

Ongoing Phase I Studies of Immune Checkpoint Inhibitors in China

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Phase I studies • Immune checkpoint inhibitors • Pharmacokinetics • Pharmacodynamics • China

ABSTRACT

Background. Cancer immunotherapy targeting immune checkpoint inhibitors (ICIs) has been shown to be a promising strategy in the treatment of various malignancies. Despite the proven efficacy and tolerability of ICIs based on 113 clinical trials globally, data regarding the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of ICIs in the Chinese population are lacking. As of June 1, 2018, not a single ICI has been approved by the China Food and Drug Administration.

Materials and Methods. Currently, there are 26 ongoing phase I studies actively investigating the safety, antitumor activity, and PK/PD profiles of six multinational corporation (MNC)-developed ICIs and eight domestic-developed ICIs

in the Chinese population. Data regarding study designs, treatment interventions, targeted populations, and the current states of these studies were collected and summarized.

Results. We outlined 8 phase I studies assessing MNC-developed ICIs and 18 phase I studies assessing domestic-developed ICIs in the Chinese population in this article, in order to provide researchers with a clear picture of the status quo of ICI research and developments in China.

Conclusion. Immuno-oncology in China remains at a preliminary stage. Despite the substantial amount of phase I studies of ICIs, early-phase studies with designs incorporating characteristics of Chinese patients are still lacking. *The Oncologist* 2019;24(Special Issue):S11–S20

Implications for Practice: Cancer immunotherapy targeting immune checkpoint inhibitors (ICIs) has led to a paradigm shift in the treatment of various malignancies. However, data regarding the pharmacokinetic and pharmacodynamic profiles of ICIs in the Chinese population are lacking. Currently, there are 26 phase I studies actively investigating 14 ICIs in China. In this article, we outlined all the ongoing phase I studies of multinational corporation-developed ICIs and domestic-developed ICIs targeting the Chinese population, hoping to shed some light on the status quo of ICI research and developments in China.

INTRODUCTION

Along with surgery, radiotherapy, chemotherapy, and targeted therapy, immunotherapy is emerging as a new pillar of current cancer treatment [1]. Targeting key immune checkpoints to restore the antitumor activity of T lymphocytes has been proved to be a safe and effective strategy for patients with advanced or metastatic malignancies in several international randomized controlled trials (RCTs) [2–13].

Ipilimumab, a human cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blocking antibody, was the first immune

checkpoint inhibitor (ICI) approved by the U.S. Food and Drug Administration (FDA) for previously treated advanced melanoma [14]. By the end of May 2017, the U.S. FDA had approved another five ICIs, including two anti-programmed cell death protein 1 (PD-1) antibodies (nivolumab and pembrolizumab) and three anti-programmed death-ligand 1 (PD-L1) antibodies (atezolizumab, durvalumab, and avelumab), for the treatment of multiple malignancies [15, 16]. However, despite the efficacy and tolerability of ICIs

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shown in 113 RCTs globally [2–13], not a single ICI has been approved by the China Food and Drug Administration (CFDA) as of the end of May 2018. In the era of immuno-oncology, China has lagged far behind its Western counterparts.

Fortunately, both the Chinese government and domestic biopharmas have realized this problem and are trying to close the gap between China and the West. By the end of November 2017, there are 10 domestic-developed ICIs being evaluated in phase I trials internationally and domestically. Another 11 domestic-developed ICIs are either in application for clinical trials or at preclinical stages (Table 1).

Altogether, there are 6 multinational corporation-developed (MNC-developed) ICIs and 8 domestic-developed ICIs being actively evaluated in 26 phase I studies in China (Table 2). Here, we outline all the ongoing phase I studies of ICIs in China, hoping to shed some light on the status quo of ICI research and development (R&D) in China and to identify challenges for future early-phase studies in the era of immuno-oncology.

MNC-DEVELOPED AGENTS

Anti-PD-1 Antibody

Nivolumab (Bristol-Myers Squibb; CheckMate077, NCT03195478, and CTR20171020)

Currently, there are three ongoing phase I studies of nivolumab among Chinese patients: CheckMate 077 (NCT02593786/CTR20150755), NCT03195478 (CTR20170731), and CTR 20171020.

CheckMate 077 is the first phase I study evaluating the safety, tolerability, PK profile, and preliminary antitumor activity of nivolumab monotherapy in Chinese patients. Compared with CA209-003 (NCT00730639) [17], the first-in-human study of nivolumab mostly including white patients, CheckMate 077 enrolled Chinese patients with advanced or metastatic nasopharyngeal carcinoma (NPC), lung cancer, hepatocellular carcinoma (HCC), and gastric cancer. Both studies excluded patients with chronic infections (e.g., human immunodeficiency virus [HIV] and hepatitis B virus [HBV] or C [HCV]) and patients with targetable driver mutations (e.g., epithelial growth factor receptor [EGFR] mutation, anaplastic lymphoma kinase [ALK] rearrangement). There is no requirement for tumor PD-L1 expression levels in both studies. Primary objectives of CheckMate 077 were the safety and tolerability of nivolumab in Chinese patients. Secondary objectives were PK/PD characteristics and preliminary antitumor activity.

Preliminary results of the first 15 patients were released at the 2017 Chinese Society of Clinical Oncology annual meeting [18]. Based on the released data, the safety and tolerability profiles of nivolumab in Chinese patients were similar to those of white patients. The most common treatment-related adverse events (TRAEs) were rash, decreased appetite, and fatigue. One patient discontinued treatment because of treatment-related serious (grade 3–4) adverse events, pancreatitis and cerebral hemorrhage. The most common immune-related adverse event (IRAE) was grade 1–2 skin events. Grade

Table 1. The development of all domestic ICIs

ICI	Company	Stage of development
PD-1 inhibitor		
SHR1210	Jiangsu HengRui Medicine Co. Ltd.	Phase III RCT
BGB-A317	BeiGene Co. Ltd.	Phase III RCT
IBI-308	Innovent Biologics (Suzhou) Co. Ltd.	Phase III RCT
JS001	Shanghai Junshi Bioscience Co. Ltd.	Phase II RCT
GLS-010	Harbin Gloria Pharmaceutical Co. Ltd. and WuXi AppTec Co. Ltd.	Phase I RCT
CBT-501/GB226	CBT Pharmaceuticals, Inc.	Phase I RCT
BAT1306	Bio-Thera Solutions, Ltd	Approve for RCT
AK103	Akeso Biopharma, Inc.	Approve for RCT
LZM009	Livzon Pharmaceutical Group Inc.	IND (37)
HLX10	Shanghai Henlius Biotech, Inc.	IND (103)
AK105	Akeso Biopharma, Inc.	Preclinical
SSI-361	Anhui Anke Biotechnology (Group) Co., Ltd.	Preclinical
PD-1/CTLA-4 coinhibitor		
AK104	Akeso Biopharma, Inc.	Phase I RCT
PD-L1 inhibitor		
KN035	3D Medicines (Sichuan) Co. Ltd.	Phase I RCT
CS1001	CStone Pharmaceuticals Co. Ltd.	Phase I RCT
SHR1316/HTI-1088	Jiangsu HengRui Medicine Co. Ltd.	Phase I RCT
STI-A1014	Lee's Pharmaceutical Holdings Limited	IND (55)
KL-A167	Sichuan Kelun Pharmaceutical Co., Ltd.	IND (35)
TQB2450	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	IND (51)
AK106	Akeso Biopharma, Inc.	Preclinical
HLX09	Shanghai Henlius Biotech, Inc.	Preclinical

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; IND, investigation new drug (the drug has finished preclinical stage but has not been approved by the China Food and Drug Administration for clinical trials); PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RCT, randomized controlled trial.

3 adverse events (AEs) were seen in three patients; no grade 4 AE or death was observed.

PK parameters of nivolumab among Chinese patients were also comparable to those of white patients [17]. However, the Tmax (median time of maximum serum concentration, hours)

Table 2. Ongoing phase I studies of immune checkpoint inhibitors conducted in China

No.	Agents	Identifiers	Locations	Tumor types ^a	Enrollment	Launched date	Current status
International agents							
1	Nivolumab	NCT02593786 CheckMate077 CTR20150755	Guangzhou, China	NPC, NSCLC, SCLC, HCC, CRC, gastric cancer	56	12/25/2015	Recruiting
2	Nivolumab	CTR20171020	China; Thailand	NSCLC	400 ^b	9/25/2017	Recruiting
3	Pembrolizumab	NCT02835690 KEYNOTE032	Beijing, China	NSCLC	42	8/4/2016	Ongoing, not recruiting
4	Atezolizumab/ atezolizumab+ gemcitabine- cisplatin	NCT02825940 IMYO29233	Beijing, China; Guangzhou, China; Harbin, China; Shanghai, China	Solid tumors	120 ^c	8/4/2016	Recruiting
5	Durvalumab/ durvalumab +tremelimumab	NCT02978482	Beijing, China; Changchun, China	Solid tumors other than HCC	26	12/1/2016	Ongoing, not recruiting
6	Avelumab	CTR20171035	Beijing, China	Dose escalation: solid tumors Dose expansion: esophageal squamous cell carcinoma	74	11/10/2017	Recruiting
7	Ipilimumab	NCT02516527	Guangzhou, China	Malignant melanoma	36	10/16/2015	Recruiting
8	Nivolumab +ipilimumab	NCT03195478 CTR20170731	Beijing, China	Solid tumors	27	7/27/2017	Recruiting
Domestic agents							
1	SHR1210	NCT02742935	Guangzhou, China	Breast cancer, gastrointestinal cancer	96	4/1/2016	Enrolling participant (by invitation only)
2	SHR1210	NCT02738489	Guangzhou, China	Malignant melanoma	36	4/1/2016	Enrolling participant (by invitation only)
3	SHR1210	NCT02721589	Guangzhou, China	Lung cancer	45	4/1/2016	Enrolling participant (by invitation only)
4	SHR1210	CTR20160175	Guangzhou, China	Solid tumors, especially lung cancer, NPC, esophageal carcinoma, gastric carcinoma, and HCC	32–51	3/30/2016	Recruiting
5	JS001	NCT02857166 CTR20160176	Guangzhou, China	Adenocarcinoma of solid tumor	24	3/1/2016	Ongoing, not recruiting
6	JS001	NCT02836834 CTR20160274	Beijing, China	Lung cancer, lymphoma	90	8/1/2016	Recruiting
7	JS001	NCT02836795 CTR20160187	Beijing, China	Malignant melanoma, urological cancer	35	4/1/2016	Ongoing, not recruiting
8	JS001	NCT02838823 CTR20160412	Beijing, China	TNBC	27	7/1/2016	Recruiting
9	JS001 + axitinib	NCT03086174 CTR20170109	Beijing, China	Kidney cancer, malignant melanoma	24	3/31/2017	Recruiting
10	JS001+ gemcitabine- cisplatin	NCT03251313 CTR20160813	Shanghai, China	TNBC	33	11/1/2017	Not yet open for recruitment
11	JS001 + radiotherapy	CTR20160976	Shanghai, China	TNBC	54	12/9/2016	Not yet open for recruitment

(continued)

Table 2. (continued)

No.	Agents	Identifiers	Locations	Tumor types ^a	Enrollment	Launched date	Current status
12	BGB-A317	CTR20160872	Guangzhou, China; Beijing, China; Harbin, China; Hangzhou, China; Shanghai, China; Nanjing, China	Solid tumors	240 ^d	12/19/2016	Recruiting
13	IBI-308	NCT02937116 CTR20160735	Beijing, China; Guangzhou, China	Solid tumors	104 ^e	10/1/2016	Ongoing, not recruiting
14	GLS-010	CTR20170433	Beijing, China	Solid tumors, especially gastric carcinoma, esophageal carcinoma	84	5/18/2017	Recruiting
15	GLS-010	CTR20170692	Beijing, China	Solid tumors, especially TNBC, HCC	84	7/27/2017	Not yet open for recruitment
16	CBT-501/GB226	CTR20170262	Beijing, China; Changsha, China; Harbin, China	Solid tumors, lymphomas	72	7/24/2017	Not yet open for recruitment
17	KN035	NCT03101488 CTR20170036	Beijing, China	Solid tumors	14–36	3/21/2017	Recruiting
18	CS1001	NCT03312842 CTR20170916	Beijing, China; Shanghai, China	Solid tumors, lymphomas	300 ^f	9/6/2017	Not yet open for recruitment

^aAll are advanced or metastatic tumors refractory or recurrent or intolerant to any available effective standard therapy.

^bCTR20171020 is a single-arm study investigating nivolumab in Asian patients with refractory/metastatic NSCLC. It plans to enroll 400 patients to fully investigate grade 3–5 adverse events, which usually have low occurrence rates.

^cNCT02825940 includes two cohorts, which investigate atezolizumab monotherapy and atezolizumab + chemotherapy, respectively.

^dCTR20160872 is a single-arm, phase I/II study that aims to investigate the safety, PK/PD profiles, and preliminary antitumor activity of BGB-A317 in Chinese patients.

^eNCT02937116/CTR20160735 is a phase IA/IB study with six cohorts investigating IBI308 monotherapy and IBI308 + chemotherapy in three different types of solid tumors. It also aims to explore biomarkers that can predict efficacy of IBI308.

^fNCT03312842/CTR20170916 is a phase IA/IB study with five dose escalating cohorts that aims to investigate the safety, PK/PD profiles, and preliminary antitumor activity of CS1001.

Abbreviations: CRC, colorectal cancer; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer.

in Chinese patients (Cycle 1 Day 1 [C1D1]: median = 4.00, range = 0.45–4.00; Cycle 3 Day 1 (C3D1): median = 8.00, range = 4.0–48.17) tended to be longer than the T_{max} in white patients (C1D1: median = 2.1, range = 0.8–8.00; C3D1: median = 4.0, range = 1.0–8.0). The median effective half-life of nivolumab among Chinese patients was 566 hours, whereas it was 611 hours among white patients.

The NCT03195478 (CTR20170731) study is a dose-escalation study assessing the safety, tolerability, PK profile, and preliminary efficacy of nivolumab plus ipilimumab in Chinese patients. Patients who had prior immune-oncology therapy or chronic HIV, HBV, or HCV infections are ineligible. Participants are treated with nivolumab (3 mg/kg, once every 2 weeks) plus ipilimumab (1 mg/kg, once every 6 weeks; Cohort A), nivolumab (3 mg/kg, once every 3 weeks) plus ipilimumab (1 mg/kg, once every 3 weeks) for four cycles followed by nivolumab monotherapy (240 mg fixed dose, once every 2 weeks; Cohort B), or nivolumab (1 mg/kg, once every 3 weeks) plus ipilimumab (3 mg/kg, once every 3 weeks) followed by nivolumab monotherapy (240 mg fixed dose, once every 2 weeks; Cohort C). The primary objective is to determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of nivolumab plus ipilimumab. Secondary outcomes are PK parameters and preliminary efficacy. The study was launched on July 27, 2017, and is currently recruiting participants.

The CTR20171020 study is an international, multicenter, single-arm study investigating the safety and tolerability of nivolumab monotherapy in Asian patients with refractory/metastatic non-small cell lung cancer (NSCLC). Chinese hospitals account for 80% of the centers (24/28), and Lu S. from Shanghai Chest Hospital is the global principal investigator of the study. Patients carrying positive EGFR mutations or ALK rearrangements who were refractory or recurrent to the first-line target therapy are eligible. Patients who tested positive for HBV infection but had HBV DNA ≤500 IU/mL can also be enrolled. Patients are excluded if they failed to be enrolled into any other PD-1/PD-L1 study solely because of low or negative predictive biomarkers. The study enrolled its first domestic patient on the September 30, 2017, and is currently recruiting participants domestically and globally. Instead of simply copying the design of foreign trials, CTR20171020 is the first study considering characteristics of Asian patients. By including EGFR-mutant NSCLC and patients with chronic, inactive HBV infections, its results are definitely worth expecting.

Pembrolizumab (Merck & Co.; KEYNOTE 032)

The KEYNOTE 032 (NCT02835690/MK-3475-032) study is a randomized dose-escalation phase I study targeting Chinese patients with advanced NSCLC. The dose-escalation scheme is 2 mg/kg, 10 mg/kg, and 200 mg once every three

weeks for 35 administrations or until disease progression or unacceptable toxicity. Cycle 1 is 28 days instead of 21 days. Primary objectives are safety, tolerability, and PK profile of pembrolizumab monotherapy. The study was launched on the August 4, 2016, and is currently recruiting participants.

Anti-PD-L1 Antibody

Atezolizumab (F Hoffmann-La Roche/Genentech Inc.; IMYO29233)

The IMYO29233 (NCT02825940) study is a phase I study investigating the PK profile, safety, and preliminary antitumor activity of atezolizumab monotherapy and atezolizumab plus chemotherapy in Chinese patients with advanced solid tumors. Patients in the monotherapy cohort receive atezolizumab 1,200 mg intravenously once every 3 weeks until confirmed disease progression or unacceptable toxicity. Patients with treatment-naïve stage IV NSCLC are enrolled in the combination cohort and receive atezolizumab (1,200 mg) on Day 1 combined with gemcitabine (1,250 mg/m²) on Days 1 and 8 plus cisplatin (75 mg/m²) on Day 1 of a 21-day cycle. The cycle will repeat four or six times at the discretion of investigators, followed by atezolizumab (1,200 mg) alone once every 3 weeks. There is no requirement for tumor PD-L1 expression levels in the monotherapy cohort, but patients enrolled into the combination cohort must have positive PD-L1 expression (PD-L1 expressed by ≥1% of the tumor cells). Primary outcomes are safety, tolerability, and PK profiles of atezolizumab monotherapy and atezolizumab plus chemotherapy in Chinese patients. The study is recruiting participants and is estimated to be completed by July 10, 2020.

Durvalumab (AstraZeneca; NCT02978482)

The safety, tolerability, and antitumor activity of durvalumab (MEDI4736) was first assessed and confirmed in the NCT01693562 study. The PK/PD profile and feasibility of durvalumab in combination with tremelimumab, a CTLA-4 inhibitor, are now being evaluated in three phase I studies (NCT02262741, NCT01975831, and NCT02978482). The completed NCT02262741 study targeted recurrent/metastatic head and neck squamous cell carcinomas with positive PD-L1 expression (PD-L1 expressed by ≥1% of the tumor cells), whereas the ongoing NCT01975831 study in the U.S. and NCT02978482 study in China target patients with advanced/metastatic solid tumors, regardless of tumor PD-L1 expression levels.

The NCT02978482 study consists of two cohorts. Participants in the monotherapy cohort are treated with durvalumab 20 mg/kg once every 4 weeks until disease progression or unacceptable toxicity, whereas participants in the durvalumab + tremelimumab cohort receive durvalumab 20 mg/kg once every 4 weeks plus tremelimumab 1 mg/kg once every 4 weeks for four cycles, followed by durvalumab (20 mg/kg once every 4 weeks) alone. The primary outcomes include PK parameters and safety data. The study was completed on November 15, 2018, but results have not been published yet.

Avelumab (Merck KGaA and Pfizer; CTR20171035)

Avelumab is the latest ICI approved by the U.S. FDA for the treatment of metastatic Merkel cell carcinoma and refractory, locally advanced, or metastatic urothelial carcinoma. The CTR20171035 study is the first domestic study of avelumab that aims to characterize the PK/PD profiles of avelumab monotherapy in Chinese patients. The study consists of a dose-escalation phase and a dose-expansion phase, the latter of which targets patients with advanced esophageal squamous cell carcinoma (ESCC). Patients are enrolled regardless of tumor PD-L1 expression levels. Patients tested positive for HIV, HBV, or HCV infections are ineligible. Participants will be treated with avelumab 10 mg/kg intravenously once every 2 weeks until disease progression or unacceptable toxicity. The primary outcomes include DLT, PK data, and preliminary antitumor activity. The study first released information on November 10, 2017, and is currently recruiting participants.

Anti-CTLA-4 Antibody

Ipilimumab (Bristol-Myers Squibb; NCT02516527 and NCT03195478)

The NCT02516527 study is a randomized, open-label, dose-escalation phase I study investigating ipilimumab monotherapy in Chinese patients. Patients with advanced or metastatic malignant melanoma regardless of tumor PD-L1 expressions are eligible. Participants are treated with ipilimumab 3 mg/kg or 10 mg/kg intravenously once every 3 weeks for four cycles, followed by ipilimumab monotherapy (3 mg/kg or 10 mg/kg) every 12 weeks until either 3 years, disease progression, or unacceptable toxicity. The primary objective is to assess the safety and tolerability of ipilimumab monotherapy and to determine the DLT and MTD. Secondary objectives are the PK profile and preliminary antitumor activity. The study was launched on October 16, 2015, and is estimated to be completed on November 26, 2019.

The safety, tolerability, PK profile, and efficacy of ipilimumab plus nivolumab in Chinese patients with pretreated advanced or recurrent solid tumors are being assessed in the NCT03195478 study as mentioned above.

DOMESTIC-DEVELOPED AGENTS

Anti-PD-1 Antibody

SHR1210 (Jiangsu HengRui Medicine Co. Ltd.; NCT02742935, NCT02738489, NCT02721589, and CTR20160175)

SHR1210 is the first ICI independently developed by Chinese biopharmas. Its new drug application (NDA) had been submitted to the Chinese Center for Drug Evaluation (CDE) on April 19, 2018, using Hodgkin lymphoma as the lead indication.

Currently, there are four ongoing phase I trials assessing the safety and tolerability of SHR1210 monotherapy in Chinese patients. The CTR20160175 study is a dose-escalation study that evaluates SHR-1210 monotherapy in Chinese patients with advanced or metastatic solid tumors (particularly focusing on lung cancer, NPC, esophageal carcinoma, gastric

carcinoma, and HCC). The dose-escalation scheme is 1 mg/kg, 3 mg/kg, 10 mg/kg, and 200 mg on Day 1 of the first 28 days, followed by unchanged dosages of SHR-1210 every 2 weeks. Safety and tolerability are the primary outcomes. Secondary outcomes include PK parameters, immunogenicity, and preliminary antitumor activity. The study enrolled its first patient on April 6, 2016, and is currently recruiting participants. NCT02742935, NCT02738489, and NCT02721589 target patients with refractory advanced or metastatic breast cancer/gastrointestinal cancer (NCT02742935), malignant melanoma (NCT02738489), and lung cancer (NCT02721589), respectively.

According to the latest released results of NCT02742935 [19, 20], treatment with SHR1210 in advanced/refractory ESCC resulted in an objective response rate of 33.3% and a median progression-free survival of 3.6 months. The most common TRAEs were reactive capillary hemangiomas (76.7%, 23/30), which was believed to be related to the activation of vascular endothelial growth factor (VEGF)/VEGF receptor pathway. In the intense market competition of ICIs, this adverse event, although not life-threatening, may be a flaw for SHR1210. Jiangsu HengRui is now actively dealing with this problem by combining SHR1210 with chemotherapy or antiangiogenic agents.

JS001 (Shanghai Junshi Bioscience Co. Ltd.; NCT02857166, NCT02836834, NCT02836795, NCT02838823, NCT03086174, NCT03251313, and CTR20160976)

JS001 is the first domestic-developed ICI granted clinical trial approval by the CFDA. On March 9, 2018, Chinese CDE formally accepted its NDA, with melanoma as the lead indication. Preclinical study of JS001 found that it could specifically bind to PD-1 antigen with an EC₅₀ of 21 nmol/L, and could competently block the binding of PD-1 antigen to PD-L1 and PD-L2 with IC₅₀ of 3.0 and 3.1 nmol/L, respectively [21].

Currently, there are five phase I studies evaluating JS001 monotherapy in Chinese patients with various malignancies. The NCT02857166 (CTR20160176) study was the first-in-human study of JS001 recruiting patients with adenocarcinoma of the stomach or gastroesophageal junction, ESCC, NPC, cholangiocarcinoma, and pancreatic ductal cell carcinoma. It adopted the classic 3 + 3 dose escalation design and contained a dose expansion cohort using a fixed-dose of 240 mg once every 2 weeks. There was no restriction on patients' PD-L1 expression levels. Preliminary study results were released at the 2017 European Society for Medical Oncology annual meeting (1186P). A total of 25 patients were included. No DLT or MTD was identified. The elimination half-life ranged between 6 and 15 days. Among 13 evaluable patients, 1 patient with melanoma achieved confirmed complete remission, 2 achieved confirmed partial remission, and 2 achieved stable disease.

The NCT02836834 (CTR20160274), NCT02836795 (CTR20160187), and NCT02838823 (CTR20160412) studies are all single-center dose-escalation studies evaluating the tolerability and PK profile of JS001 in patients with refractory advanced or metastatic lung cancer/lymphoma (NCT02836834), malignant melanoma/urological cancer (NCT02836795), and triple-negative breast cancer (TNBC; NCT02838823), regardless of their PD-L1 expression levels. These

studies all adopted identical dose-escalation schemes. Planned dosage levels are 1 mg/kg, 3 mg/kg, and 10 mg/kg intravenously once every 2 weeks until disease progression or unacceptable toxicity. Their primary objectives are to assess the safety, tolerability, DLT, and MTD of JS001 monotherapy. All studies were launched in 2016 and are currently recruiting participants.

The possibility of combining JS001 with other treatment modalities for advanced or metastatic solid tumors is also under investigation. The NCT03086174 (CTR20170109) study is a dose-escalation phase Ib study evaluating the safety, tolerability, and PK profile of JS001 plus axitinib in Chinese patients with refractory stage IV kidney cancer and advanced melanoma. The NCT03251313 (CTR20160813) study and the CTR20160976 study both target patients with refractory advanced or metastatic TNBC. The NCT03251313 study investigates the tolerability and PK profiles of JS001 plus gemcitabine-cisplatin, and the CTR20160976 study evaluates the feasibility of JS001 in combination with radiotherapy. All these studies were launched in 2017.

BGB-A317 (BeiGene Co. Ltd.; NCT02407990, CTR20160872, NCT02795182, and NCT02660034)

BGB-A317 is a novel anti-PD-1 antibody designed and developed independently by BeiGene, a rising star of the Chinese anticancer drug R&D. It is distinguished from the currently approved PD-1 antibodies with its inability to bind to Fcγ receptor I (FcγRI/CD64) and its unique binding signature to PD-1, both of which granted BGB-A317 high affinity and superior specificity toward PD-1 [22].

Two phase I studies (NCT02407990 and CTR20160872) evaluating BGB-A317 monotherapy are recruiting participants from international and domestic centers, respectively. The CTR20160872 study is a domestic, multicenter phase I study that aims to investigate the safety, PK/PD data, antitumor activity, MTD, and the recommended phase II dose of BGB-A317 for Chinese patients with refractory advanced or metastatic solid tumors. Patients are excluded if they failed to be enrolled into other PD-1/PD-L1 trials solely because of low or negative predictive biomarkers. It includes a dose-escalation section and a dose expansion section. The dose-escalation section adopts a modified 3 + 3 design to determine the DLT and MTD of BGB-A317 monotherapy. The dose expansion section divides participants based on their tumor types to further assess the antitumor activity of BGB-A317 in different malignancies. The study enrolled its first patient on December 28, 2016.

The feasibility of BGB-A317 in combination with other novel agents in the treatment of advanced cancers is also being explored. The NCT02795182 study, a multicenter phase Ib study in Australia, assesses the combination of BGB-A317 and BGB-3111, a Bruton's tyrosine kinase inhibitor, in patients with B-cell malignancies. The NCT02660034 study, another multicenter phase Ib study in Australia, investigates BGB-A317 in combination with BGB-290, a selective poly ADP-ribose polymerase inhibitor, in patients with advanced solid tumors. Both studies were started in 2016 and are recruiting participants.

IBI-308 (Innovent Biologics [Suzhou] Co. Ltd.; NCT02937116)

IBI-308 is an anti-PD-1 antibody developed by Innovent Biologics (Suzhou) Co. Ltd. On December 13, 2017, only 1 year after getting its clinical trial approval, Innovent Biologics submitted an NDA of IBI-308 to the CFDA, making it the first Chinese biopharma filing an NDA of ICIs. However, this NDA was withdrawn at the end of February 2018 for unknown reasons.

The NCT02937116 (CTR20160735) study is a domestic, multicenter, first-in-human phase I trial of IBI308 monotherapy and IBI308 plus chemotherapy in Chinese patients with advanced or recurrent solid tumors. It consists of phases Ia and Ib. Phase Ia assesses the safety and PK profiles of four dosage levels of IBI308 (1 mg/kg, 3 mg/kg, 10 mg/kg, and 200 mg, once every 3 weeks) adopting the classic 3 + 3 dose-escalation scheme. Phase Ib evaluates the tolerability and antitumor activity of IBI308 monotherapy (200 mg once every 3 weeks) in patients with malignant melanoma (Cohort A), gastrointestinal carcinoma (Cohort B), and NSCLC (Cohort C), as well as the feasibility of IBI308 in combination with chemotherapy in treatment-naïve advanced nonsquamous NSCLC without targetable driver mutations (e.g., EGFR mutations or ALK rearrangement; Cohort D), squamous NSCLC (Cohort E), and adenocarcinoma of the stomach or gastroesophageal junction (Cohort F). Patients previously exposed to PD-1/PD-L1 inhibitors are precluded. Patients previously treated with anti CTLA-4 antibodies are eligible if they show full resolution of IRAEs, no history of grade 4 IRAEs, a minimum of a 12-week interval from the first dose of the anti CTLA-4 antibody, and a minimum of a 6-week interval from the last dose. Patients who have unequivocal disease progression after one dose of the anti CTLA-4 antibody can also be considered for enrollment. The primary outcomes are safety and preliminary antitumor activity. Secondary outcomes are PK parameters. The study was launched in October 2016. It has finished recruitment in 2017, but no results have been published yet.

GLS-010 (Harbin Gloria Pharmaceutical Co. Ltd. and WuXi AppTec Co. Ltd.; CTR20170433 and CTR20170692)

GLS-010 is a PD-1 inhibitor codeveloped by Chinese and American biopharmas. Two multicenter phase I studies (CTR20170433 and CTR20170692) are ongoing to evaluate the safety, tolerability, preliminary antitumor activity, and PK profile of GLS-010 monotherapy in Chinese patients. The CTR20170433 study targets patients with gastric carcinoma and esophageal carcinoma, whereas the CTR20170692 study targets TNBC and HCC. Non-HCC patients with HBV or HCV infection and HCC patients with HBV and HCV coinfection are precluded from enrollment. The planned dose levels are 1 mg/kg, 4 mg/kg, 10 mg/kg, and 240 mg once every 4 weeks. The CTR20170433 study enrolled its first patient in China on July 13, 2017; the CTR20170692 study is not yet open for recruitment.

CBT-501/GB226 (CBT Pharmaceuticals, Inc.; NCT03053466 and CTR20170262)

In preclinical studies, CBT-501 showed comparable efficacy profile to nivolumab and pembrolizumab both in vitro and

in vivo. Also, CBT Pharmaceuticals claimed that CBT-501 had lower undesirable antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. However, no clinical data of CBT-501 are available yet.

The CTR20170262 study is a domestic, multicenter phase I trial targeting advanced or recurrent solid tumor and lymphoma patients in China. Patients previously treated with PD-1/PD-L1/PD-L2 or CTLA-4 inhibitors are ineligible. Participants assigned to three cohorts are treated with three planned dose levels (1 mg/kg, 3 mg/kg, 10 mg/kg) on Day 1 and Day 15 of a 28-day cycle. The NCT03053466 study is a multicenter dose-escalation study conducted in Australia with identical designs. The primary objectives of both studies are to assess the safety and tolerability of CBT-501. Secondary objectives are the PK profile and preliminary efficacy.

Anti-PD-L1 Antibody

KN035 (3D Medicines [Sichuan] Co. Ltd.; NCT03101488, NCT02827968, and NCT03248843)

KN035 is a PD-L1 inhibitor that adopts a different method of administration. Instead of being given intravenously, it is injected subcutaneously. The safety and PK profile of KN035 monotherapy in patients with advanced or metastatic solid tumors are under investigation in three dose-escalation phase I studies in China (NCT03101488 [CTR20170036]), the U.S. (NCT02827968), and Japan (NCT03248843), respectively. The inclusion and exclusion criteria are identical among the three studies. Patients are considered for enrollment regardless of their PD-L1 expression levels. Patients previously exposed to PD-1 or PD-L1 antibodies are excluded. Patients previously treated with ipilimumab can be enrolled if they show full resolution of IRAEs, no history of grade 4 IRAEs, a minimum of a 12-week interval from the first dose of ipilimumab, and a minimum of a 6-week interval from the last dose, or have unequivocal disease progression after one dose of ipilimumab. The primary objectives are safety and tolerability assessed by TRAEs and DLT. The secondary outcomes are PK and PD parameters. The studies in China and the U.S. are recruiting participants; the study in Japan is not open for recruitment yet.

CS1001 (CStone Pharmaceuticals Co. Ltd.; NCT03312842)

CS1001, a fully human, full-length anti-PD-L1 antibody developed by the Open Monoclonal Technology Inc. transgenic animal platform, mirrors natural human immunoglobulin G4 and therefore can reduce the risk of immunogenicity and potential toxicity in patients. The NCT03312842 (CTR20170916) study is a domestic, phase Ia/Ib, open-label study evaluating the safety, tolerability, PK profile, and antitumor activity of CS1001 in Chinese patients with advanced malignancies. The study consists of a dose-escalation part and an expansion part. The dose-escalation part adopts a modified 3 + 3 design. Planned dose levels are 3 mg/kg, 10 mg/kg, 20 mg/kg, 40 mg/kg, and 1,200 mg fixed dose once every 3 weeks until disease progression or unacceptable toxicity. Primary outcomes are safety and tolerability assessed by AEs, DLT, and MTD. Secondary outcomes are PK parameters and immunogenicity. The study is currently

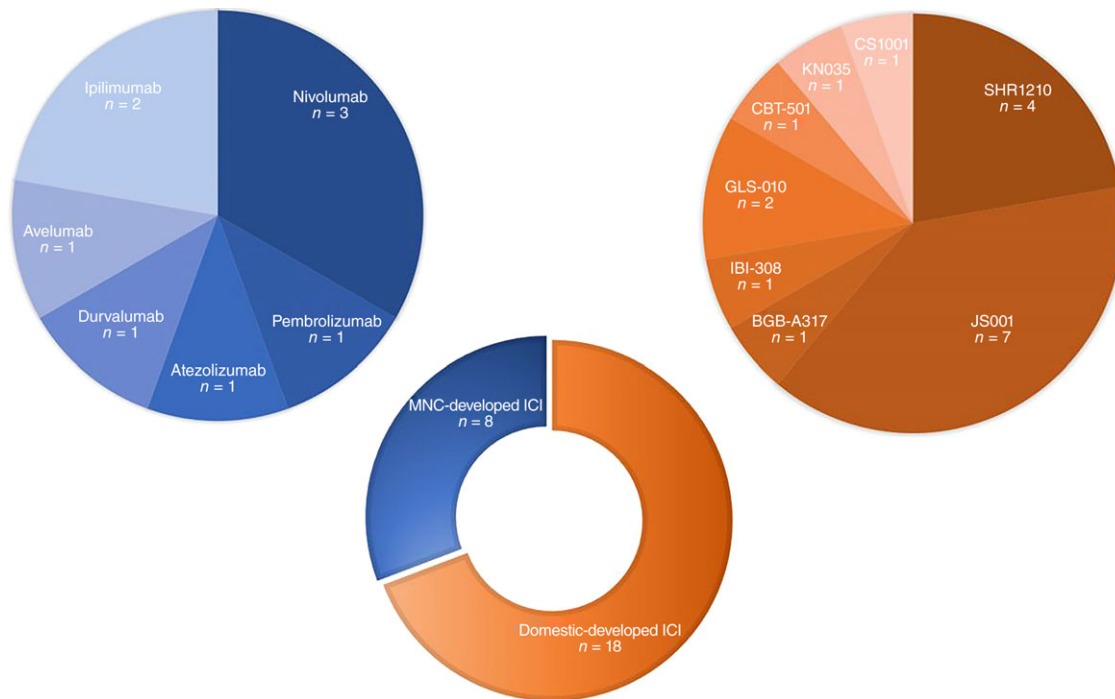


Figure 1. Ongoing phase I studies of MNC-developed ICIs and domestic-developed ICIs in the Chinese population. Among the 26 ongoing phase I studies of ICIs, 8 studies aim to assess the six MNC-developed ICIs in Chinese patients (the blue pie), and 18 evaluate the eight domestic-developed ICIs (the orange pie). The number of studies in the blue pie adds up to nine because one study aims to assess nivolumab in combination with ipilimumab and was thus counted twice. Abbreviations: ICI, immune checkpoint inhibitor; MNC, multinational corporation.

recruiting participants and is estimated to be completed in March 2021.

DISCUSSION

To date, a total of six MNC-developed ICIs and eight domestic-developed ICIs are being evaluated in 26 different phase I studies (Fig. 1). The majority of ongoing phase I studies in China investigate the safety, tolerability, and PK/PD profile of ICI monotherapy, whereas the remaining studies assess the feasibility of combining ICIs with other treatment modalities, attempting to provide new strategies for the treatment of advanced malignancies.

For MNC-developed agents, all the approved ICIs have shown promising efficacy and tolerability in various malignancies in large-scale RCTs. However, it remains unclear whether these agents are equally safe and effective among Chinese patients. According to the results of CheckMate 077, the safety, tolerability, and PK/PD profile of nivolumab monotherapy in Chinese NSCLC and NPC patients were generally comparable to those of white patients [17]. Although the PK data were slightly different between the two populations, it is still unknown whether these discrepancies are clinically relevant. Future studies of MNC-developed ICIs specified for Chinese patients are needed to verify the tolerability and efficacy of these agents in the Chinese population.

As for the domestic-developed agents, despite the rapid development of domestic-developed ICIs in China, we are still far behind our international counterparts in the field of immuno-oncology. Here, we identified some problems that

are worth further consideration in future clinical and preclinical studies. First, the absence of a reliable predictive biomarker for the efficacy of PD-1/PD-L1 inhibitors has led to inconsistent inclusion criteria in clinical trials. Some studies only enrolled patients with positive PD-L1 expression status (PD-L1 expressed at $\geq 1\%$ of tumor cells), whereas other studies enrolled patients regardless of PD-L1 expression levels. This is a common problem shared by international and domestic trials, which may result in a potential bias of phase I studies. Second, the inclusion and exclusion criteria of current phase I studies in Chinese patients fail to incorporate characteristics of the Chinese population. Despite of the heavy burden of HBV infection in China [23], only one study (CTR20171020) enrolls patients who test positive for HBV infections. The majority of current phase I studies elect to exclude patients with chronic HBV or HCV infections. Although it is understandable that excluding patients with chronic infections may reduce the risk of TRAEs and guarantee the safety and tolerability of the tested agent, it is still unknown whether it's necessary and scientifically solid to exclude all patients who test positive for HBV/HCV infections from ICI treatments regardless of their viral load. Moreover, the relationship between HBV infection and the efficacy and tolerability of ICIs also warrants further investigation. It was reported by Lin et al. that the expression of PD-L1 in NSCLC was increased in patients with chronic hepatitis B [24]. Therefore, additional phase I studies or phase IV studies assessing the safety, tolerability, and efficacy of ICIs in HBV/HCV-positive cancer patients are urgently needed.

With the rapid development of novel agents and treatment strategies, phase I studies in the immuno-oncology

era have evolved from simple safety and PK/PD investigating studies to proof-of-concept or proof-of-mechanism studies that assess antitumor activities [25]. The “seamless drug development strategy” now becomes the trend that more and more phase I studies progress from a first-in-human study to expansion phase that can be used to directly support drug registration. However, among the 26 phase I studies in China, only 12 consist of dose expansion phases that aim to investigate preliminary antitumor activities. Only five studies plan to explore prognostic biomarkers for immunotherapy. And several domestic-developed ICIs are investigated in multiple studies with different indications but identical designs. Undoubtedly, conducting early-phase oncology trials in China may be beneficial because of their lower cost of operations and large patient populations [26]. However, these advantages could be easily offset by the lack of patient enrichment strategies or inefficient study designs. In this sense, China still has a long way to go.

CONCLUSION

Cancer immunotherapy is a newly emerging and ever-changing field of current cancer treatment. ICI monotherapy has led to paradigm shifts in the treatment for various malignancies. Combining ICIs with other treatment modalities is also gradually becoming the focus of future studies. Immuno-oncology in China remains at a preliminary stage. Phase I studies exploring the safety, antitumor

activity, and PK/PD profiles of ICIs in Chinese patients are essential foundations for selecting clinical drug delivery modes and planning future large-scale phase II/III RCTs of immunotherapy in the Chinese population.

ACKNOWLEDGMENTS

This work was supported by National Key R&D Program of China (Grant No. 2016YFC0905500, 2016YFC0905503), Science and Technology Program of Guangdong (Grant No. 2017B020227001, Grant No. 2016A020215084), Science and Technology Program of Guangzhou (Grant No. 201607020031, Grant No. 201400000001-2), Chinese National Natural Science Foundation Project (Grant No. 81772476, Grant No. 81572659, Grant No. 81602011), Pearl River Nova Program of Guangzhou (Grant No. 201610010048), and National Natural Science Funds for Young Scholars of China (Grant No. 81502355).

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DISCLOSURES

The authors indicated no financial conflicts of interest.

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