Cancer drug development in China: recent advances and future challenges

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Over the past 10 years, the Chinese Government, academic organizations, and biopharmaceutical companies have tried to transition the nation from a consumer of generic drugs into a developer of innovative therapies. Here, we present a timeline of recent innovative cancer drug development, with a particular focus on four case studies that have reshaped perceptions of what can be done in China. We present metrics comparing China with other countries alongside analysis of what national authorities are doing to close the gap in areas where China still lags behind the West.

Introduction

The Chinese biopharmaceutical industry is undergoing a transformation as the Government tries to move to an innovation-driven economy by 2020. After two decades of ever-rising investment, China now accounts for almost 18% of worldwide research and development (R&D) spending across all industries [1]. Healthcare is a particular priority, with the Government facing the dual challenges of maintaining the growth of the biopharmaceutical industry and improving the health of the population.

Widespread tobacco use, unhealthy lifestyles, and an aging population have contributed to cancer becoming a major problem in China. One-third of global lung cancer cases and approximately one-half of all diagnoses of gastric, liver, and esophageal cancer cases occur in China [2]. Improving outcomes for these patients is a priority and work towards this goal attracted some of the US$2.7 billion the Government allocated to a special drug R&D fund from 2008 to 2010 [3].

Over the past 10 years, the number of clinical trials conducted in China has increased substantially, with the number of early-phase studies tripling since the 2007 Provisions of Drug Registration promulgated in China. In addition to clinical trials conducted for the purpose of drug registration, the number of investigator-initiated trials (IITs) in China has doubled. To optimize drug development and registration timelines, multinational pharmaceutical companies are expected to conduct more clinical trials in China as part of their simultaneous global development (SGD) strategies. However, industry-sponsored clinical trials (IITs) have increased in number only incrementally over the past 5 years because of a lengthy new drug clinical trial authorization (CTA) approval timeline (Fig. 1).

Since the Major New Drug Innovation Program (MNDIP) started in 2009, approximately half of the projects funded by the initiative have involved R&D of oncology therapies [4]. As well as investing heavily in R&D, the Chinese Government has strengthened intellectual property rights and made regulations more amenable to innovation as it aims for the discovery of 100 innovative new drugs by 2020. The platform for this ambitious goal has been laid over the past two decades, but challenges remain.

To assess the health of the Chinese clinical development ecosystem as it embarks on this mission, we analyzed four sets of innovative oncology studies that have reshaped perceptions of the R&D capabilities of China. The first of these examined a series of lung cancer trials that validated molecularly targeted treatment pathways. The second detailed an early example of Chinese-led innovation. The third and fourth case studies examined why the unique characteristics of cancer in China make such locally driven drug development essential.

Each case represents a milestone in the evolution of the Chinese oncology ecosystem, with many of the same researchers and sites featuring in each one. This continuity has enabled China to build
on the lessons learned in each event and, in doing so, strengthen its R&D capabilities. The Chinese Society of Clinical Oncology (CSCO) has supported this process by working with its international peers to prepare sponsors and investigators to develop investigational drugs and improve multiple aspects of the research infrastructure. Through such work, the drug developments discussed in the following case studies overcame the significant challenges that they faced at the outset.

**Oncology R&D in China: four case studies that reshaped the sector**

The following case studies have become examples of the collaborative problem solving that the Government, industry, academia, and international partners will need to perform for China to achieve its ambitious goals. Discussions here synthesize the key lessons gained from the cases, and how they can be applied on a larger scale to overcome the challenges faced in China today.

**Case study 1: how China moved the world towards targeted therapies**

When AstraZeneca began its IRESSA Pan-ASia Study (IPASS) in 2006, the Chinese clinical development sector was in its infancy. That year, IPASS was one of 200 trials registered on ClinicalTrials.gov that planned to enroll patients at a Chinese site. Concerns about regulatory impartiality towards foreign drugs, the need for more alignment with international clinical trial standards, and the availability of qualified staff all stymied interest in running trials in China. For many sponsors, the risks simply outweighed the rewards.

This is no longer the case. In 2013, more than 1000 studies with Chinese trial sites were registered on ClinicalTrials.gov and the ability of the country to produce high-quality data for submission to regulators, international journals, and health technology assessment (HTA) agencies is now accepted. The success of the IPASS trial, results from which were published in the *New England Journal of Medicine* [5], is partly responsible for the shift in both perceptions and reality since 2006.

IPASS was an open-label, randomized, parallel-group study to compare the efficacy of the non-small cell lung cancer (NSCLC) drug gefitinib of AstraZeneca with carboplatin-paclitaxel chemotherapy as a first-line treatment. Chinese trial sites recruited almost one third of the 1217 patients enrolled in the study and, in doing, so hinted at the opportunities presented by the huge population of the country. Judged on scale alone, IPASS was an important trial for the development of the R&D ecosystem in China.

However, the bigger impact of IPASS stems from the central role that Chinese researchers had in developing the complex trial and the far-reaching global implications of the data that it generated. The discovery that patients with NSCLC and with epidermal growth factor receptor (EGFR) mutations responded better to gefitinib compared with the general population began the shift towards molecularly targeted treatment pathways for lung cancer. Subsequent Chinese trials had a key role in accelerating this transition.

In the wake of IPASS, F. Hoffmann-La Roche turned to Chinese sites to study the effect of its therapy in patients with activating EGFR mutations. Tony Mok, Yi-Long Wu, and other veterans of the IPASS trial were enlisted to work on FASTACT-2, which confirmed many of the lessons learned in the earlier study. Median overall survival (OS) in patients with the EGFR mutation was 31.4
months, compared with 20.6 months for the broader population. The data were published in *The Lancet Oncology* in 2013 [6].

The findings of AstraZeneca and Roche added to data generated by a collaborative research clinical group, the Chinese Thoracic Oncology Group (CTONG) [7]. In 2011 [8] and 2012 [9], CTONG papers published in *The Lancet Oncology* described its OPTIMAL and INFORM Phase 3 trials, both of which focused on the targeted therapy field. Collectively, IPASS, FASTACT-2, OPTIMAL, and INFORM reshaped treatment modalities and the lung cancer drug development paradigm by showing the value of targeted therapies. The series of internationally acclaimed NSCLC studies also demonstrated what Chinese trial sites were capable of attracting top global companies. Amgen, Eli Lilly, Sanofi, and Pfizer have each worked with clinical trial sites that participated in FASTACT-2.

**Case study 2: an early success for Chinese innovation.**

Whereas the NSCLC studies put Chinese trial sites on the map internationally, in isolation they did little to counter the continuing perception that local companies are better at following than innovating. The trials were codeveloped and conducted by Chinese researchers, but the drugs that they tested emerged from the laboratories of overseas companies. Icotinib was different. Here was an example of an EGFR tyrosine-kinase inhibitor (TKI) developed in China [10].

In 2005, Zhejiang Beta Pharma advanced icotinib into clinical development. After five Phase 1, two Phase 1/2 and one Phase 3 trials conducted within 5 years [11–14], it became the third company to win approval for an EGFR TKI in China. The clinical program is evidence of how China not only has learned from global firms, but also has the skill and knowledge to move beyond their templates. Icotinib has the same mechanism of action as gefitinib and erlotinib and is viewed as a ‘me-too’ drug, but Zhejiang Beta Pharma decided not to copy the R&D models of Roche and AstraZeneca because of the changing development environment.

Instead, Zhejiang Beta Pharma designed its own double-blind, randomized controlled trials that brought icotinib to market faster and at lower cost than is typical in the West, but still adhering to global quality and ethical standards. Regular communications with the Center for Drug Evaluation (CDE) helped foresee and prevent delays, showing both local and global companies how to streamline development timelines in China. Icotinib went from early-phase development to launch in just 8 years [15]. Zhejiang Beta Pharma has passed the savings on to the healthcare system, giving Chinese patients a drug with better tolerability and similar effectiveness compared with gefitinib at a lower cost. Although the studies had flaws, such as incomplete OS data and the decision not to use biomarkers, they still added to knowledge of NSCLC, particularly the fact that only certain patients benefit from targeted maintenance therapy or second-line targeted treatment.

**Case study 3: Chinese-specific tumor types**

The unique characteristics of the Chinese population are one factor that attracted trials to China, with the higher prevalence of EGFR mutations pulling in NSCLC studies. However, the ethnic differences between China and the West also cause problems. China is disproportionately affected by hepatocellular carcinoma (HCC), with more than half of global new cases occurring in the country [2]. Additionally, the prognosis is poorer. Given best supportive care (BSC), the average Westerner will live 6–9 months: the average survival in China is half that [16].

For drug developers, the differences that underpin these survival expectations are problematic. HCC in China, which is a clearly unmet medical need, is primarily caused by hepatitis B, whereas in the West, hepatitis C and alcoholic cirrhosis are the main drivers. When hepatitis B is the cause, HCC has different oncogenic driver mutations, protein functions, and intracellular signaling pathways. When developing a targeted drug, this effectively makes HCC in China a different disease than in the West. In the EACH study, Chinese researchers tried to meet this need by designing and running a trial with sites in China, Korea, Thailand, and Taiwan. Chinese sites recruited 70% of the 370 patients, each of whom was given either doxorubicin or an infusion of fluorouracil, leucovorin, and oxaliplatin, known as FOLFOX4. When data were first presented at the American Society of Clinical Oncology (ASCO) meeting in 2010, they demonstrated the validity of a systemic chemotherapy regimen with lighter toxicity [17].

FOLFOX4 increased OS by 1.47 months, a significant change for a population in which individuals are only expected to live up for to 4 months. Progression-free survival (PFS) and response rate also improved. Although the trial missed its primary endpoint, the positive trends of clinical advantage and significant unmet need meant that it nonetheless showed that the therapy is an effective choice, and it was approved by the China Food and Drug Administration (CFDA). The treatment is well suited to patients with milder symptoms, or those with poorer economic conditions.

**Case study 4: anticancer drug originates in China**

The disease heterogeneity that defines HCC is also seen in gastric cancer, with different epidemiology, etiology, tumor location, pathological biology, clinical manifestations, and disease management in China compared with the West. Again, China accounts for around half of global new cases occurring every year, and the combination of later diagnosis, lower removal rate, and higher incidence of metastases makes this disease particularly devastating. In China, the 5-year survival rate is less than 50% [18] and, therefore, the unmet need is enormous.

With gastric cancer in China being associated with a unique mix of causes and outcomes, a treatment developed for overseas markets can be unsuccessful in this country. There is a need for drugs developed in China, for Chinese patients. The evidence is so clear that Jiangsu Hengrui Medicine Co. is currently working to meet this need. Its clinical gastric cancer candidate, the vascular endothelial growth factor receptor (VEGFR) inhibitor apatinib, is being developed by Chinese researchers for Chinese patients.

Data from a Phase 2 trial of apatinib, which recruited 144 patients at 22 sites across China, was published in *the Journal of Clinical Oncology* in 2013 [19]. Having demonstrated that apatinib was associated with statistically significant increases in OS and PFS and had tolerable toxicities, Jiangsu Hengrui Medicine Co. advanced the drug into Phase 3 development. In total, 273 patients were recruited at 37 Chinese sites and, again, statistically and clinically significant survival benefits were seen [20].

Apatinib is now waiting for new drug application (NDA) approval. The decision would have significant implications for patients and the treatment of gastric cancer. Jiangsu Hengrui Medicine tested apatinib in heavily pretreated patients with metastatic gastric...
cancer (mGC) who had experienced treatment failure with two or more lines of chemotherapy regimens. In clinical trials, apatinib was shown to improve health outcomes for these difficult-to-treat patients, suggesting that its antiangiogenic approach has potential.

For China, the successful completion of a Phase 3 trial of an innovative drug by an independent local company represents the culmination of the decade of work as discussed in the case studies presented previously. The clinical trial sites of the country have gone from being on the fringes of global development to working with local companies and multinational giants to design and run first-time studies using innovative medicines. What comes next depends on the optimization of overall drug development capabilities, but such optimization will facilitate continuation of their upward trajectory.

The next steps: four areas in which China must improve
The case studies presented above demonstrate how far China has come in just 10 years. However, there are still areas in which the drug development capability of the country can improve. Here, four problem areas for China are examined: (i) early-phase development and regulatory oversight; (ii) pharmacogenomic and biomarker-driven studies; (iii) site network building; and (iv) data quality. Each is a potential constraint on the growth of Chinese cancer drug development, but initiatives are already in place to drive improvements.

Step 1: early-phase development and regulatory oversight
Although several Chinese companies are dedicated to innovative drug development, overall capabilities are still weak because of the lack of overall clinical development strategy. Limited awareness of risk and complexity is a particular bottleneck to innovative drug development [21]. Investigators must also gain experience of early-phase development if China is to truly participate in SGD programs from the earliest stages of clinical development. Although the number of early-phase trials in China has tripled in recent years, the decision of the CDE to prioritize the strengthening of the field will lead to further gains.

The strategy of the CDE of encouraging drug innovation and allocating resources to reviewing trial applications, despite human resource constraints at CFDA, has already begun to pay dividends [22]. New drug CTA filings have increased fourfold since 2007, among which domestic innovative drug (Category 1 and 2) submissions have tripled (Fig. 2). However, the goal is to make further enhancements. For example, average review timeline is

![Graph showing number of filings and approvals for antitumor new drug clinical trial authorizations (CTAs) and new drug applications (NDA) by the China Food and Drug Administration (CFDA) from 2007 to 2013.](http://www.drugdiscoverytoday.com)

**FIGURE 2**
The number of filings and approvals for antitumor new drug clinical trial authorizations (CTAs) and new drug applications (NDA) by the China Food and Drug Administration (CFDA) from 2007 to 2013 is compared for domestic and imported drug license (IDL) drugs, respectively. The CFDA classifies domestic chemical entities into six categories. Categories 1–4 are defined as ‘new drugs’ and categories 1 and 2 are further segmented as ‘innovative drugs.’ CTA filings of two major categories, category 1 and 3, are also analyzed and presented in this figure. The graph is based upon data summarized in China Pharmaceutical Pipeline Monitor (CPM), China National Pharmaceutical Industry Information Center in May 2014. Category 1: drugs not yet approved in any country. Category 2: drugs seeking approval for a new route of administration not yet approved in any country; Category 3: drugs that are approved in some countries, but not in China. Category 4: drugs made by changing the acidic or alkaline radicals or metallic elements of the salt of a drug approved in China without changing the original pharmacological effects. In addition, CFDA designates previously approved therapies outside China as imported drugs and requires clinical data from trials conducted in China to support an IDL application.
testing part of its guidelines and encouraged hospitals to add capacity. CFDA approved the first next-generation sequencing diagnostic products in 2014. In addition, multiple efforts from the Chinese Government are underway, including funding supports and applied technology innovation service platforms for pharmacogenomics that are proposed to help local pharmaceutical companies during the drug discovery process. Furthermore, increasing numbers of global trials conducted in China have optional pharmacogenomics assessments. Interestingly, patients with NSCLC in a current Phase 2 study will be allocated a specific treatment arm based on their primary genetic profiling analysis, and it remains open to add new candidate compounds with targetable genetic alterations. The innovative design of the cluster trials suggests a profound impact on future cancer R&D in China [29].

In these areas, CDE can learn from its regulatory peers in the USA and Europe. Events such as the Advanced Clinical Trial Workshop China (ACT China), which is run by CSCO and the Society for Translational Oncology (STO), provide a platform for the spread of regulatory ideas and practices by bringing representatives from the CFDA, US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) together. At ACT China 2013, CFDA, FDA, and EMA discussed the way forward for biomarker-driven targeted drug development in China. CSCO also has a biomarker committee and exchanges ideas with its global peers.

**Step 3: clinical trial site network building**

China can clear another bottleneck by learning site network-building skills from such exchanges. CFDA has accredited 173 good clinical practice (GCP) oncology trial sites, but there is room for growth. In the USA, the National Cancer Institute’s Clinical Trials Cooperative Group Program includes 3100 institutions and 14,000 investigators. Given the population of China, the country could become the global engine of cancer research and improving outcomes for its people in the process.

The China Thoracic Oncology Group (CTONG) behind the OPTIMAL and INFORM trials, is working to realize this ambition. The organization, which now comprises 23 sites, was founded in 2007 to bring together researchers, physicians, and healthcare professionals at public institutions across China. Together, the collaborators work to design multicenter clinical trials, promote standardization, modernization, and internationalization, improve treatment and diagnosis, and provide evidence for therapies.

Currently, the network was running over 20 trials and had approximately 20,000 patients with lung cancer in its database; however, it is still in its infancy. If China is to improve cancer outcomes for not only its population, but also patients around the world, trials such as the OPTIMAL study that helped erlotinib become registered for first-line therapy must become commonplace. In this era of personalized medicine, China can develop more collaborative clinical trial groups and solve the problems facing its existing organizations.

**Step 4: data quality**

The issue of data quality has become a rate-limiting factor in drug development and is seriously affecting the objective evaluation of drug efficacy and safety, negatively impacting the R&D of...
innovative drugs as well as their competitiveness in the global market. Regulating data management and ensuring the authenticity and integrity of data is vital to the future of Chinese oncology drug development. Educational efforts should focus on equipping clinical trial investigators to closely follow GCP principles, and meticulously record their activities in a timely manner.

The long duration and complexity of cancer trials make the timely resolution of data queries both particularly important and challenging. Experienced Contract Research Organization (CRO) partners who proactively communicate to resolve issues on time would be essential. Patients with advanced cancer often have shorter survival and higher drop-out rates because of the relatively high frequency of serious SAEs caused by antitumor drugs. The reliance on PFS, ORR, and time to tumor progression as endpoints makes evaluations susceptible to interference by subjective judgment. Independent clinical event committees (CECs) and data monitoring committee (DMCs) must be expanded to mitigate this risk in China.

Concluding remarks

Although the four next steps discussed above represent significant challenges for China, they look manageable, especially when considered in light of how much Chinese drug development capabilities have improved over the past decade. With the significant support of the government and through CFDA’s reforms of the regulatory framework, China has become a favorable location for drug development. By continuing to refine its policies, CFDA can help China fulfill its potential in this field.

Other stakeholders will also have important roles. The case studies show the value of collaboration among regulators, academia, and industry. If China is to replicate, and expand upon, the successes of the past decade in the coming years, it must continue along this path, with local players learning from each other and their global peers. Projects such as CSCO’s Oncology Drug Clinical Development and Safety Evaluation Committee (a collaborative platform for academia, regulators, and industry) provide an example of such learning.

If China can address the four constraints discussed, and work through Government, academic organizations, and biopharmaceutical companies suggests that it can, the country will have laid the groundwork for cancer drug development that will improve the lives of patients in China and around the world.

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