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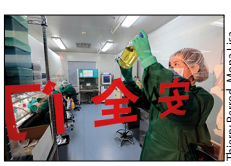
Challenges in anticancer drug R&D in China

The availability of innovative drugs in China has long been compromised by the so-called drug lag, in which a lengthy drug review processes, scarcity of domestically developed innovative drugs, overly strict policies in clinical trial application, and import drug registration has impeded drug innovation.[1,2] To tackle this dilemma, the Chinese Government has issued a series of regulatory reforms on drug administration since 2017.[3-7] The changing landscape of drug research and development (R&D) in China is captured by an annual report of China's phase 1 oncology studies (appendix).

The report shows that there were 180 phase 1 oncology trials done in mainland China in 2017, making it the second highest region for phase 1 oncology trials second to Europe (n=241). However, despite the boom in phase 1 studies, there has been a paucity of experienced and fully equipped study sites and a severe inequality in the geographical distribution of studies done across China. 180 phase 1 trials were done in only 18 facilities (figure), 107 (59%) of which were finished by five study sites only. 132 (73%) of these studies were done in either Beijing, Shanghai, or Guangzhou, the three biggest cities in China. The rest of the studies were also done in major cities in China. This imbalanced distribution of phase 1 study sites partly reflects the disparities in medical resources between regions in China.

Collaboration and communication between different study sites, sponsors, and contract research organisations is difficult and rare to come by. For multicentre phase 2–3 studies, the strategy of building a collaborative group has shown to work. For example, the China Thoracic Oncology Group, which was founded in 2007, is a network dedicated to the development of phase 2–3 studies in lung cancer and contributed to the OPTMAL[8] and INFORM[9] trials, two multicentre, randomised, phase 3 studies that respectively established the standard first-line and maintenance therapy for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer. However, more than 10 years later, no such organisation exists for phase 1 studies in China.

Repetitive study designs in phase 1 trials is another problem that could compromise China's agenda to become the global engine of drug innovation. Of the 180 phase 1 studies that were done in 2017, 21 (12%) were bioequivalence or bioavailability studies of generic drugs, 67 (37%) were pharmacokinetic or pharmacodynamic studies, 76 (43%) investigated drug tolerability, and only 16 (9%) were first-in-human studies of innovative treatments. Trials sponsored by multinational biopharmaceutical companies are all pharmacokinetic or pharmacodynamic studies that aim to characterise the pharmacokinetic and pharmacodynamic profile of the drug for the Chinese population. Nine of the 19 trials sponsored by multinational pharmaceutical companies were pharmacokinetic or pharmacodynamic bridge studies that merely serve to accelerate regulatory approvals in China. Bridge studies are relatively small-scale studies that investigate the differences in pharmacokinetic, pharmacodynamic, and clinical properties of a drug. With these studies, foreign clinical data can be used to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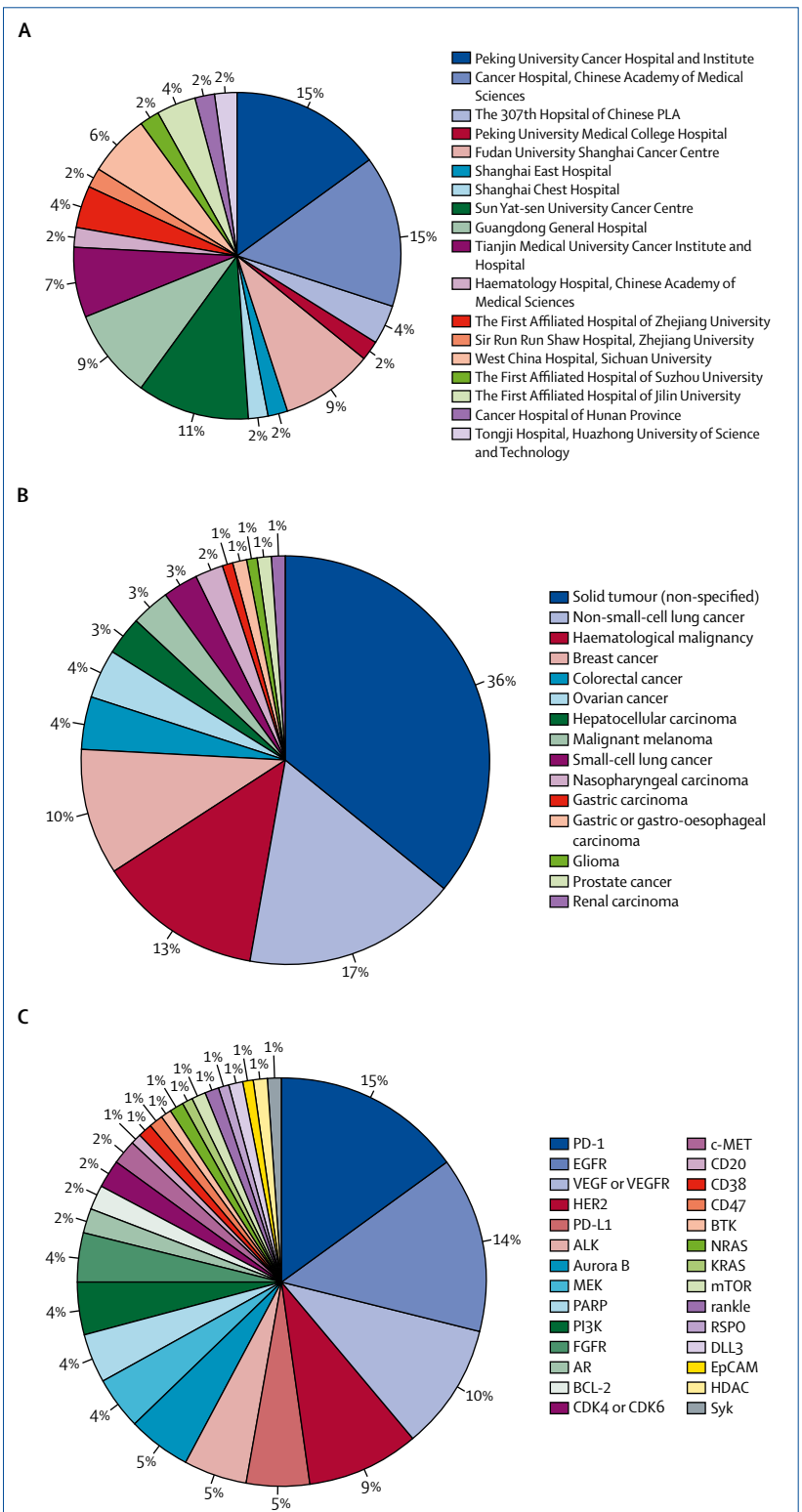

Figure: **Distribution of main study sites (A), investigated tumours (B), and therapeutic targets (C) in current phase 1 oncology trials in China**

support regulatory approval of the drug in China, and thus accelerate the registration process. As for patient selection, most phase 1 trials in China simply imitate the studies done abroad and fail to include characteristics of the Chinese population. For instance, despite the heavy burden of hepatitis B virus (HBV) in China, only one trial (CTR20171020) out of the 29 studies investigating programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors enrolled patients who tested positive for HBV infections.

In terms of tumour types, gastric carcinoma, hepatocellular carcinoma, oesophageal carcinoma, and nasopharyngeal carcinoma are four common malignancies in China, and the Chinese population account for at least 50% of the global morbidity and mortality for each of these cancers. However, among the 116 phase 1 trials targeting specific tumour types (figure), only two trials (2%) targeted gastric carcinoma, five (4%) targeted hepatocellular carcinoma, two (2%) targeted gastric or gastro-oesophageal carcinoma, and three (3%) targeted nasopharyngeal carcinoma. The most studied tumour types in phase 1 trials are still lung cancer (n=36 [31%]), haematological malignancy (n=23 [20%]), breast cancer (n=18 [16%]), and colorectal cancer (n=8 [7%]).

The lack of new molecular entities in phase 1 studies is also worrisome. Despite the large number of investigational new drugs classified as so-called type 1 innovative drugs by the National Center for Drug Evaluation each year, most of them are drugs modified from existing molecular entities. Among the 115 studies investigating small molecular targeted drugs (figure), 21 (18%) target the EGFR pathway. Currently, there are at least 18 domestically developed EGFR tyrosine kinase inhibitors, all of which are categorised as type 1 innovative drugs. However, only two of them are novel molecular entities. Likewise, 29 (16%) phase 1 studies targeted the PD-1/PD-L1 pathway. Thus far, there are 12 PD-1 inhibitors and eight PD-L1 inhibitors being developed by 15 Chinese biopharmaceutical companies. Given the high cost and high risk in discovering new molecular entities, most Chinese biopharmaceutical companies, even those with the research capability and abundant funding, tend to avoid such risks and instead focus on follow-on drugs with best-in-class potential.[2] These strategies, although understandable, might not promote innovative drug R&D in the long-term. For true

innovations to occur in China, a clearer line needs to be drawn between improvement and invention.

Nevertheless, 2017 also witnessed several heartening changes to anticancer drug R&D in China. To deal with the shortage of clinical trial sites, the China Food and Drug Administration (CFDA) plans to abolish the current clinical trial agency accreditation system.[3,5] Under the new record management system, medical facilities can avoid the lengthy certification process of registering a new trial, and only need to register on the CFDA's website to get approval for doing clinical trials.[5] To cultivate a more innovation-friendly drug R&D ecosystem, the CFDA shifted their clinical trial regulatory policy from strict entry, tolerant exit, to tolerant entry, strict exit.[3,5] Instead of overemphasising the approval of clinical trial applications, current policies focus more on the quality control of trials and post-marketing pharmacovigilance.[5] Clinical trial data falsification is now a felony with at least 3 years in prison. A 60-day investigational new drug filing system has been adopted to loosen restrictions on clinical trial applications, which are now considered to be approved if no negative review opinions are given within 60 working days after the application.[5] On Nov 5, 2018, the first batch of drugs approved for clinical trials under this new system was released on the CFDA website, marking the implementation of this historic reform.

Another move the CFDA has done to overcome drug lag is to adjust the regulations on drug registration of imported drugs, which was enacted on Oct 10, 2017.[5,6] Synchronised phase 1 studies of import drugs and data from clinical trials done abroad can now be used directly to support registration. To spur drug innovation, a stricter definition of innovative drugs and a four-colour light strategy have been applied to prioritise drug reviews on the basis of how innovative they are.[4,7] In the four-colour light strategy, no-light drugs (highest priority) are innovative drugs that are not listed in any other country in the world; green-light drugs are urgently needed drugs that are listed in other countries, but not in China; yellow-light drugs are generic drugs with alternatives in China; red-light drugs (unlikely to be approved) are drugs for indications that are in the restricted catalogues. The definition of innovative drugs has been narrowed down, from nationally innovative drugs (drugs not listed in China) to globally innovative drugs (drugs not listed in any other country). According to the previous definition, novel molecular entities and drugs modified from existing molecular entities were both classified as innovative drugs and received the same treatment. Most biopharmaceutical companies therefore tended to focus on the latter to reduce risk of their drug R&D process. Under this new definition, drugs modified from existing molecular entities are no longer considered to be innovative, and no longer receive preferential treatment. The scale of the National Center for Drug Evaluation is also anticipated to expand substantially to accelerate the drug review process. On Aug 29, 2018, the CFDA officially changed its name to the National Medical Products Administration. This change allows the administration to not only specialise in drug regulations, but also to expand its territory to all biomedicine-related products, including computer software.

To facilitate cooperation between study sites, sponsors and contract research organisations, the Chinese Phase 1 Oncology Trial consortium was founded in June, 2017. By involving China's top cancer centres, key contract research organisations, and international and domestic biopharmaceutical companies, the consortium provides a platform for sharing experience and expertise. For studies targeting less common carcinogenic mutations, the consortium provides assistance in patient recruitment by referring patients with specific mutations to corresponding clinical sites. The consortium summit is held every 6 months to discuss existing problems in current phase 1 trials and to review recent advances in anticancer drug R&D with experts from the National Center for Drug Evaluation.

In this environment, Chinese biopharmaceutical companies have started to shift their focus from generic drugs to innovative drug R&D, tripling the number of investigational new drugs filings at the centre. In 2017, 161 (89%) of phase 1 studies were sponsored by Chinese biopharmaceutical companies. Recently, results of two phase 1 trials were published[10] that explored SHR-1210, a PD-1 inhibitor, alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma, potentially leading to paradigm changes in the treatment of this malignancy.[10]

Novel study designs and drugs are also emerging. 49 (27%) of the 180 phase 1 studies identified adopted biomarker-based patient selection. This proportion is higher than the 58 (17%) of 351 studies that were

described by Schawaederle and colleagues in their study investigating the effect of biomarker-based strategy in the setting of phase 1 oncology trials.[11] ML-007, an EGFR T790M tyrosine kinase inhibitor showed the potential to penetrate the blood–brain barrier in animal models. Therefore, unlike phase 1 studies of other EGFR T790M tyrosine kinase inhibitors, the first-in-human study of ML007 (CTR20180977) includes patients with untreated, symptomatic brain metastasis. In the field of immuno-oncology, China is also catching up with the rest of the world. Among the 16 first-in-human studies initiated in 2017, five studies investigated cell therapies, four investigated combinational immunotherapy treatment, and two investigated antibody–drug conjugates. In a 2018 report of the global immuno-oncology landscape, three Chinese facilities made it to the top 15 clinical pipelines in immuno-oncology from 655 organisations worldwide.[12]

To fulfil its agenda in health care and biomedicine innovation, China still has a long way to go. Innovative drug R&D in China is still developing, but if we keep cultivating it in an innovative friendly manner, China's R&D pipeline will eventually blossom.

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