Acta Pharmaceutica Sinica B 2022;12(3):1536−1537

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

NEWS

The evolving treatment paradigm of lung cancer in China

Lung cancer is the leading cause of cancer death in China[1]. Generally, 65%−70% of lung cancer patients are already at an advanced, inoperable stage at diagnosis. Therefore, there has been a surge in drug development to address the unmet medical needs of lung cancer. In recent years, benefiting from the precise molecular classification of lung cancer, the number of clinical trials testing drugs in lung cancer has increased rapidly in China, enhancing R&D capacities and the impactful regulatory reform. It thus has led to significant improvements in drug accessibility.

From 2013 to 2021, there were 2114 lung cancer-related clinical trials registered in China, including 751 phase I–II trials (35.5%), 261 phase III trials (12.3%), 143 phase IV trials (6.8%), and 959 other types of trials (investigator initiating trials accounting for 45.4%) (Fig. 1). Among them, there were 150 multi-regional clinical trials (MRCTs), which consisted of 33 phase I–II clinical trials (22.0%), 114 phase III clinical trials (76.0%) and 3 other types of trials (2.0%). The top three targets most investigated were EGFR, PD1, and VEGFR, accounting for 16.4% (346), 12.0% (254), and 10.6% (225), respectively (Fig. 1), consistent with their success in the international market.

From the perspective of drug approval, there has been a marked increase in drug approvals for lung cancer since 2018 (Table 1). Notably, one imported and seven domestic drugs had been granted marketing authorizations to treat lung cancer in 2021 in China.

In the meantime, the time lag in drug development between China and the international market is dramatically shortened. For example, the US Food and Drug Administration (FDA) approved capmatinib for lung cancer with MET-14 exon skipping mutation in 2020. One year later, the National Medical Products Administration (NMPA) of China approved savolitinib, another new drug for the same target.

The approval of the homegrown targeted and immunotherapeutic drugs has been speeded up in China; meanwhile, new indications have been added. From 2004 to 2020, most lung cancer drugs approved by the FDA are for the treatment of advanced lung cancer, but few for postoperative adjuvant therapy of early-stage lung cancer, of which the current standard treatment is still chemotherapy[2]. However, adjuvant chemotherapy only improves the 5-year survival rate by 5.3%[3]. In 2018, China's researchers found that EGFR-TKI can decrease the risk of postoperative recurrence for patients with early-stage lung cancer[4,5]; it thus has changed the treatment protocol. In April 2021, the NMPA-approved osimertinib for postoperative adjuvant therapy of lung cancer with EGFR mutation, based on the result of ADAURA trial (ClinicalTrials.gov identifier, NCT02511106) led by Prof. Yilong Wu[6]. In June 2021, based on the outcome of EVIDENCE trial (ClinicalTrials.gov identifier, NCT02448797)[7], icotinib was approved by the NMPA for the postoperative adjuvant treatment of early-stage lung cancer with EGFR mutation.

In terms of immune checkpoint inhibitors, the FDA-approved atezolizumab for postoperative adjunctive therapy of lung cancer in October 2021, based on the result of IMpower-010 trial (ClinicalTrials.gov identifier, NCT02486718)[8]. In addition, clinical studies of sintilimab, tislelizumab, and toripalimab for perioperative

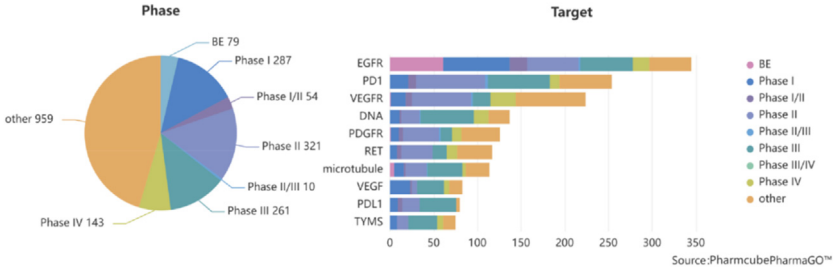

Figure 1 Lung cancer-related clinical trials in China from 2013 to 2021.

Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2022.01.010

Table 1 Approved drugs for lung cancer in China and the US.

Target	FDA-approved new drug (approved year)	Domestic NMPA-approved domestic new drug (approval year)	Time difference of first approval/year
EGFR	Erlotinib (2004), afatinib (2013), gefitinib (2015)	Icotinib (2011)	7
VEGFR	Bevacizumab (2006)	Anlotinib (2018), QL1101 (2019), IBI305 (2020), LY01008 (2021), BP102 (2021)	12
Endostatin	–	Endostar (2006)	–
ALK	Crizotinib (2011), ceritinib (2014), alectinib (2015), brigatinib (2020), lorlatinib (2020)	Ensartinib (2020)	9
EGFR-T790M	Osimertinib (2015)	Almonertinib (2020), furmonertinib (2021)	5
PD1	Nivolumab (2015), pembrolizumab (2016), cemiplimab (2021)	Camrelizumab (2020), sintilimab (2021), tislelizumab (2021)	5
PD-L1	Atezolizumab (2016)	Sugemalimab (2021)	5
ROS1	Crizotinib (2016), lorlatinib (2018), entrectinib (2019)	–	–
BRAF V600E	Dabrafenib+trametinib (2016)	–	–
NTRK	Larotrectinib (2018), entrectinib (2019)	–	–
RET	Selpercatinib (2020)	Pralsetinib (licensed-in, 2021)	1
KRAS G12C	Sotorasib (2020)	–	
MET exon 14-skipping mutation	Capmatinib (2020), tepotinib (2021)	Savolitinib (2021)	1
EGFR exon 20 insertion mutations	Mobocertinib (2021), amivantamab (2021)	–	–

–Not applicable.

immunotherapy have been carried out in China (Supporting Information Table S1).

The result of CheckMate-816 trial (ClinicalTrials.gov identifier, NCT02998528) released in November 2021 indicates that nivolumab combined with chemotherapy significantly improved the overall complete remission rate of operation for early-stage lung cancer. Additionally, the positive results of sintilimab and toripalimab were revealed in the clinical trials for the same indication (Supporting Information Table S2).

While patients benefit from EGFR, ALK, and ROS1 targeted drugs in advanced lung cancer, the drug resistance of targeted therapies and brain metastasis have been concerned. Drug combinations and rare targets could provide a potential solution to these issues. For patients without driver mutations, it needs to identify which groups can benefit from immunochemotherapy, and select a safe and effective plan. For early-stage lung cancer, EGFR-targeted therapy and immunotherapy in the perioperative period can improve patients' outcomes. Future studies should be performed to explore the targeted therapies besides EGFR and the combination with immunotherapy. There are still many challenges to be overcome, such as whether chemotherapy is needed before immunotherapy, what is the best course of medication, how to achieve long-term survival benefits, and how to identify people at high risk of recurrence after surgery.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2022.01.010.

References

1. National Health Commission of the People's Republic of China. *China health statistics 2021*. Beijing: Peking Union Medical College Press; 2021.
2. Chaft JE, Rimner A, Weder W, Azzoli CG, Kris MG, Cascone T. Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer. *Nat Rev Clin Oncol* 2021;**18**:547–57.
3. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008;**26**:3552–9.
4. Yue D, Xu S, Wang Q, Li X, Shen Y, Zhao H, et al. Erlotinib *versus* vinorelbine plus cisplatin as adjuvant therapy in Chinese patients with stage IIIA EGFR mutation-positive non-small-cell lung cancer (EVAN): a randomised, open-label, phase 2 trial. *Lancet Respir Med* 2018;**6**:863–73.
5. Zhong WZ, Wang Q, Mao WM, Xu ST, Wu L, Wu L, et al. Gefitinib *versus* vinorelbine plus cisplatin as adjuvant treatment for stage II–IIIA (N1–N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol* 2018;**19**:139–48.
6. Wu YL, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2020;**383**:1711–23.
7. He J, Su C, Liang W, Xu S, Wu L, Fu X, et al. Icotinib *versus* chemotherapy as adjuvant treatment for stage II–IIIA EGFR-mutant non-small-cell lung cancer (EVIDENCE): a randomised, open-label, phase 3 trial. *Lancet Respir Med* 2021;**9**:1021–9.
8. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet* 2021;**398**:1344–57.

Wei Xie[a], Shuanghuan Liu[b], Guanqiao Li[c], Huiyan Xu[a], Liyun Zhou[a,*]

[a]*Pharmcube (Beijing) Co., Ltd., Beijing 100020, China*

[b]*National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China*

[c]*Tsinghua Clinical Research Institute (TCRI), School of Medicine, Tsinghua University, Beijing 100089, China*

[*]Corresponding author.

E-mail address: zhouliyun@pharmcube.com (Liyun Zhou)

Received 14 December 2021