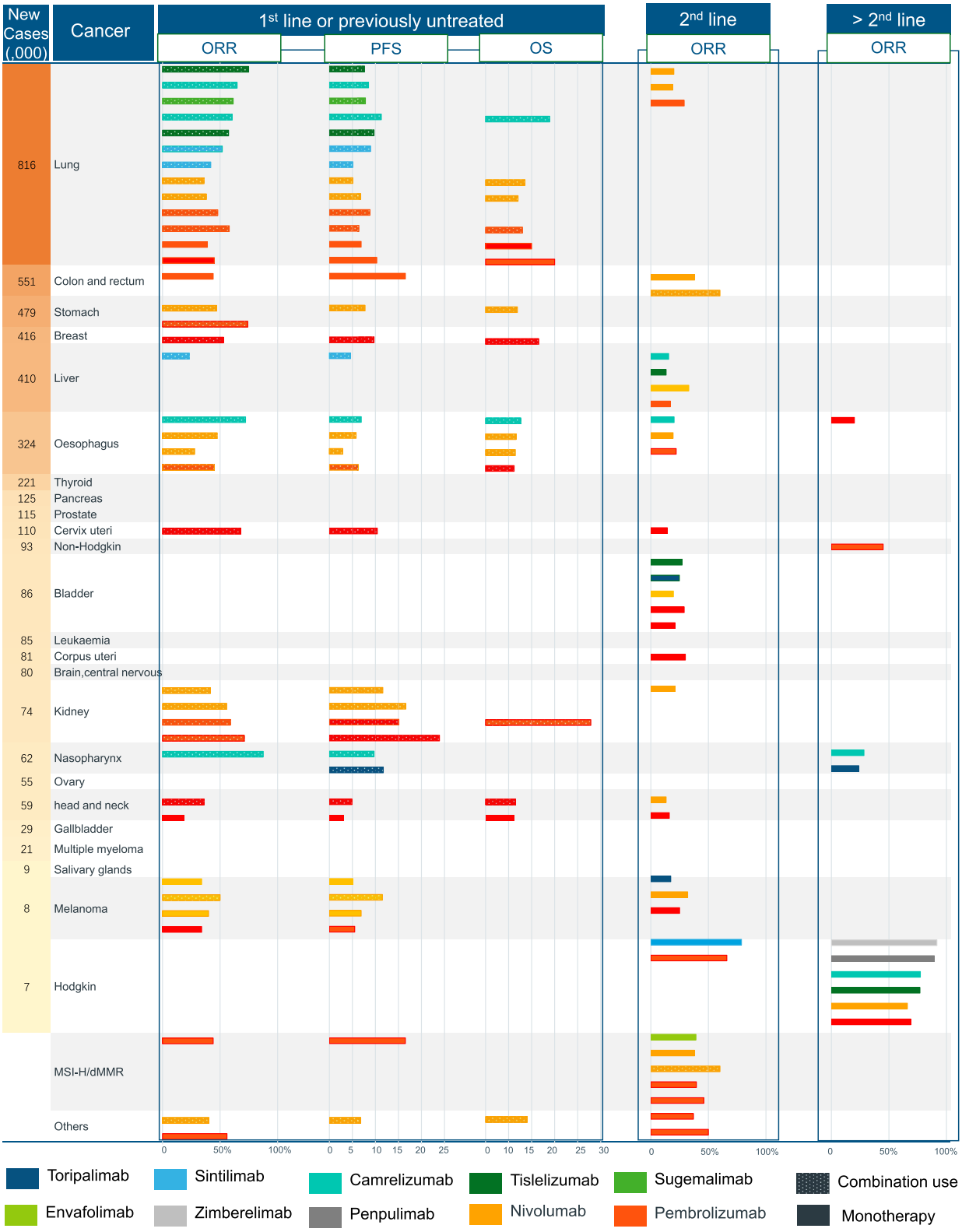

FIGURE 6 Clinical trial results in different indications of eight novel PD-1/PD-L1 inhibitors approved in China compared with nivolumab and pembrolizumab in the United States. These indications were approved before 2022 and are ranked by the number of new cases in China in 2020. The results of clinical end points are displayed in the first-line, second-line, and later line settings. Clinical trial results of these drugs are represented by different colors, and monotherapy and combination use are shown in different fill patterns. MSI-H/dMMR indicates high microsatellite instability/deficient mismatch repair; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

ranks first, and this is also the top cancer with the most new cases. Before the year 2022, one half of eight PD-1/PD-L1 drugs in China were approved as first-line treatment for lung cancer. It is observed that the majority of first-line treatments are basically combination therapies. Although nivolumab and pembrolizumab as monotherapy in the first-line setting were approved for lung cancer, melanoma, or cancers with expression biomarkers like PD-L1 or high microsatellite instability/deficient mismatch repair. The Chinese domestic PD-1/PD-L1 inhibitors were all used in combination to get approval for the first-line setting. The top six cancer types with the largest number of new cases[13] are covered by PD-1/PD-L1 drugs as first-line treatment. In addition, approvals for the treatment of bladder cancer and Hodgkin lymphoma are mainly designed for second-line and later line settings. Within our data set, the approvals still uncover thyroid cancer, pancreatic cancer, and prostate cancer, etc.

As shown in Figure 6, the ORR of first-line therapy is generally higher than that for second-line or later lines of treatment for the same cancer type. Based on the outcomes from the listed clinical trials, Chinese domestic PD-1/PD-L1 inhibitors have clinical performance similar to that of nivolumab and pembrolizumab. However, to our knowledge, no head-to-head studies have been published to date. The development of PD-1/PD-L1 inhibitors in China must fully draw on the clinical experience from nivolumab and pembrolizumab. It can be noted that all PD-1/PD-L1 inhibitors have a striking ORR in the second-line or later line treatment of Hodgkin lymphoma.[40] This common advantage facilitates the first new drug application filing of five Chinese domestic PD-1/PD-L1 products. The distinct monotherapy efficacy of nivolumab in melanoma[41] and of pembrolizumab in high microsatellite instability/deficient mismatch repair–expressing tumors[42] also has prompted the selection of the first-approved indication for toripalimab[43] and envafolimab,[44] respectively.

The clinical success of nivolumab and pembrolizumab pressures the late comers to create differentiation. Sintilimab in combination with bevacizumab filled the gap as first-line treatment for hepatocellular carcinoma by achieving better PFS and OS over sorafenib.[36] Also, camrelizumab and toripalimab have been approved for nasopharyngeal cancer,[32,34] which was not covered by nivolumab or pembrolizumab.

Conversely, we can still see serious homogeneity competition of launched PD-1/PD-L1 products in China, especially in lung cancer and Hodgkin lymphoma, let alone 80 more PD-1/PD-L1 inhibitors in the pipelines.[3] Meanwhile, serious duplicate development because of the *me-too* business strategy brings commercial disaster. The average annual treatment cost of PD-1/PD-L1 products in China is 80% less than that in the United States.[45] After the collapse of the domestic market, these PD-1/PD-L1 products are trying to find a way out into foreign markets. The first to go abroad was sintilimab, for which a biologics license application was submitted to the FDA with clinical evidence solely from trials conducted in China. With the lack of head-to-head studies, those trials could not address whether sintilimab provided better benefits versus existing nivolumab or pembrolizumab for the treatment of nonsmall cell lung cancer. Without fulfilling an unmet need,[46] sintilimab failed the listing in the United States.[47]

The NMPA also noticed this duplicate development and issued the new 2021 Guideline, which highlights clinically unmet needs. In detail, the me-too drugs must be supported by head-to-head studies that establish superior benefits over the best approved drugs. This inevitably puts forward higher requirements for the development of new drugs in China. The regulatory flexibility will no longer be widely applicable, and we may see a lower proportion of surrogate end points from single-arm trials to support approval.

DISCUSSION

Since 2015, there has been a significant increase in the number of novel drugs replenishing the existing drug pipelines.[48] Oncology has dominated the investigational new drug and new drug applications,[3] and clinical trials for cancer treatments have surged in China.[6] Here, we have traced the progress of new anticancer drugs to get a glimpse of drug discovery in China.

Growing numbers of studies document this exciting change, including: (1) reimbursement policies, such as centralized procurement to reduce generic drug prices at the national level[49] and save reimbursement costs for new drugs; (2) changes in regulation, such as the NMPA initiating a big change by expanding review staff, introducing expert reviewers, and adjusting the approval process by using expedited programs similar to those used by the FDA[4,50–52]; and (3) the drug pipelines and the increasing number of trials as well as the distribution of indications or targets.[6,16,53] However, little is known about the clinical evidence supporting the first new drug application filings and the expanded clinical development of recent new oncology drugs in China. In this context, the current review provides a systematic observation and elaboration.

In general, clinical trials conducted in China have been upgraded to a level similar to that of trials conducted the United States in many respects of trial design, especially after China's participation in the ICH, but there is still distance between the two countries in terms of the implementation and operational details of clinical trials. With the high incidence rates and disease burdens in oncology, China's innovation in drug approvals has demonstrated a quick increase and has peaked in the past few years. Notably, the 2021 Guideline signals a trend toward tighter oncology drug registration. The situation of eight new PD-1/PD-L1 drugs being approved one after another in China will likely not reappear in the future unless the late comers show superior efficacy. It is highly possible that the Chinese drug authority will start to limit the repetition of development on crowded targets, and pipeline drugs designed for high-frequency targets (PD-1/PD-L1, EGFR, HER2, etc.) will be the first batch of candidates to encounter the influence of the 2021 Guideline. It remains to be determined how many novel drugs will have to wait for conditional approval, how many novel drugs targeting the same proteins will be approved, and what the effects will be on the Chinese anticancer drug market. In this uncertain and dynamic environment, a

comprehensive understanding of the characteristics of successful clinical trials and insight into the landscape of clinical research in China with an international benchmark will undoubtedly help and guide developers and investors who have entered or intend to enter the Chinese oncology drug market.

AUTHOR CONTRIBUTIONS

Yuan-Jia Hu: Conceptualization and writing–review and editing. **Jing Yang**: Data curation, formal analysis, and writing–original draft. **Ji Yang**: Data collection and data validation.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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