Evolution of Early-Phase Anticancer Drug Investigations in China

In recent years, China has implemented a revised drug administration law and registration regulation. The purpose is to accelerate the development of new innovative drugs. Policies, such as the “60 working day silent approval of investigational new drug applications” and “Technical Guiding Principles for the Acceptance of the Overseas Clinical Trial Data of Drugs,” have had a positive association with timelines for trial startup and marketing of new innovative drugs in China. These policies have been associated with significantly increased anticancer drug trials and more diversified anticancer therapies that benefit patients.1,2 In this article, we present our analysis of phase 1 clinical trials performed in China from 2017 to 2021.

Methods | Details of oncology phase 1 trials in solid tumors were obtained from INFORMA database (https://pharma.id.informa.com). One-hundred sixty-one trials were excluded from the 1526 identified trials based on the exclusion criteria (Methods in the Supplement). The average annual growth rates (AAGR) of trials were calculated as $Z = (X/Y)^{1/3}-1$. The variables X and Y represent the trial numbers in 2021 and 2017, respectively.

Results | A total of 996 drugs were tested in phase 1 trials in China. Most drugs (461 [46%]) were immuno-oncology drugs (Figure, A), among which cell therapy (200 [20%]) constituted the largest category (Figure, B). Nine trials conducted in China during the 4-year period included first-in-class drugs with novel targets (Table). For example, GNC-035, GNC-038, and GNC-039 were the first tetra-specific antibodies targeting immune antigens; CBP-1008 was the first bispecific ligand drug conjugate.

In addition, 1359 phase 1 trials of anticancer drugs were initiated, with an AAGR of 23%. Sixty-three phase 1 trials were global multicenter trials, accounting for less than 5% of the total number. Most global multicenter trials were sponsored by Chinese pharmaceutical enterprises (32 of 48 sponsors [67%]). Haihe Biopharma sponsored the most global trials (5 [8%]), followed by BeiGene (4 [6%]), and Novartis (3 [5%]). Institutes that coparticipated with Chinese sites in global multicenter trials were mainly from the US (52 [83%]), followed by Australia (19 [30%]), Taiwan (14 [22%]), and the Republic of Korea (13 [21%]).

Furthermore, an increase of phase 1 trials with a seamless design occurred from 67 in year 1 (2017) to 123 in year 4 (2022) (AAGR, 22%). A total of 358 trials (26%) were biomarker-guided studies with an AAGR of 21%. A master-protocol design was also introduced into those biomarker-guided trials, including umbrella (2 [1%]) and basket (13 [4%]) trials.

Discussion | This cohort study examined how the reformed and increasingly supportive drug registration regulation in China was associated with the acceleration of the conduct and increase in the number of early-phase trials. The focus of these
early-phase trials is transitioning into testing more innovative drugs targeting novel targets, more trials with adaptive designs, and multicenter global trials.

The reformed drug regulation has not only boosted the early-stage development of innovative drugs in China, but was also associated with the pharmaceutical industry value chain supporting a shift from development of me-too to first-in-class drugs in China.3-6 Also supporting the drug development in China is the population of 1.4 billion individuals and the associated many patients and potential trial participants, which was followed by accelerated enrollment of patients into trials.

A study limitation is that the success rates of those phase 1 trials were not calculated because of the relatively narrow study time span, and it deserves to be further investigated in future studies. Nevertheless, obvious improvements in regulatory policies have already had a positive association with innovative drug development, and additional improvements are already being planned. China’s fourteenth 5-year plan (2021-2025) includes increased investment into basic research that aims to further transform drug development from me-too into innovative first in class. All of the previously described points suggest a bright future of innovative drug research and development in China.

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Table. Novel Targets of Phase 1 Clinical Trials Performed in China

| Novel target/target group | First-tested year | Type of drug | Specific drug | Sponsor (trials in China) |
|---------------------------|-------------------|--------------|---------------|--------------------------|
| ROR2                      | 2018              | CAR-T cell   | CCT301-59 CAR-T cells | Shanghai PerHum Therapeutics Co, Ltd |
| BTLA                      | 2018              | Monoclonal antibody | JS004 | Shanghai Junshi Bioscience Co, Ltd |
| Nectin4/FAP dual target   | 2019              | CAR-T cell   | Nectin4/FAP-targeted CAR-T cells | Sixth Affiliated Hospital of Wenzhou Medical University |
| TRPV6/FRA dual target     | 2019              | Bispecific ligand drug conjugate | CBP1008 | Coherent Biopharma (Suzhou) Co, Ltd |
| TRAILR2/CDH17 dual target | 2020              | Bispecific antibody | BI 905711 | Boehringer Ingelheim |
| IRE-1α                    | 2020              | IRE-1α inhibitor | ORIN1001 | Fosun Orinove (Suzhou) PharmaTech |
| CD19/CD3/PD-L1/4-1BB      | 2020              | Tetra-specific Antibody | GNC-038 | Sichuan Baili Pharmaceutical Co, Ltd |
| CD3/4-1BB/PD-L1/ROR1      | 2021              | Tetra-specific Antibody | GNC-035 | Sichuan Baili Pharmaceutical Co, Ltd |
| EGFvIII/CD3/4-1BB         | 2021              | Tetra-specific Antibody | GNC-039 | Sichuan Baili Pharmaceutical Co, Ltd |

Abbreviations: BI, Boehringer Ingelheim; BTLA, B- and T-lymphocyte attenuator; CAR-T, chimeric antigen receptor T-cell; CDH17, cadherin 17; EGFR, epidermal growth factor receptor; FRA, folate receptor alpha; FAP, fibroblast activation protein; IRE-1α, inositol-requiring enzyme 1α; PD-L1, programmed cell death ligand 1; ROR2, receptor tyrosine kinase-like orphan receptor 2; TRPV6, transient receptor potential cation channel subfamily V member 6.

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Inhibition of SARS-CoV-2 Omicron BA.1 and BA.4 Variants After Fourth Vaccination or Tixagevimab and Cilgavimab Administration in Patients With Cancer

Patients with cancer are at high risk for severe COVID-19 and show impaired immune responses after vaccination. Specifically, levels of neutralizing antibodies against variants of concern, including Delta (B.1.617.2) and Omicron (B.1.1.529), are lower in patients with cancer than in those without. Fourth vaccination dose or administration of monoclonal neutralizing antibodies, such as tixagevimab and cilgavimab, is being considered, although data supporting this strategy are limited, especially in the context of currently circulating variants, such as BA.4.

Methods | To analyze variant-specific humoral immunity after active and passive SARS-CoV-2 immunization in patients with hematologic-oncologic diseases, we compared antibody levels against the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 hu-1 and Omicron sublineages BA.1 or BA.4 after the third and fourth vaccinations or administration of tixagevimab and cilgavimab in patients with cancer. Moreover, the inhibition of the interaction between these RBDs and the receptor angiotensin-converting enzyme 2 (ACE-2) was evaluated as described previously. The study was approved by the institutional review boards of the Medical University of Vienna and the Südtiroler Sanitätsbetrieb. All patients provided written informed consent before serum sampling (eMethods in the Supplement). The study was performed according to the Declaration of Helsinki, complying with all applicable amendments and institutional guidelines and national law, and we followed relevant portions of the STROBE reporting guideline.

Results | In total, 72 patients (median [range] age, 74 [48-89] years; 47 men [65.3%], 25 women [34.7%]) were included. Of these patients, 54 (75.0%) received a fourth vaccination (21 had solid tumors, and 33 had hematologic malignant neoplasms) and 18 (25.0%) received tixagevimab and cilgavimab as passive immunization.

We analyzed the levels of anti-RBD antibodies after the third and fourth vaccinations. Median (range) anti-RBD levels increased in patients with hematologic malignant neoplasms undergoing B-cell-targeted therapy, particularly against Omicron sublineages BA.1 (before vs after fourth vaccination: 0.154 [0.059-1.556] optical density vs 0.969 [0.057-1.306] optical density; \( P = .02 \)) and BA.4 (0.245 [0.052-1.270] optical density vs 0.966 [0.052-1.383] optical density; \( P = .02 \)). There were no differences in antibody levels among patients with other hematological diseases. Similarly, there was a pronounced increase in median (range) antibody levels against RBDs in patients with solid malignant neoplasms for all investigated variants of concern before vs after the fourth vaccination, including hu-1 (1.157 [0.121-2.210] optical density vs 1.438 [0.213-1.801] optical density; \( P = .02 \)), BA.1 (0.721 [0.103-1.486] optical density vs 1.026 [0.146-1.553] optical density; \( P = .003 \)), and BA.4 (0.556 [0.119-1.496] optical density vs 1.220 [0.251-1.423] optical density; \( P = .002 \)).

We also investigated the capacity of patients’ serum samples to inhibit RBD and ACE-2 interaction. The inhibitory potential against RBD and ACE-2 interaction was generally higher after the fourth vaccination than after the third vaccination, especially for sublineages BA.1 and BA.4, in both patients with hematological disease (Figure 1) and those with solid tumors (Figure 2A).

Furthermore, we evaluated the inhibitory capacity of tixagevimab and cilgavimab as a preexposure prophylaxis for RBD and ACE-2 interaction. We observed a difference according to