

# Retrospect and Prospect for Lung Cancer in China: Clinical Advances of Immune Checkpoint Inhibitors

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

**Key Words.** Biogenetics • Checkpoint inhibitors • Immunotherapy • Lung cancer

## ABSTRACT

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in China. The recent emergence of immunotherapy treatment options, such as the use of programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitors, has also led to a paradigm shift in the treatment of non-small cell lung cancer, and has provided promising directions for the treatment of small cell lung cancer. This review provides a summary of the developmental process of immunotherapy, especially immune checkpoint inhibitors in lung cancer, ongoing international and domestic clinical trials in this field, and the challenges and considerations related to the use of immunotherapy in Chinese patients with lung cancer, with the aim of providing detailed information

for future immunotherapy-related clinical trials in China. Research regarding immune checkpoint inhibitors in China is several years behind similar research in several developed countries. However, although PD-1/PD-L1 inhibitor-related clinical trials remain in their early stages in China, increased efforts by Chinese clinicians, researchers, and government staff have been directed toward trying to introduce novel drugs into the clinical setting. Because of the specific characteristics of Chinese patients with lung cancer (such as high epidermal growth factor receptor mutation rates, later disease stages, and different toxicity profiles), large-scale clinical trials targeting the Chinese population or Chinese participation in multinational trials should be promoted. *The Oncologist* 2019;24(Special Issue):S21–S30

**Implications for Practice:** As the leading cause of cancer-related morbidity and mortality, lung cancer is a major public health problem in China. Immunotherapy based on programmed cell death protein 1/programmed death-ligand 1 checkpoint inhibitors may result in new treatment directions and a paradigm shift for Chinese patients with lung cancer. Although checkpoint inhibitor-related clinical trials remain in their early stages in China, increased efforts by Chinese clinicians, researchers, and government staff have been directed toward trying to introduce novel drugs into the clinical setting by encouraging the development of large-scale clinical trials targeting the Chinese population and promoting Chinese patients with lung cancer to participate in international trials.

## INTRODUCTION

Immunotherapy has been one of the breakthrough technologies in cancer therapy during the last decade. According to the antitumor mechanism, immune-oncology (I-O) is divided into three classes: active immunity (including vaccines, cytokines, and checkpoint inhibitors), passive immunity (adoptive cell infusion and targeted monoclonal antibodies), and hybrid immunity (combination of active and passive methods). Vaccines stimulate a patient's own immune system to mount a response to tumor antigens, and generate an active immune response against tumor antigens. Cytokines are considered nonspecific immune

stimulation, and boost activity of immune effector cells and stromal cells at the tumor sites. Immune checkpoints exist to dampen or terminate immune activity to guard against autoimmunity and allow for self-tolerance. However, tumors can take advantage of these immune checkpoint pathways to evade destruction. Checkpoint inhibitors have demonstrated delayed tumor growth and increased survival. Compared with the difficult and convoluted development pathways of other antitumor classes, such as vaccines and cytokines, checkpoint inhibitors received great attention when they first appeared. Inhibitors for many

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checkpoints, including cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1 [and its ligand programmed death-ligand 1 (PD-L1)]), B7-H3, B7x, lymphocyte-activation gene 3, mucin domain-containing molecule-3, V-domain Ig suppressor of T-cell activation, and B- and T-cell lymphocyte attenuator, have been described and studied [1]. To date, the best characterized and most clinically studied checkpoints are CTLA-4, PD-1, and PD-L1 [2].

Lung cancer, a leading cause of death worldwide, is classified histologically as either non-small cell lung cancer (NSCLC, accounting for approximately 85% of lung cancer, including squamous [SQCC] or non-squamous cell carcinoma [non-SQCC]) or small cell lung cancer (SCLC, accounting for approximately 15% of lung cancer). In China, the situation is particularly urgent. In contrast to lung cancer incidence rates in most Western countries, where lung cancer death rates are decreasing, the rates in China are still increasing, and lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer-related death [2]. More than 50% of patients with lung cancer present with metastases at the time of diagnosis. The prognosis for patients with metastatic or stage IV disease is extremely poor, with 5-year survival rates reported as less than 5%. Limited treatment options are available for both advanced NSCLC and SCLC, and response rates to standard chemotherapy range between approximately 15% and 30%.

Recently, as has been experienced with other solid tumors, the emergence of PD-1/PD-L1 inhibitors has led to a paradigm shift in the treatment of NSCLC and has provided promising directions for the treatment of SCLC. In this article, we summarize the developmental process of immunotherapy in lung cancer, ongoing international and domestic clinical trials in this field, and the challenges relating to immunotherapy in the Chinese lung cancer patient population in the hope of providing detailed information for future immunotherapy-related clinical trials in China.

## CURRENT STATUS OF LUNG CANCER MANAGEMENT IN CHINA

### Epidemiology

Lung cancer has been the leading cause of cancer-related morbidity and mortality for many years in China, accounting for 35.78% of all newly diagnosed lung cancer cases and 37.56% of lung cancer deaths worldwide [3]. In 2015, 733,300 patients were diagnosed, and 610,200 patients died from lung cancer [4], with a mortality rate that has increased 464.84% in the past several decades [5]. More than 50% patients were estimated to harbor distant metastases at initial diagnosis. As a leading risk factor, approximately 52.4% and 19.4% of lung cancer can be attributed to smoking in men and women, respectively [3]. Other risk factors include air pollution (environmental exposure to asbestos, nickel, chromium, and arsenic and indoor exposure to radon, unventilated coal-fueled stoves, and cooking fumes), chronic pulmonary disease (such as pulmonary tuberculosis, chronic bronchitis, and emphysema), and genetic mutations [6].

Histologically, NSCLC accounts for approximately 85% of lung cancer. Comparing SQCC with non-SQCC such as adenocarcinoma and other histological types, adenocarcinoma has replaced SQCC as the most predominant histological lung cancer subtype in China. In the past several years, the proportion of adenocarcinoma has increased to 43.36%–46.80%, while the proportion of SQCC has decreased to 24.16%–32.23% [6]. The change in predominant histological type has also influenced the molecular epidemiology of Chinese patients with NSCLC. Patients with adenocarcinoma and those of East Asian ethnicity have the highest risk of harboring epidermal growth factor receptor (*EGFR*) mutations; the prevalence of *EGFR* mutations in those patients is relatively higher than that in patients from Western countries, accounting for approximately 28.4% of the unselected NSCLC Chinese population, 40.3%–64.5% of patients with adenocarcinoma, and 75% of certain clinically enriched populations (i.e., patients who were nonsmokers with adenocarcinoma), although accounting for only approximately 2.1%–8.0% of patients with SQCC [5]. Other documented gene variations included anaplastic lymphoma kinase (*ALK*) rearrangements (1.5%–10%), ROS proto-oncogene 1 (*ROS1*) fusions (1%–2%), RET rearrangements (1.3%–1.9%), mesenchymal-epithelial transition factor (*c-MET*) gene amplification (4.5%), v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations (1.5%–3.0%), human epidermal growth factor receptor 2 (*HER2*) mutations (2.4%–5.94%), fibroblast growth factor receptor (*FGFR*) mutations (0.6%–3.5%), and discoidin domain receptor tyrosine kinase 2 (*DDR2*) mutations (0.5%–4.6%) [6]. With a deepening understanding of the molecular mechanisms, targeted therapies and the concomitant molecular tests have played an increasingly important role in the road map of lung cancer management [6].

### Standard of Treatment

In China, the standard for advanced NSCLC treatment is comprehensive treatment, mainly using systemic therapy [7]. According to the China Experts Consensus on the Diagnosis and Treatment of Advanced Stage Primary Lung Cancer (2016 Version) [8], *EGFR* tyrosine kinase inhibitors (TKIs; drugs approved by the China Food and Drug Administration [CFDA] include gefitinib [2010], erlotinib [2017], afatinib [2017], and icotinib [2014]) could be used as the first-line systemic therapy in patients with sensitizing *EGFR* mutations that are documented before the application of first-line therapy. For patients with locally advanced or metastatic NSCLC who have *ALK* or *ROS1* rearrangements, crizotinib (approved in 2013) is recommended as the first-line therapy. For patients without driving genes, such as *EGFR* mutations or *ALK* rearrangement, platinum-based regimens remain the mainstay of first-line systemic therapy. In China, gemcitabine (27.4%), docetaxel (16.2%), paclitaxel (13.5%), and pemetrexed (9.2%) are the most common choices in platinum-based doublet chemotherapy regimens for first-line chemotherapy [7]. For patients with unresectable, locally advanced, metastatic or recurrent non-SQCC, bevacizumab (a recombinant monoclonal antibody that inhibits the vascular endothelial growth factor pathway, approved

in 2015) is an option in combination with chemotherapy. Second-line choices for systematic therapy include docetaxel, pemetrexed, and EGFR-TKIs (drugs approved by the CFDA include gefitinib [2005], erlotinib [2006], afatinib [2017], icotinib [2011], and osimertinib [only for *EGFR* T790M mutation-positive patients, 2017]); third-line choices include clinical trials or the best supporting treatment. Recently, PD-1 inhibitor nivolumab (approved by the CFDA in June 2018) became a new second-line choice for patients with locally advanced or metastatic NSCLC with intolerance to or progression after previous platinum-based chemotherapy.

For patients with extensive-stage SCLC (accounting for two thirds of patients with SCLC) in China, chemotherapy is the most important and standard first-line treatment. The recommended first-line chemotherapy regimens for patients with an Eastern Cooperative Oncology Group performance score (ECOG PS) of 0–2 include etoposide + cisplatin, etoposide + carboplatin, irinotecan + cisplatin, or irinotecan + carboplatin. If treatment fails, patients with recurrence or progression within 3 months are encouraged to participate in clinical trials; topotecan, irinotecan, gemcitabine, or paclitaxel are considered for patients with recurrence within 3–6 months [8].

## Dilemmas and Challenges

### Treatment Disparity

Large disparities in the treatment of lung cancer in China may affect the clinical outcomes of patients. According to recent studies, 20.6% of Chinese patients with stage I NSCLC are overtreated, and 20.1% of stage II patients are undertreated. Although China has adopted the National Comprehensive Cancer Network clinical practice guidelines for lung cancer and a Chinese-specific version is available, only 19.6% of stage IIIA patients and 30.7% of stage IIIB patients receive the recommended systematic therapy [9]. Treatment disparities can be attributed to socioeconomic factors, including high medical costs, insufficient insurance coverage, or the lack of oncologist and patient compliance with advanced therapies [9]. In real-world settings, treatment disparities between different areas, or between the domestic consensus and global guidelines, may hinder the introduction, or obscure the authentic efficacy, of globally emerging novel drugs.

### Standstill in the Outcome Improvement of SCLC

Systemic treatment options for patients with SCLC have not improved significantly over the last few decades. Most patients relapse (approximately 80% of limited-stage patients and almost all extensive-stage patients) within the first year after initial therapy. Patients with refractory or drug-resistant relapse are less responsive to most drugs (response rate  $\leq 10\%$ ), and the response rate for patients with sensitive relapse is only 25% [10]. Treatment limitations encourage the research and development of novel agents, such as immune checkpoint inhibitors. Unfortunately, in China, there is still a long way to go for those drugs to be incorporated into clinical practice [11].

## ADVANCES IN IMMUNOTHERAPY IN CHINA

### Global Situation

#### NSCLC

NSCLC is a remarkably heterogeneous tumor that presents a large mutational load, encoding numerous potential neoantigens. Thus, agents that activate the host immune system and impede the immune escape of cancer cells in the tumor microenvironment are expected to improve clinical antitumor efficacy. Immunotherapy, represented by PD-1/PD-L1 checkpoint inhibitors, has dramatically changed the landscape for the first- and second-line treatment of NSCLC and has offered promising potential for the treatment of SCLC. To date, PD-1/PD-L1 inhibitors have been used widely or studied intensively in many clinical settings, such as monotherapy or combination therapy (including combinations between two different checkpoint pathways, with chemotherapy, with targeted drugs, with antiangiogenesis drugs, with surgery as neoadjuvant therapy, and with radiotherapy), as first-line or subsequent-line therapy, in the general population and in specific subgroups.

Approved PD-1/PD-L1 inhibitors for NSCLC include nivolumab (2015, second line), pembrolizumab (2015, second line in patients with PD-L1 expression  $\geq 1\%$ ; 2016, first line in patients with PD-L1  $\geq 50\%$ ), atezolizumab (2016, second line), and durvalumab (2018, second line). Checkmate-017 and Checkmate-057 have shown significantly better efficacy and safety profiles with nivolumab than with docetaxel when treating patients with advanced, previously treated SQCC (i.e., objective response rate [ORR]: 20% vs. 9%;  $p = .008$ ) [12] and non-SQCC patients [13], which led to the approval of nivolumab as a second-line treatment of NSCLC. Based on the positive efficacy and safety profiles demonstrated by pembrolizumab (KEYNOTE-010) and atezolizumab (OAK), they were successively approved as second-line drugs for NSCLC. The KEYNOTE-024 study showed that pembrolizumab was associated with significantly longer progression-free survival (PFS) and overall survival (OS) and with fewer adverse events than platinum-based chemotherapy in patients with PD-L1 expression  $\geq 50\%$  advanced NSCLC (median PFS: 10.3 months vs. 6.0 months;  $p < .001$ ), which led to the 2016 approval of pembrolizumab as a first-line therapy for patients with previously untreated, advanced NSCLC with high PD-L1 expression ( $\geq 50\%$ ). In the 2018 AACR annual meeting, the OS of KEYNOTE-024 was reported. Pembrolizumab showed OS benefit over chemotherapy as first-line therapy for advanced NSCLC with PD-L1 tumor proportion score  $\geq 50\%$  (median OS of 30.0 months vs. 14.2 months,  $p = .002$ ). The results will further enhance the role of pembrolizumab as a new standard of care for first-line therapy for advanced NSCLC that express high levels of PD-L1.

Currently, a series of randomized clinical trials of PD-1/PD-L1 inhibitors as first-line therapies are ongoing, including Checkmate-012 (nivolumab monotherapy or combined with platinum-based doublet chemotherapy, erlotinib, bevacizumab, or ipilimumab), CheckMate-816 (nivolumab and ipilimumab as neoadjuvant therapy), NCT02309177 (nivolumab with nab-P and carboplatin), KEYNOTE-001/021/042

(pembrolizumab monotherapy, combined with chemotherapy or targeted therapy), MYSTIC (durvalumab combined with tremelimumab), BIRCH (atezolizumab monotherapy), IMpower 130/131/132 (atezolizumab with chemotherapy), and NCT02088112 (durvalumab with gefitinib) [14].

The latest articles and abstracts published in the 2018 ASCO annual meeting have reported a series of recent results on the advances of immune checkpoint inhibitors in lung cancer. Focusing on immune checkpoint inhibitor monotherapy, 5-year follow-up results from the CA209-003 study ( $n = 129$ ) showed promising long-term OS and durable responses in a proportion of patients with pretreated advanced NSCLC receiving nivolumab treatment [15]. The estimated 5-year OS rate was 16% for all nivolumab-treated patients. Seventy-five percent of the 5-year survivors received no further therapy after nivolumab and were without evidence of progressive disease at last follow-up before the data cutoff. Similarly, 4-year follow-up results from the KEYNOTE-001 study ( $n = 550$ , 101 treatment-naïve; 449 previously treated) demonstrated long-term OS benefit for both treatment-naïve and previously treated advanced NSCLC with positive PD-L1 expression. ORR was 41.6% and 22.9%, median OS was 22.3 months and 10.5 months, and estimated 4-year OS rate was 27.2% and 16.4% for treatment-naïve and previously treated patients, respectively. Kaplan-Meier curves for OS appeared to plateau after 42 months for treatment-naïve patients and 36 months for previously treated patients [16]. In the latest results from KEYNOTE-042, the benefit of first-line pembrolizumab treatment has expanded to the previously untreated advanced/metastatic NSCLC population with PD-L1 expression  $\geq 1\%$  and without sensitizing *EGFR* or *ALK* alterations, but not only limited to high PD-L1-expressing population (PD-L1  $\geq 50\%$ ) [17]. Compared with standard first-line chemotherapy, pembrolizumab significantly improved OS in patients with PD-L1  $\geq 50\%$  (hazard ratio [HR]: 0.69;  $p = .0003$ ), PD-L1  $\geq 20\%$  (HR: 0.77;  $p = .002$ ), and PD-L1  $\geq 1\%$  (HR: 0.81;  $p = .0018$ ).

As data presented in the ATLANTI study ( $n = 444$ ) showed, even patients with heavily pretreated, *EGFR/ALK* mutation-positive advanced NSCLC may also benefit from greater than or equal to third-line PD-1/PD-L1 inhibitors treatment, with durable efficacy and a promising effect on OS [18]. For high PD-L1 expressing ( $\geq 25\%$ ) and *EGFR/ALK* (+) patients, median OS after anti-PD-L1 antibody durvalumab treatment was 13.3 months, which was similar to the median OS of extremely high PD-L1 expressing ( $\geq 90\%$ ) and *EGFR/ALK* (-) patients (13.2 months), and with a 1-year OS rate of up to 53%. In contrast, the median OS of PD-L1  $< 25\%$  and *EGFR/ALK* (+) patients was only 9.9 months. Avelumab is another emerging PD-L1 inhibitor. Two-and-a-half-year follow-up from the JAVELIN Solid Tumor trial ( $n = 154$ ) showed that avelumab as sequential-line therapy was associated with durable responses and long-term OS in patients with platinum-treated advanced NSCLC [19]. The ORR was 14.1%, median duration of response was 17.5 months, PFS rates at 6 months and 1 year were 24.2% and 16.5%, and OS rates at 1 and 2 years were 42.5% and 25.0%, respectively, during a median follow-up period of 33.9 months, and increased PD-L1

**Table 1.** Checkpoint inhibitors made by foreign companies that applied for new drug clinical trial application in China (until April 25, 2018)

Drug	Pharmaceutical company	Date of IND approval
Nivolumab	Bristol-Myers Squibb	7/27/2015
Pembrolizumab	Merck Sharp & Dohme	2/18/2016
Atezolizumab	Roche	11/19/2015
Durvalumab	AstraZeneca	8/8/2016
Avelumab	Merck KGaA/Pfizer	11/16/2016
PDR001	Novartis	5/18/2017

Abbreviation: IND, investigational new drug.

expression seemed to be associated with higher ORR and improved OS.

Focusing on the combination therapy of immune checkpoint inhibitors, recent results were also remarkable. In the Checkmate-012 study, first-line combination therapy with nivolumab and CTLA-4 inhibitor ipilimumab demonstrated a manageable safety profile and promising, durable efficacy in advanced NSCLC [20]. The pooled ORR was 43%, median PFS was 8.0 months, and 1- and 2-year OS rate was 76% and 49%, respectively. Efficacy was enhanced in patients with PD-L1 tumor expression  $\geq 1\%$ . Encouraging activity and improved OS was also observed for first-line nivolumab plus platinum-based doublet chemotherapy in patients with advanced NSCLC, showing an ORR of 46%, disease control rate of 89%, median OS of 19.2 months, and 1-, 2-, and 3-year OS rate of 71%, 37%, and 25%, respectively [21]. Based on the results from Checkmate-012 and considering tumor mutational burden (TMB) an emerging predictive biomarker, phase III study Checkmate-227 further examined survival benefit with first-line nivolumab plus ipilimumab among patients with advanced NSCLC with a high TMB ( $\geq 10$  mutations/Mb) [22]. Median PFS was significantly longer with first-line nivolumab plus ipilimumab than with chemotherapy among patients with NSCLC and a high tumor mutational burden (7.2 months vs. 5.5 months; HR: 0.58;  $p < .001$ ), irrespective of PD-L1 expression level. It is noteworthy that the Checkmate-227 study is also being conducted in China.

Based on the solid evidence from a series of randomized controlled trials, pembrolizumab plus platinum-containing chemotherapy has been approved by the U.S. FDA for first-line treatment in advanced, nonsquamous NSCLC. The latest results from the KEYNOTE 021 G cohort demonstrated that in patients with previously untreated stage IIIB/IV non-squamous NSCLC without *EGFR* mutations/*ALK* translocations, the risk of death for the pembrolizumab plus chemotherapy arm was reduced by nearly half compared with chemotherapy alone (HR: 0.56; nominal  $p = .0151$ ) after a median follow-up period of 24 months [23]. The combination of pembrolizumab and standard first-line chemotherapy (carboplatin + pemetrexed) significantly improved the treatment response and survival prognosis in patients with non-squamous NSCLC (pembrolizumab + chemotherapy arm vs. chemotherapy arm: ORR: 57% vs. 30%;  $p = .0016$ ; median PFS: 24.0 months vs. 9.3 months;  $p = .0049$ ; median

**Table 2.** Ongoing international clinical trials of programmed cell death protein 1 and PD-L1 inhibitors on lung cancer with participating Chinese centers (until April 25, 2018)

Registration number <sup>a</sup>	Drug	Enrollment (Chinese/total)	Indication	Phase	Population	Status in China
CTR20170158	Durvalumab	170/1,100	Adjuvant therapy	III	Completely resected stage IB–IIIA NSCLC	Not recruiting
CTR20170046	Durvalumab; tremelimumab	160/800	First-line	III	Advanced NSCLC	Recruiting
CTR20170012	Durvalumab	352/440	First-line	III	Advanced NSCLC, PD-L1-high expression	Recruiting
CTR20171020	Nivolumab	380/400	Second-line	III	Advanced NSCLC	Recruiting
CTR20170694	Nivolumab	130/810	Maintenance	III	Extensive-disease SCLC	Recruiting
CTR20170541	Nivolumab; ipilimumab	80/500	Second-line	III	Advanced NSCLC, <i>EGFR</i> mutation/T790m-, TKI failure	Not recruiting
CTR20170340	Nivolumab; ipilimumab	377/2,211	First-line	III	Advanced NSCLC	Recruiting
CTR20160578	Nivolumab	78/480	Second-line	III	Relapsed SCLC after platinum-based chemotherapy	Closed
CTR20150767	Nivolumab	450/500	Second-line	III	Advanced NSCLC	Closed
CTR20170044	Pembrolizumab	400/560	First-line	III	Advanced lung squamous carcinoma	Recruiting
CTR20160205	Pembrolizumab	600/740	Second-line	III	Advanced NSCLC	Recruiting
CTR20160097	Pembrolizumab	350/1,240	First-line	III	Advanced NSCLC, PD-L1+	Closed
CTR20160103	Pembrolizumab	40 (Chinese only)	PK and PD	I	Advanced NSCLC	Closed
CTR20171629	Atezolizumab	50/441	First-line	III	Advanced NSCLC	Not recruiting
CTR20170064	Atezolizumab	170/568	First-line	III	Advanced nonsquamous NSCLC	Recruiting
CTR20160994	Atezolizumab	150/555	First-line	III	Advanced NSCLC, PD-L1-high expression	Recruiting
CTR20160988	Atezolizumab	100/500	First-line	III	Extensive-disease SCLC	Recruiting
CTR20160510	Atezolizumab	150/760	Adjuvant therapy	III	Completely resected stage IB–IIIA NSCLC	Recruiting
CTR20160054	Atezolizumab	450/562	Second-line	III	Advanced NSCLC	Closed
CTR20171000	Avelumab	65/1,095	First-line	III	Advanced NSCLC, PD-L1+	Recruiting

<sup>a</sup>The registration numbers are from the China Food and Drug Administration database ([www.chinadrugtrials.org.cn](http://www.chinadrugtrials.org.cn)).

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD, pharmacodynamics; PD-L1, programmed death-ligand 1; SCLC, squamous cell lung cancer; TKI, tyrosine kinase inhibitor.

OS: not reached vs. 21.1 months;  $p = .0151$ ). The larger-scale phase III study KEYNOTE-189 further confirmed the conclusion [24] that in patients with previously untreated metastatic non-squamous NSCLC, the addition of pembrolizumab to standard chemotherapy resulted in significantly better response and longer overall survival and progression-free survival than chemotherapy alone ( $p < .001$  for each comparison). In patients with previously untreated metastatic squamous NSCLC (KEYNOTE-407), the addition of pembrolizumab to standard chemotherapy also significantly improved treatment response (ORR almost doubled in the pembrolizumab + chemotherapy arm: 58.4% vs. 35.0%;  $p = .0004$ ), with a tolerable safety profile [25].

Other combination regimens containing immune checkpoint inhibitors such as durvalumab plus CTLA-4 inhibitor tremelimumab [26], durvalumab plus gefitinib (NCT02088112) [27], atezolizumab plus chemotherapy with or without bevacizumab (IMpower 131 and 150) [28, 29], and atezolizumab plus alectinib (in *ALK*-positive patients) [30] also showed positive

efficacy and acceptable toxicity, which may provide more options for combination therapy with immune checkpoint inhibitors in the future.

Identifying optimal populations that have the greatest potential to benefit from I-O optimizes therapeutic efficacy; therefore, the investigation of potential predictive biomarkers has become a hot spot in I-O-related fields [31]. PD-L1 has been widely accepted as a predictive biomarker of the anti-PD-1/L1 therapy responses of many cancers; nevertheless, immunogenic mutation loads, such as microsatellite instability-high and TMB, also show significant response to checkpoint blockade, which is probably due to PD-1/L1 status and tumor-infiltrating lymphocyte content [32]. In the Checkmate-026 study ( $n = 541$ ), the PFS benefit was more obvious in patients with high TMB when comparing the efficacy of nivolumab and standard chemotherapy (median PFS of 9.7 vs. 5.8 months; ORR: 46.8% vs. 28.3%), which was consistent with the improved survival data shown in Checkmate-227 [33].

**Table 3.** Checkpoint inhibitors made by domestic companies that applied for new drug clinical trial application in China (until April 25, 2018)

Drug	Target	Monoclonal antibody type	Pharmaceutical company	Date of IND approval
JS001	PD-1	Humanized IgG4	Junshi	1/14/2016
SHR-1210	PD-1	Humanized IgG4	Hengrui	1/20/2016
BGB-A317	PD-1	Humanized IgG4	BeiGene	9/3/2016
IBI308	PD-1	Fully human IgG4	Innovent	9/4/2016
GB226	PD-1	Humanized IgG4	Genor	12/22/2016
KN035	PD-L1	Humanized PD-L1 single domain antibody Fc fusion protein	Alphamab	1/11/2017
GLS-010	PD-1	Fully human IgG4	WuXi AppTec	3/15/2017
CS1001	PD-L1	Fully human IgG4	Cstone	7/17/2017
BAT1306	PD-1	Humanized mAb	Bio-Thera	9/14/2017
SHR-1316	PD-L1	Humanized IgG4	Hengrui	9/14/2017
AK103	PD-1	Humanized mAb	Akeso	9/14/2017
KL-A167	PD-L1	Humanized mAb	Kelun	9/27/2017
LZM009	PD-1	Humanized mAb	Livzon	10/26/2017
TQB2450	PD-L1	Humanized IgG1	CTTQ	11/1/2017
STI-A1014	PD-L1	Fully human mAb	Lee's Pharm	1/17/2018
HLX10	PD-1	Fully human mAb	Henlius	3/20/2018

Abbreviations: IgG, immunoglobulin G; IND, investigational new drug; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

### SCLC

PD-1/PD-L1 inhibitors have also shown promising results in patients with SCLC. Nivolumab monotherapy showed favorable efficacy for patients with recurrent SCLC in the phase I/II Checkmate-032 trial ( $n = 98$ ; ORR: 10%; median OS: 4.4 months; 1-year OS rate: 33%; median PFS: 1.4 months; treatment-related adverse events: 13%) [34]. Preliminary results from the KEYNOTE-028 study were also remarkable. Patients with PD-L1-positive, chemotherapy-treated, extensive-stage SCLC benefitted from pembrolizumab treatment ( $n = 24$ ; ORR: 33%; median OS: 9.7 months; 1-year OS rate: 35.7%; median PFS: 1.9 months), although the small sample size might affect the potency of the statistical data [35]. Recently, combination regimens, including nivolumab and ipilimumab (Checkmate-032), and ipilimumab and chemotherapy, have also been under evaluation.

### Ongoing International Clinical Trials in China

Research regarding immune checkpoint inhibitors in China is several years behind similar research in developed countries (e.g., U.S.). However, greater efforts by Chinese clinicians, researchers, and government staff have encouraged Chinese patients with lung cancer to participate in global randomized clinical trials. As of April 25, 2018, a total of six checkpoint inhibitors made by foreign companies have applied for new drug clinical trial application in China (Table 1).

To date, Chinese sites are involved in 20 global clinical trials, including 10 first-line trials, 6 second-line trials, 2 adjuvant therapy trials, 1 maintenance therapy trial, and 1 trial for study of pharmacokinetics and pharmacodynamics (Table 2). Representative international trials enrolling patients from Chinese medical centers include KEYNOTE-042, NCT03003962, NEPTUNE, IMpower 133, IMpower 210, MK-3475-033, and

CheckMate-078 (conducted by Chinese sites and Chinese hospitals accounted for >70% of the centers), etc. Thus, the latest advances in those global trials as previously described may also reflect the situation of Chinese patients to a certain extent.

CheckMate 078 (CTR20150767) was the third phase III study to demonstrate improved OS with nivolumab compared with docetaxel in patients with advanced, previously treated NSCLC (median OS of 12.0 months vs. 9.6 months;  $p = .0006$ ). More importantly, CheckMate 078 was the first phase III study to show benefit of a checkpoint inhibitor in an East Asian (predominantly Chinese, 90%) patient population. Overall, the safety and efficacy of nivolumab were consistent with the global CheckMate 017 and 057 trials. In June 2018, nivolumab became the first immune checkpoint inhibitor to be approved as second-line therapy for locally advanced or metastatic NSCLC in China.

### Domestic Drugs

During the last few years, the overall clinical research environment in China has significantly improved, leading to an increase in the development of emerging domestic drugs. As of April 25, 2018, a total of 16 checkpoint inhibitors made by domestic companies have applied for new drug clinical trial application in China (Table 3).

JS-001 (CTR20180275, CTR20171117), SHR1210 (CTR20180077, CTR20170322, CTR20170299, CTR20170090), IBI308 (CTR20170380), and BGB-A317 (CTR20171112, CTR20170361) are the front-runners in the competition and have been approved by the CFDA for clinical trials among patients with lung cancer (Table 4). Moreover, other drugs (GB226, KN035, GLS-010, CS1001, BAT1306, etc.) are also approved by the CFDA for clinical trial.

**Table 4.** Ongoing clinical trials with domestic programmed cell death protein 1 or programmed death-ligand 1 inhibitors on advanced lung cancer (until April 25, 2018)

Registration number <sup>a</sup>	Drug	Enrollment	Indication	Phase	Population	Study design/details	Primary endpoint	Status
CTR20180077	SHR-1210	135	Second-line	II	Extensive-disease SCLC	Randomized, open-label, parallel group study. Key inclusion criteria: ED-SCLC progressed after platinum-based chemotherapy; ECOG PS 0~1; life expectancy $\geq 8$ weeks	AEs; ORR	Not recruiting
CTR20170322	SHR-1210	412	First-line	III	Advanced nonsquamous NSCLC	Randomized, open-label, parallel group study. Key inclusion criteria: IIIB/IV stage nonsquamous NSCLC; <i>EGFR/ALK</i> (-); ECOG PS 0~1; life expectancy $\geq 3$ months	PFS	Recruiting
CTR20170299	SHR-1210	120	Second-line	II	Advanced NSCLC	Single-arm, open-label, multicenter study. Key inclusion criteria: IIIB/IV-stage NSCLC progressed or recurrent after multimodal therapy; ECOG PS 0~1; PD-L1 $\geq 50\%$ if <i>EGFR/ALK</i> (+)	ORR	Recruiting
CTR20170090	SHR-1210	118	Second-line+	III	Advanced nonsquamous NSCLC	Nonrandomized, open-label study. Key inclusion criteria: IIIB/IV-stage NSCLC; $\geq 1$ measurable lesion; ECOG PS 0~1; life expectancy $\geq 12$ weeks	AEs; SAEs; ORR	Recruiting
CTR20170380	IBI308	266	Second-line	III	Advanced LSQ	Randomized, open-label, parallel group study. Key inclusion criteria: IIIB/IIIC/IV-stage NSCLC; <i>EGFR/ALK</i> (-); $\geq 1$ measurable lesion; ECOG PS 0~1; life expectancy $\geq 12$ weeks	OS	Recruiting
CTR20171112	BGB-A317	640	Second-line	III	Advanced NSCLC	Randomized, open-label, parallel group study. Key inclusion criteria: IIIB/IV-stage NSCLC progressed during or after platinum-based chemotherapy; ECOG PS 0~1	OS	Not recruiting
CTR20170361	BGB-A317	60	First-line	II	Advanced NSCLC; Extensive-disease SCLC	Nonrandomized, single-arm, open-label study. Key inclusion criteria: locally advanced or metastatic NSCLC or ED-SCLC; systematic therapy naïve; <i>EGFR/ALK</i> (-)	ORR	Recruiting
CTR20180275	JS001	40	Second-line	II	Advanced NSCLC, <i>EGFR</i> mutation/T790m-, TKI failure	Nonrandomized, single-arm, open-label study. Key inclusion criteria: advanced or recurrent NSCLC; sensitive <i>EGFR</i> mutation (+); $\geq 1$ measurable lesion; ECOG PS 0~1; life expectancy $\geq 3$ months	ORR	Not recruiting

(continued)

Table 4. (continued)

Registration number <sup>a</sup>	Drug	Enrollment	Indication	Phase	Population	Study design/details	Primary endpoint	Status
CTR20171117	JS001	30	PK and PD	I	Advanced NSCLC	Nonrandomized, open-label, parallel group, PK/PD study. Key inclusion criteria: advanced NSCLC failed or intolerant to standard therapy; $\geq 1$ measurable lesion; ECOG PS 0~1; life expectancy $\geq 6$ months	AUC 0-T	Recruiting

<sup>a</sup>The registration numbers are from the China Food and Drug Administration database (www.chinadrugtrials.org.cn).

Abbreviations: AEs, adverse events; ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; ED, extensive disease; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; SAEs, serious adverse events; SCLC, squamous cell lung cancer; TKI, tyrosine kinase inhibitor.

In the 2018 ASCO annual meeting, results from a phase Ib study of SHR-1210 plus apatinib for previously heavily treated advanced nonsquamous NSCLC patients were presented [36]. Twenty-seven patients after failure of  $\geq 2$  lines of systemic therapies were treated with SHR-1210 in combination with apatinib (250 mg or 375 mg) up to disease progression or intolerable toxicity. The pooled ORR and disease control rate was 41.2% and 94.1% in the two arms with different apatinib dosage, and the median PFS was 24 weeks in the apatinib 250 mg arm and not reached in the apatinib 375 mg arm, respectively. Although higher ORR seemed to be observed in the apatinib 375 mg arm, dose-limiting toxicity resulted in dose reduction of apatinib to 250 mg in a portion of patients (nearly 50%). Thus, considering the balance of efficacy and safety, SHR-1210 in combination with apatinib at a dose of 250 mg was well tolerated with promising antitumor effect, even in previously heavily treated NSCLC patients. A further phase II trial based on SHR-1210 plus apatinib 250 mg regimen is ongoing.

### Exploring Biomarkers

Although none of the four global PD-L1-detecting antibodies (28-8, 22C3, SP142, and SP263) have been listed in China yet, pathologists in most Chinese hospitals have spontaneously conducted PD-L1 expression studies and consensus studies (for detecting antibodies). In China, 28-8, 22C3, SP142, SP263, E1L3N, and BP6001 are commonly used research-oriented antibodies. At present, the expert opinion on PD-L1 detection in China is being developed, which may provide authoritative guidance for the exploration of PD-L1 biomarkers in the Chinese population [37].

## SPECIAL FOCUS: DIFFERENCES BETWEEN CHINA AND OTHER COUNTRIES

### Ethnicity

The characteristics of Chinese patients are different from those of patients from Western countries, and specific ethnic features should be considered factors in trial designs (i.e., the Chinese population has relatively high rates of hepatitis B virus infection and traditional medicine use). Furthermore, Chinese patients with NSCLC may have more

driver gene mutations, different gene profiles, better clinical responses to chemotherapy, and different toxicity profiles. Although the JapicCTI-132072 trial, conducted in Japan, showed that the clinical efficacy of the PD-1 inhibitor nivolumab as a second-line regimen in Asian NSCLC patients is consistent with that in Western patients (Independent Review Committee assessed ORR of 25.7%, median OS of 16.3 months, and median PFS of 4.2 months) [38], more direct and robust evidence is still necessary for the clinical application of novel immunotherapy drugs.

### Biogenetics

#### EGFR Mutation

The prevalence of *EGFR* mutations is approximately 50% among Chinese patients with NSCLC, which is significantly higher than that in Western countries. The presence of *EGFR* mutations and *ALK* rearrangements (alterations typically associated with a lack of tobacco exposure) have been suggested to be associated with lower ORR to PD-1 inhibitors. Therefore, trials to test whether the ORR to immunotherapy can be improved by administering concurrent TKI therapy in *EGFR*-positive patients and large-scale clinical trials specifically targeting the Chinese population should be conducted.

#### PD-L1 Expression

Results from a single-center study showed that the PD-L1 expression rate in Chinese NSCLC patients might be different from that in Western countries. International studies showed that PD-L1 expression profiles were similar in different sample storage states (fresh or archived specimens), histological types (SQCC or adenocarcinoma), patient groups (treated or untreated), and tumor sites (primary or metastatic). Regardless of whether patients had SQCC or non-SQCC such as adenocarcinoma, the proportion of patients with PD-L1  $< 1\%$ ,  $1\% - 49\%$ , or  $\geq 50\%$  was 1:2:2, which meant that 40% of patients had positive PD-L1 expression ( $\geq 50\%$ ) [39]. However, a single-center study ( $n > 1,000$ ) conducted by the Pathology Department of Sun Yat-sen Hospital in China showed that PD-L1 expression in Chinese NSCLC patients is related to histological type (Yuan Li, private data). A higher proportion of patients with



adenocarcinoma expressed negative PD-L1 levels; patients with PD-L1 <1% accounted for 79% of all adenocarcinoma patients, whereas patients with PD-L1 ≥50% accounted for only 7.6%. In SQCC patients, the proportions of patients with PD-L1 <1%, 1%–49%, or ≥50% was similar to those in patients from Western countries (1:1:1). The reason for the different PD-L1 expression profiles between Chinese and foreign populations remains unclear. Therefore, it has been suggested that it would be prudent to carry out a nationwide, multicenter study to clarify the PD-L1 expression profiles in Chinese NSCLC patients, to confirm whether there are ethnic differences and whether the results of international studies are applicable to the Chinese population [40].

## Unmet Demands

### Limited Access to Novel Drugs and Promising Directions

Ongoing international clinical trials rarely target, or even consider, the characteristics of the Chinese population, and according to the Chinese drug introduction policy, drug-related research and approval in China is always several years behind that in developed countries of the world. Thus, Chinese patients always have limited access to promising, novel drugs [37].

## CONCLUSION

As the leading cause of cancer-related morbidity and mortality, lung cancer is a major public health problem in China, and immunotherapy based on PD-1/PD-L1 inhibitors may result in new treatment directions and a paradigm shift for the Chinese lung cancer population. PD-1/PD-L1

inhibitor-related clinical trials remain in their early stages in China, although greater efforts by personnel of various departments have been directed toward trying to introduce novel drugs into the clinic. Considering the specific characteristics of the Chinese population with lung cancer (such as high *EGFR* mutation rates, later disease stages, and different toxicity profiles), large-scale clinical trials targeting the Chinese population, or participation in multinational trials, should be promoted.

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## DISCLOSURES

The authors indicated no financial relationships.

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