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Advances on anticancer new drugs in China and the USA in 2020: from ongoing trial to drug approval ☆

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ABSTRACT

Objectives: To describe and compare the research and development (R&D) pipeline of cancer new drugs and newly approved drugs in China and the USA in 2020, thus to provide decision-making evidence for related stakeholders.

Methods: Clinical trials and tested cancer new drugs information in China and the USA were respectively acquired from Information Disclosure Platform for Drug Clinical Studies and Trialtrove database. Drug approval was tracked from the official release. Subgroup comparison in terms of initiated trials and drugs were conducted between the two countries.

Results: In 2020, 577 trials on 335 cancer new drugs were registered in China, accounting for 22.6% of all clinical drug trials, while in the USA, 916 trials on 678 cancer new drug trials were captured, accounting for 19.9% of the total. Relatively, a lower proportion of earlier phase (76.9% vs 87.4%), global (17.7% vs 39.0%), and top 20 pharmaceutics contribution (15.8% vs 43.2%) were found for cancer drug trials initiated in China. The fight against solid tumor took top billing in both countries, and the different distribution of cancer indications associated with cancer spectrum was also observed. Compared with the USA, more targeted agents (87.5% vs 77.0%, $P < 0.001$) and less immune agents (30.7% vs 41.6%, $P < 0.001$) were tested in China. In addition, 16 and 18 anticancer new drugs were approved in China and the USA, with 6 (37.5%) and 17 (94.4%) drugs being firstly approved worldwide, respectively. Among them, 32 drugs were granted by at least one expedited program, and 31 drugs were approved based on evidence from surrogate endpoints. A total of 17 cancer types were covered, and only one drug was targeted on digestive cancers, including gastric, liver, and esophageal cancers.

Conclusions: R&D of anticancer new drugs is substantial, and great progress has been made in both China and the USA in 2020. The difference and gap between China and the USA highlight that more efforts should be paid to anticancer drug R&D on innovative agents and cancers unique to Chinese populations, as well as to facilitate global synchronous R&D in China.

1. Introduction

Cancer is a worldwide public health problem and is the leading cause of death in most countries. China and the USA have the world's heaviest burden of cancer, taking the top two places.[1,2] There were almost 8.6 million new cases of cancer and 4.4 million cancer deaths in the two countries in 2020, accounting for 44.6% and 44.2% of the global new cases and deaths, respectively.[1] An aging population, increasingly unhealthy lifestyles, and high exposure to environmental carcinogens indicate an increasing trend in cancer incidence as well as unmet medical needs. Drug therapy is the main treatment strategy for cancer, especially in those patients with advanced stages. It is of vital importance to improve outcomes of patients with cancer by promoting the process of cancer new drugs research and development (R&D) and delivery all over the world.

The USA has been leading the world in new drug R&D. Benefiting from a series of incentive policies issued in the past decade, China has achieved tremendous progress in the R&D of cancer drug as well.[3] Chi-

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nese drug market has become the second-largest pharmaceutical market on behalf of the emerging market only behind the USA.[4] The landscape of clinical trials continues to evolve over time as scientific breakthroughs and technological innovations emerge. Assessing the latest advances could provide insights into the competitive trial pipeline and unmet clinical needs, revealing priorities and strategies of the industry at large, as well as individual companies. However, a summary and comparison on the landscape of cancer clinical trials and drug approval in China and the USA are of paucity.

Therefore, the goals of this study were (1) to describe and compare R&D pipeline of anticancer new drugs in China and the USA in 2020, (2) to describe and compare new anticancer drug approvals in China and the USA in 2020, and (3) to put forward recommendations to further promote the development of oncological new drugs, especially in China, thus to provide essential data for all related stakeholders to make adaptive adjustment in cancer new drug R&D in time.

2. Materials and methods

2.1. Data source

Data involved in this study was acquired from several databases. National Medical Products Administration (NMPA) Registration and Information Disclosure Platform for Drug Clinical Studies, which are designated and authorized for registration use officially, were systematically searched for registered trials in China.[5] Trialtrove database, which is known as the industry's gold standard for clinical trials intelligence globally, was used to identify registered trials in the USA.[6] NMPA and Food and Drug Administration (FDA) were tracked for drug approvals in China and the USA to ensure data reliability and integrity.[7,8]

2.2. Data processing and key indicators

A total of 2548 drug trials registered in China and 4594 in the USA in 2020. All trial inclusion and data processing were done by HYH and HLM independently, and a third expert (DWW) was invited to arbitrate until reaching a consensus in case of any disagreement.

Regarding registered trials of cancer new drugs, eligible trials had to satisfy all the following inclusion criteria: (1) trials registered within 2020, (2) therapeutic area was limited to anticancer drugs, excluding drugs for cancer supportive care, (3) drug type belonged to innovative drugs, excluding generic drugs and biosimilar drugs, (4) study was for registration purpose, excluding investigator-initiated studies, (5) study region included China or the USA.

The following public information were available for all identified eligible trials: date of first issue, sponsor name, study phase, primary tested drug, targeted cancer type, trial region or scope, other registration items, etc. All identified eligible trials were processed mainly by the following steps. Firstly, based on whether the sponsor of the trial is one of the top 20 global enterprises, sponsor type was reclassified into two categories.[9] Then, drug classification information was supplemented regarding primary tested drugs, including drug type (chemicals, biologic agent, and nature medicine), mechanism of drug action (cytotoxic, targeted, or immune agent).

In terms of drug approvals, all cancer drugs marketed in 2020 were summarized, including its generic name, developer, sponsor type, expedited program granted, indication, primary endpoint of pivotal studies, globally approval status, and drug lag. For drugs approved in China in 2020, we also described their status in the USA, and vice versa. Regarding expedited programs to accelerate drug development and review, the usage of the three common programs, including priority review, accelerated or conditional approval, and breakthrough therapy, was extracted.[10,11] Drug lag was defined as the time between a new drug first approved globally and the time it was subsequently approved in China or the USA.

The main indicators of this study were the number of initiated cancer drug trial, the number of involved tested drug, and the number of launched medicines. The usage of the expedited program, the surrogate endpoint, and the length of drug lag was also calculated. We will also look at the contribution of top 20 pharmaceutics from the perspective of both pipeline and approval drugs, as well as which patients will likely benefit from new therapies.

2.3. Statistical analysis

SAS statistical software, version 9. 4 (SAS Institute, Cary/NC, USA) was used for data processing and analysis. For descriptive analysis, no. (%) was used for numerical variables. Chi-square test was used for comparison of distribution of initiated trials between China and the USA, including by study phase, trial scope and sponsor type, as well as involved tested drugs by drug type, and mechanism. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Cancer drug trials

Within 2020, there were 577 anticancer new drug trials registered in China, accounting for 22.6% of the total clinical trials of drugs in the country, while in the USA, a total of 916 cancer new drug trials were captured, accounting for 19.9% of the total. In terms of the phase distribution, there were less phase I (54.4% vs 58.2%), phase II (22.5% vs 29.3%), and more phase III trials (21.8% vs 11.6%) in China compared with those in the USA ($\chi^2 = 31.08$, $P < 0.001$). Regarding the trials scope, 82.3% of the trails in China were domestic, and the proportion of global trials was significantly lower than that in the USA (17.7% vs 39.0%, $\chi^2 = 78.67$, $P < 0.001$). As for the trial contribution by top 20 pharmaceutics, a remarkable higher contribution rate was observed in the USA (43.2% vs 15.8%, $\chi^2 = 122.81$, $P < 0.001$). More detailed information was displayed in Table 1.

For the trials initiated in 2020, 25 cancer types and 21 cancer types were identified in China and the USA, respectively (Fig. 1). The fight against solid tumor took top billing in both China and the USA, with 155 (26.9%) and 216 (23.6%) trials, respectively. The nine most common specifically targeted cancer types in the registered clinical trials in China were as follows: lung cancer (90, 15.6%), lymphoma (67,11.6%), breast cancer (55, 9.5%), leukemia (30, 5.2%), hepatocellular carcinoma (28, 4.9%), gastric carcinoma (26, 4.5%), esophageal cancer (18, 3.1%), prostate cancer (16, 2.8%), and pancreatic cancer (11, 1.9%), which was different from the situation in the USA to some extent. Specifically, leukemia (108, 11.8%), lymphoma (102, 11.1%), lung cancer (81,8.8%), breast cancer (65,7.1%), multiple myeloma (57, 6.2%), prostate cancer (43, 4.7%), skin cancer (39,4.3%), head and neck squamous cell carcinoma (32, 3.5%), and glioblastoma multiforme (31, 3.4%) were the top 9 common specifically targeted cancer types in the USA (Fig. 1).

The top 20 sponsors of cancer new drug trials were shown in Fig. 2, which led 45.2% and 53.2% of included trials in China and the USA. Overall, among the top 20 sponsors, the USA had 15 belonging to the top 20 pharmaceutics, while China had only 7. In detail, Hengrui initiated the most cancer drug trials in China, with a total of 67 (11.6%), followed by Chia Tai Tianqing (24, 4.2%), Roche (23, 4.0%), Innovent (17, 2.9%), and CSPC (14, 2.4%). In the USA, MSD initiated the most trials (58, 6.3%), followed by AstraZeneca (56, 6.1%), Bristol Myers Squibb (52, 5.7%), Roche (48, 5.2%), and Johnson & Johnson (30, 3.3%).

3.2. Primary tested cancer drugs

In total, 335 and 678 anticancer new drugs were involved in China and the USA, respectively (Table 2). Although multiple effective drug types are available, the vast majority were chemicals and biological

Table 1
Cancer new drug trials in China and the USA in 2020.

Item	China		USA		Chi-square statistic	*P* value
	N	%	N	%		
Trial phase					31.08	<0.001
Phase I	314	54.4%	533	58.2%		
Phase II	130	22.5%	268	29.3%		
Phase III	126	21.8%	106	11.6%		
Phase IV	7	1.2%	9	1.0%		
Trial scope					78.67	<0.001
Global	102	17.7%	357	39.0%		
Domestic	475	82.3%	559	61.0%		
Top 20 pharmaceutics					122.81	<0.001
Yes	91	15.8%	396	43.2%		
No	486	84.2%	520	56.8%		

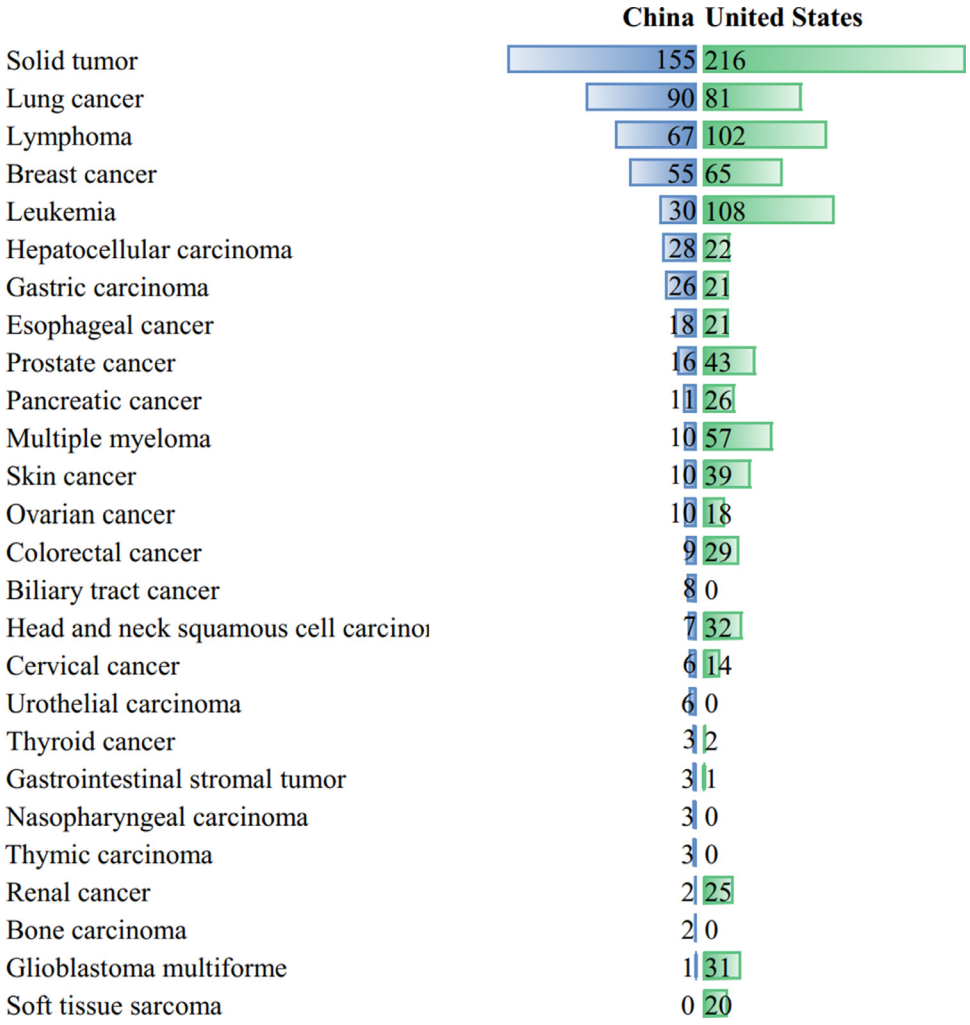

Fig. 1. Cancer type distribution of new drug trials in China and the USA in 2020.

agents, and significant difference in drug type distribution between the two countries were also observed ($\chi^2 = 669.63$, $P < 0.001$). In terms of mechanism, the most common type was targeted agent, accounting for 87.5% in China, which was higher than 77.0% in the USA ($\chi^2 = 11.70$, $P < 0.001$), followed by immune agent. Relatively, the USA was more inclined to shift its focus on immune agent (41.6% vs 30.7%, $\chi^2 = 11.2$, $P < 0.001$). Cytotoxic agent was less common in both China and the USA, accounting for 5.7% and 3.8%, respectively. Similar to trial contribution, drug contribution by top 20 pharmaceutics in the USA was also higher than that in China (35.5% vs 12.5%, $\chi^2 = 58.96$, $P < 0.001$) (Table 2).

3.3. Newly approved cancer drugs

A total of 16 (No.1–16) and 18 (No.17–34) cancer new drugs were newly approved in China and the USA in 2020, respectively, and 7 (43.8%) drugs in China and 4 (22.2%) drugs in the USA were developed by top 20 pharmaceutics (Table 3). The usage of the three common expedited programs, including priority review, accelerated or conditional approval, and breakthrough therapy, was so common in both China and the USA that 32 (94.1%) benefited from at least one of them. The priority review designation was the most frequently utilized (91.2%), followed by accelerated or conditional approval (61.8%), and no obvious differ-

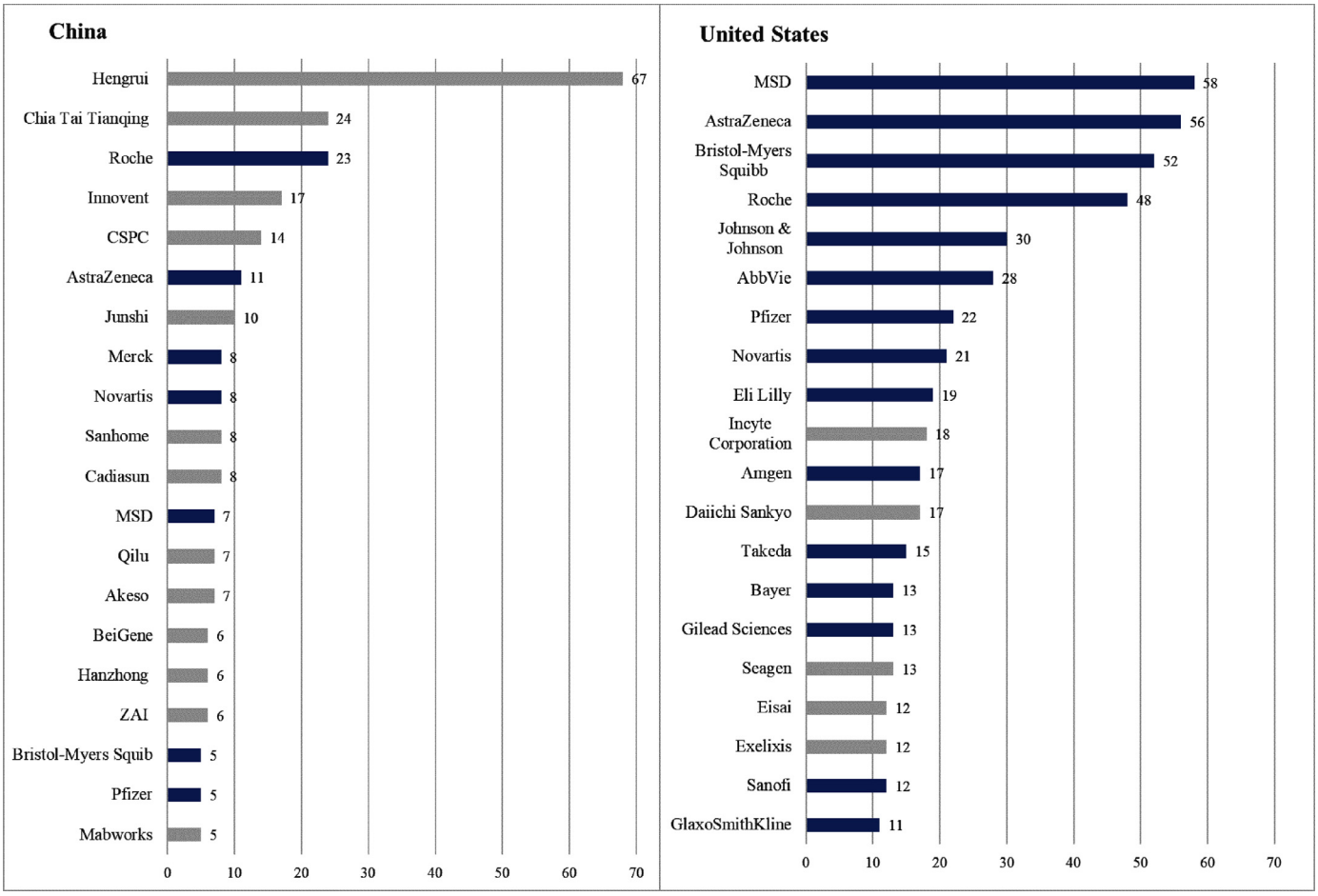

Fig. 2. Top 20 sponsors of cancer new drug trials in China and the USA in 2020.

Table 2
Cancer new drug in China and the USA in 2020.

Item	China		USA		Chi-square statistic	*P*-value
	N	%	N	%		
Drug type					669.63	<0.001
Chemicals	195	58.2%	345	50.9%		
Biologic agent	138	41.2%	330	48.7%		
Nature medicine*	2	0.6%	3	0.4%		
Top 20 pharmaceutics					58.96	<0.001
Yes	42	12.5%	241	35.5%		
No	293	87.5%	437	64.5%		
Cytotoxic agent					1.78	0.182
Yes	19	5.7%	26	3.8%		
No	316	94.3%	652	96.2%		
Targeted agent					11.70	<0.001
Yes	293	87.5%	522	77.0%		
No	42	12.5%	156	23.0%		
Immune agent					11.20	<0.001
Yes	103	30.7%	282	41.6%		
No	232	69.3%	396	58.4%		

* Drugs derived from natural substances, such as plants, animals, microorganisms, and minerals, and processed simply.

ence in the usage was observed between the two countries. Relatively, the breakthrough therapy program was obviously seldomly granted in China (1/16), as it was just introduced in July 2020 in China.

Meanwhile, the usage of surrogate endpoint as single or multiple primary endpoints was widely observed in the pivotal trials of the 34 newly approved drugs, and objective response rate (ORR) and progression-free survival (PFS) were used in 17 (50.0%) and 11 (32.4%) studies, respectively. There were some other surrogate endpoints, including complete response rate, invasive disease-free survival, and sustained castration rate. Only three drugs listed in China provided evidence of overall survival (OS) benefit at the time of approval decision, including Atezolizumab, Radium [223Ra], and Venetoclax.[12-14]

With respect to indications, 17 cancer types were covered in two countries. Breast cancer (4), lymphoma (4), leukemia (4), and lung cancer (3) were the top 4 indications in China. Other indications including liver cancer, prostate cancer, ovarian cancer, fallopian tubal carci-

Table 3
Newly approval anticancer drugs in China and the USA in 2020.

No.	Drug name	Top 20 pharmaceutics	Indication	Expedited program*	Primary endpoint	First launch globally	Drug lag, year
1	Ado-trastuzumab emtansine	Yes	Breast cancer	1, 0, 0	iDFS	No	6.83
2	Atezolizumab	Yes	NSCLC, Liver cancer	1, 0, 0	PFS, OS	No	3.75
3	Almonertinib	No	NSCLC	1, 1, 1	ORR	Yes	0
4	Neratinib	No	Breast cancer	0, 0, 0	iDFS	No	2.75
5	Brentuximab	Yes	Lymphoma	1, 0, 0	ORR	No	8.58
6	Inetetamab	No	Breast cancer	1, 0, 0	PFS	Yes	0
7	Zanubrutinib	No	Lymphoma, Leukemia	1, 1, 0	ORR	No	0.58
8	Radium [223Ra]	Yes	Prostate cancer	1, 0, 0	OS	No	7.42
9	Pralatrexate	No	Lymphoma	1, 1, 0	ORR	No	10.83
10	Ensartinib	No	NSCLC	1, 1, 0	ORR	Yes	0
11	Fluzoparib	No	Ovarian cancer, FTC, PPC	1, 1, 0	PFS	Yes	0
12	Surufatinib	No	epNET	0, 1, 0	PFS	Yes	0
13	Venetoclax	Yes	Leukemia	1, 1, 0	CRR, OS	No	4.67
14	Blinatumomab	Yes	Leukemia	1, 1, 0	CRR	No	6.00
15	Orelabrutinib	No	Lymphoma, Leukemia	1, 1, 0	ORR	Yes	0
16	Abemaciclib	Yes	Breast cancer	1, 0, 0	PFS	No	3.17
17	Avapritinib	No	GIST	1, 0, 1	PFS	Yes	0
18	Tazemetostat	No	Epithelioid sarcoma	1, 1, 0	PFS	Yes	0
19	Selumetinib	Yes	Neurofibromatosis	1, 0, 1	ORR	Yes	0
20	Tucatinib	No	Breast cancer	1, 0, 1	PFS	Yes	0
21	Pemigatinib	No	Biliary tract cancer	1, 1, 1	ORR	Yes	0
22	Capmatinib	Yes	NSCLC	1, 1, 1	ORR	Yes	0
23	Selpercatinib	No	NSCLC, Thyroid cancer	1, 1, 1	ORR	Yes	0
24	Ripretinib	No	GIST	1, 0, 1	PFS	Yes	0
25	Lurbinectedin	No	SCLC	1, 1, 0	ORR	Yes	0
26	Pralsetinib	No	NSCLC	1, 1, 1	ORR	Yes	0
27	Relugolix	No	Uterine fibroids, Prostate cancer	1, 0, 0	SCR	No	1.58
28	Sacituzumab govitecan	No	Breast cancer	1, 1, 1	ORR	Yes	0
29	Belantamab mafodotin	Yes	Multiple myeloma	1, 1, 1	ORR	Yes	0
30	Isatuximab	Yes	Multiple myeloma	0, 0, 0	PFS	Yes	0
31	Tafasitamab	No	DLBCL	1, 1, 1	ORR	Yes	0
32	Naxitamab	No	Neuroblastoma	1, 1, 1	ORR	Yes	0
33	Margetuximab	No	Breast cancer	1, 1, 1	PFS, OS	Yes	0
34	Brexucabtagene autoleucel	No	Lymphoma	1, 1, 1	ORR	Yes	0

* The three expedited programs were priority review, accelerated or conditional approval, and breakthrough therapy, respectively, and “1” meant “Yes” and “0” meant “No”.

Abbreviations: CRR, complete response rate; DLBCL, diffuse large B cell lymphoma; epNET, extrapancreatic neuroendocrine neoplasm; FTC, fallopian tube cancer; GIST, gastrointestinal stromal tumors; iDFS, invasive disease-free survival; NSCLC, non-small-cell lung cancer; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; PPC, primary peritoneal carcinoma; SCLC, small cell lung cancer; SCR, sustained castration rate.

noma, peritoneal carcinoma, and extrapancreatic neuroendocrine neoplasm was approved for one drug each. In the USA, lung cancer (4), breast (3), gastrointestinal stromal tumors (GIST, 2), thyroid cancer (2), lymphoma (2), and multiple myeloma (2) ranked the first 6 indications. Except them, neurofibromatosis, epithelioid sarcoma, biliary tract cancer, prostate cancer, and neuroblastoma were approved for one drug each (Table 3). None of them indicated gastric and esophageal cancers.

Among the 34 drugs approved in 2020, 23 drugs were firstly launched worldwide, with China contributing 6 (26.1%) of them, which were all developed by domestic enterprises in China and related clinical trials have not been applied in the USA yet. The median drug lag of the other 10 drugs equaled 5.33 years. In contrast, the vast majority (17/18) of drugs newly approved in the USA in 2020 were launched for the first time worldwide, and none of them were listed in China, and there were five drugs not even in clinical development stage.[7,8]

4. Discussion

This study pioneered to summarize and compare the latest cancer drug landscape and approvals in China and the USA, which provided us with important insights into competitive trial pipeline, unmet clinical needs, and future priorities. On the one hand, we can conclude that oncology drugs are the focus and hotspot in China, the USA, and beyond. On the other hand, this study also illustrated to us the difference and gap in contribution and attraction to global oncology drug discovery between China and the USA.

R&D of oncology drug remains as the most active therapeutic area, accounting for 23.2% and 20.5% of the total registered drug clinical trails, which was nearly consistent with the global situation.[15] Despite the impact of the COVID-19 pandemic worldwide,[16] China keeps the high growing trend in 2020, regardless of the number of initiated trials, tested drugs, and marketed drugs. Compared with 2019, an increase rate of 24.5% and 38.4% was achieved for registered trials and involved original anticancer drugs.[17] The advance was largely associated with the great progress made in regulatory science in China, especially for the extensive utilization of expedited programs and surrogate endpoints in recent years, which significantly shortened the timeline of clinical development and greatly accelerated drug review.[18,19]

Though our previous review demonstrated that the proportion of phase I cancer drug trials in China increased rapidly, with an average change per year of 15%.[3] This study showed that, compared to the USA, its focus toward earlier-stage trials in China is still inadequate, which was consistent with other studies.[20,21] According to the newly approved drugs in 2020, most of the drugs in China have already launched in other countries years ago, on the contrary, almost all the drugs approved in the USA in 2020 were firstly launched all over the world, which demonstrated that most R&D on cancer drugs in China remained to be follower despite the policies support innovation. Furthermore, the leadership and innovation in drug R&D in the USA was also reflected on its distribution

of drug mechanisms that more tested products were oncology immune agents.

Moreover, it was also found that the globalization of R&D in cancer drug trials in China should be further improved to enhance its role worldwide. As the results showed, the percentages of global trials, contribution rate from top 20 pharmaceutics in initiated trials, tested drugs, and marketed drugs in China were still far behind the USA. To become more involved in earlier stage R&D lead by global enterprises, as well as to initiate more global multi-center clinical trials by domestic enterprises are the keys for China to fully integrate into the global oncology R&D system.

As for the common reasons causing the gaps above between China and the USA, on the one hand, the USA has already issued a series of incentive policies on innovative drug R&D, including priority review, breakthrough therapy, accelerated approval, free market price, and patent protection.[8] It is worth considering for stakeholders to make adaptive adjustment on new drug R&D combining the national concrete condition. On the other hand, although China has made great progress in recent years, the incomplete innovative drug ecosystem and inadequate R&D capability due to a late start were still bottlenecks that restricted the development of new drugs in China. The innovation drug R&D ability, policy flexibility, and drug ecosystem maturity were all associated with global market attractiveness.

Regarding the indication distribution of the tested drugs, the proportions of gastric, liver, and esophageal cancers were higher in China, while the percentages of hematological malignancy were lower, which is presumably associated with cancer burden spectrum in the two countries.[1] However, only one newly approved drug in China was aimed at these digestive tumors, suggesting that domestic enterprises and the government should pay more attention to these tumors unique to the Chinese population.[2] What's more, the precision medicine researches toward rare cancers that lacked effective treatment were gradually blossoming, which accounted for approximately 20% of new researches in the USA and varied worldwide.[22]

There are several limitations in our study. Only cancer drug trials for registration purposes were included while investigator-initiated trials were not involved restricted to data availability. Additionally, the study was an overall description and comparison of anticancer new drug advance was from a macro-statistic perspective, which means that it might lack in-depth focus from the perspective of cutting-edge progress, drug innovation, and clinical importance.

5. Conclusion

In summary, R&D of anticancer new drugs is substantial, and great progress has been made in both China and the USA in 2020. The usage of expedited programs and surrogate endpoints in newly listed anticancer new drugs was very high, so more attention should be paid to long-term survival and safety. The gap compared with the USA in cancer drug R&D pipeline and approvals highlights more efforts should be paid to innovative agents and cancers unique to Chinese populations, as well as to facilitating global synchronous R&D in China.

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Declaration of competing interest

The authors declare that they have no conflict of interests.

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