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Rapid advances in research on and development of anticancer drugs in China

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Summary **Cancer is a major public health issue in China, and effective anticancer drugs remain a huge unmet need. Generic drugs have long been the main products of pharmaceutical companies in China. In this decade, research on and development of innovative drugs has greatly advanced thanks to policy reforms and economic growth. Five innovative anticancer drugs - anlotinib, pyrotinib, fruquintinib, sintilimab, and toripalimab - that were developed by Chinese domestic pharmaceutical companies were approved by the National Medical Products Administration (NMPA) of China in 2018. Several novel anticancer drugs such as avitinib, flumatinib, zanubrutinib, and ensartinib may also receive approval for marketing in China in the near future. There are unprecedented opportunities for development of innovative drugs in China. In the future, innovative drug development in China is poised to shift from "me too" or "me better" drugs to "first-in-class" or "best-in-class" drugs.**

Keywords: China, anticancer drug, molecularly targeted drug, immune checkpoint inhibitor

Cancer is the second leading cause of death globally and was responsible for an estimated 9.6 million deaths in 2018 according to data from the World Health Organization (*1*). In China, there were approximately 4.3 million new cancer cases and 2.9 million cancer deaths in 2018 (*2*). This represents a substantial demand for novel anticancer drugs. Generic drugs have long been the main products of pharmaceutical companies in China due to their limited financial resources and government drug policies. In this decade, economic growth and the reform of drug policies have led to a rapid increase in the number of innovative drugs, and especially anticancer drugs, developed by Chinese domestic pharmaceutical companies.

Molecularly targeted drugs (MTDs) and immune checkpoint inhibitors (ICIs) are the focus of research on and development of anticancer drugs. Since the year 2010, 6 MDTs - icotinib, apatinib, chidamide, anlotinib, pyrotinib, and fruquintinib - and 3 ICIs - sintilimab, toripalimab, and camrelizumab - have been approved by the National Medical Products Administration (NMPA) of China (Table 1). Icotinib, a first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was approved in 2011 for use as monotherapy in patients with non-small-cell lung cancer (NSCLC) with somatic EGFR mutations. Icotinib won the State Scientific and Technological Progress Award in 2015, and this success represents a landmark in the field of drug research and development in China. In 2017, icotinib appeared to account for over a third of the Chinese market share in lung cancer therapies since attaining approval (*3*). In 2014, the NMPA approved apatinib to treat late-stage gastric carcinoma and chidamide to treat peripheral T-cell lymphoma. Both drugs are now undergoing clinical trials for additional indications. A recently completed phase 3 clinical trial showed that chidamide plus exemestane achieved the primary endpoint in patients with advanced, hormone receptor-positive, HER2-negative breast cancer that progressed after previous endocrine therapy (*4*). Based on these promising results, an application for a new indication of chidamide was submitted to the NMPA in November

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Table 1. The approved anticancer drugs originally developed by Chinese pharmaceutical companies since 2010

Drug	Target(s)	Indication(s)	Developer	Year
Icotinib	EGFR	Non-small-cell lung cancer	Betta Pharmaceuticals	2011
Apatinib	VEGFR	Gastric cancer	Hengrui Medicine	2014
Chidamide	HDAC	Peripheral T-cell lymphoma	Chipscreen Biosciences	2014
Anlotinib	VEGFR, PDGFR, c-Kit	Non-small-cell lung cancer, alveolar soft part sarcoma, clear cell sarcoma	Chiatai Tianqing	2018
Pyrotinib	EGFR, HER2	Breast cancer	Hengrui Medicine	2018
Fruquintinib	VEGFR	Colorectal cancer	Hutchison MediPharma	2018
Sintilimab	PD-1	Hodgkin's lymphoma	Innovent Biologics	2018
Toripalimab	PD-1	Melanoma	Suzhou Union Biopharm Biosciences	2018
Camrelizumab	PD-1	Hodgkin's lymphoma	Hengrui Medicine	2019

EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; HDAC, histone deacetylase; PDGFR, platelet-derived growth factor receptor; HER2, human epidermal growth factor receptor 2; PD-1, programmed cell death protein 1.

2018. The year 2018 was a fruitful one for the Chinese pharmaceutical industry since 5 innovative anticancer drugs - anlotinib, pyrotinib, fruquintinib, sintilimab, and toripalimab - were approved by the NMPA (Table 1). Clinical trials of pyrotinib, fruquintinib, and toripalimab are currently underway in the United States.

Good results are also expected in 2019. Camrelizumab has already been approved. Applications for marketing approval that were submitted in 2018 for several anticancer drugs such as avitinib, flumatinib, zanubrutinib, and ensartinib may soon receive approval. Avitinib is a third-generation EGFR inhibitor designed to treat patients with NSCLC who have developed resistance to first-generation EGFR inhibitors and who have the gatekeeper mutation of EGFR, T790M (*5*). The recently disclosed results of a phase 2 clinical trial of avitinib showed that the objective response rate was 50.2% and the disease control rate was 88% in patients with EGFR T790M+ NSCLC (*6*). An application for conditional approval of avitinib was submitted to the NMPA. Flumatinib is a selective inhibitor of BCR-ABL1 designed for treatment of Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (CML-CP) (*7*). Results from a phase 3 clinical trial showed that flumatinib is comparable to imatinib in its safety and superior in its efficacy profile at 3, 6, and 12 months, supporting flumatinib as a frontline treatment option for patients with newly diagnosed CML-CP (*7*). Zanubrutinib is an inhibitor of Bruton tyrosine kinase (BTK) targeting B-cell malignancies such as mantle cell lymphoma (MCL), chronic lymphocytic leukemia, small lymphocytic lymphoma, Waldenstrom's macroglobulinemia, and follicular lymphoma (*8*). Zanubrutinib treatment had an overall response rate of 84%, including a complete response rate of 59% in patients with relapsed or refractory MCL in a phase 2 trial (*9*). Based on these findings, an application for use of zanubrutinib to treat relapsed/refractory MCL was submitted to the NMPA. Zanubrutinib was also designated as a breakthrough therapy by the US Food and Drug Administration in January 2019. Ensartinib is a potent anaplastic lymphoma kinase (ALK) inhibitor for potential treatment of NSCLC (*10*). A phase 1/2 clinical trial showed that ensartinib treatment resulted in a response rate of 60% and median progression-free survival of 9.0 months in patients with ALK-positive NSCLC (*11*). All of these drugs showing promising clinical activity and manageable toxicity may benefit select patients in the near future.

Rapid advances in the research on and development of innovative drugs in China may be ascribed to the following factors. From the perspective of national policies, in recent years China has issued a series of supporting policies in the field of innovative drugs, such as reform of drug registration and classification, implementation of a Marketing Authorization Holder (MAH) system, priority review of innovative drugs, compensation of the duration of a drug patent, and enhancement of the protection of drug test data. A point worth noting is that the government also implemented a National Major Scientific and Technological Special Project for "Significant New Drugs Development" in 2008 (*12*). All of these reforms have eliminated policy obstacles and accelerated the speed of research on and development of innovative drugs. In the eyes of pharmaceutical companies, innovative drugs and technologies have become a hot spot for capital investment in China. Pharmaceutical companies such as Chipscreen Biosciences, BeiGene, and Innovent have announced obtaining a large amount of financing to provide capital investment for novel drug development. In addition, a large number of native and returning Chinese professionals have become a reliable human resource for drug development. Thus, there are unprecedented opportunities in China for innovative drug development thanks to the promotion of policies, capital, and qualified personnel. In the future, drug development in China is poised to shift from generic, "me too" or "me better" drugs to "first-in-class" or "best-in-class" drugs.

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