Drug development and evidence for lung cancer targeted therapy in Eastern Asia

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Summary

The development of targeted drugs in the Eastern Asia region is going through a flourishing stage. With the continuous advancement of technology and medical research, biotechnology companies and research institutions in the region have made significant progress in cancer field. The Eastern Asian region not only actively participates in clinical trials, but is also committed to developing personalized medical plans to meet the diverse genotypes and phenotypes of patients. The governments and enterprises are increasingly valuing innovation, strengthening international cooperation, and promoting drug development. This paper summarizes the development of genetic testing technology, targeted drugs approval, ongoing promising clinical trials in the field of lung cancer and the important progress made by governments in the Eastern Asian region, and proposed key factors that will contribute to the promising future prospects in the region. The targeted drug market in the Eastern Asian region is expected to drive the medical field forward.

Keywords: Drug development; Targeted therapy; Precision medicine; Lung cancer; Eastern Asia

Introduction

Lung cancer is a serious health issue that affects millions of people worldwide. According to the World Health Organization (WHO), lung cancer is the leading cause of cancer-related deaths globally, accounting for 18% of all cancer deaths in 2020.[1] About 44.5% of the lung cancer cases and 45.5% of the deaths occurred in Eastern Asia in 2020.[2]

The incidence and mortality trends for lung cancer show significant differences among regions and countries over time. The lung cancer incidence and mortality rapidly increased in most countries or regions from 1980 to 2012, particularly in Eastern Asia. However, some countries or regions demonstrated a decline or stabilization in lung cancer incidence and mortality, such as North America and Western Europe. These variations may reflect the differences in smoking prevalence, tobacco control policies, environmental factors, diagnostic methods, treatment options, and drug accessibility among different regions and countries.

Precision medicine in oncology is a type of cancer treatment that uses genomic tests to identify the specific molecular abnormalities that drive the growth and spread of cancer cells.[3] By targeting these abnormalities with drugs that interfere with their function, precision medicine can achieve better outcomes for certain patients compared with traditional chemotherapy or radiation therapy.[4] Targeted therapy is one of the main forms of precision medicine in oncology, and it employs small-molecule drugs or monoclonal antibodies to block the activity of genes that are involved in cancer development and progression.

There are some differences between Eastern Asian and Western countries in the use and development of precision medicine and targeted therapy in oncology.[5] Some of these differences are related to the prevalence and distribution of certain types of cancer, the availability and accessibility of genomic testing and targeted drugs, the regulatory and ethical frameworks, and the cultural

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and social factors that influence patients' preferences and expectations. Eastern Asian patients are known to have high incidence of mutation in the *EGFR* gene that can be targeted by drugs, such as gefitinib and osimertinib. However, these drugs are often more expensive and less accessible in Eastern Asia than in Western countries, which limits their use. Moreover, some Eastern Asian countries have stricter regulations and slower approval processes for new drugs than Western countries, which may delay the availability of novel targeted therapies.[6] In contrast, some Eastern Asian countries have invested more resources and efforts in developing their own precision medicine platforms and initiatives, such as the China Precision Medicine Initiative, the Cancer Genome Screening Project for Individualized Medicine in Japan and the Korea Precision Medicine Enterprise.[7] These initiatives aim to generate large-scale genomic data from diverse populations, develop new diagnostic tools and therapeutic strategies, and promote collaboration and innovation in precision medicine research.

Here, we summarized drug approvals in lung cancer, promising drugs and clinical trials, and the regulatory process for drug approval in Eastern Asia. As the data cutoff of December 2023, we identified relative references from public database, and ongoing studies from clinicaltrial.gov (Fig. 1).

Precision medicine development in lung cancer

Recent advances in next-generation sequencing

Genetic testing approved for clinical use

Genetic testing usually serves two purposes: therapeutic guidance and clinical trials. Companion diagnostics are required to guide clinical use, and these usually need to obtain approval by regulatory authorities (Fig. 2). Early genetic testing kits could only detect one or several genes. The *EGFR* mutation detection kit, which employs multiplex quantitative real-time polymerase chain reaction (PCR), is approved by the National Medical Products Administration (NMPA) in China, by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and by the Minister of Food and Drug Safety (MFDS) in Korea. This kit was the first one to use circulating tumour DNA (ctDNA) to guide clinical use of EGFR-TKIs.[8–10] The PCR-11 genes product was also approved by the NMPA and by the PMDA for clinical use in lung cancer.

The next-generation sequencing (NGS) is characterized by the ability to sequence millions of DNA fragments in parallel.[11] Large panel kits can simultaneously detect numerous genes and sites, saving tumour tissue and reducing time and cost. However, in November 2017, MSK-IMPACT, the first large NGS panel product was approved for multiple types of cancer by the FDA. In China, the largest gene panel, with 425 genes, was approved in December 2023 for *EGFR* and *ALK*-negative non-squamous non-small cell lung cancer (NSCLC), but so far it lacks universal adaptation for multiple cancer detection. The frequency of gene fusions in lung cancer is 8%–12%, which is important to detect to guide clinical use of targeted agents, such ALK- or ROS1-TKIs.[12] However, DNA/NGS is less sensitive than RNA/NGS at detecting gene fusions.[13] The future of molecular pathology is gene detection at both the DNA and RNA levels. Progress is needed for the regulatory authorities in Asia to follow up the steps of the FDA.

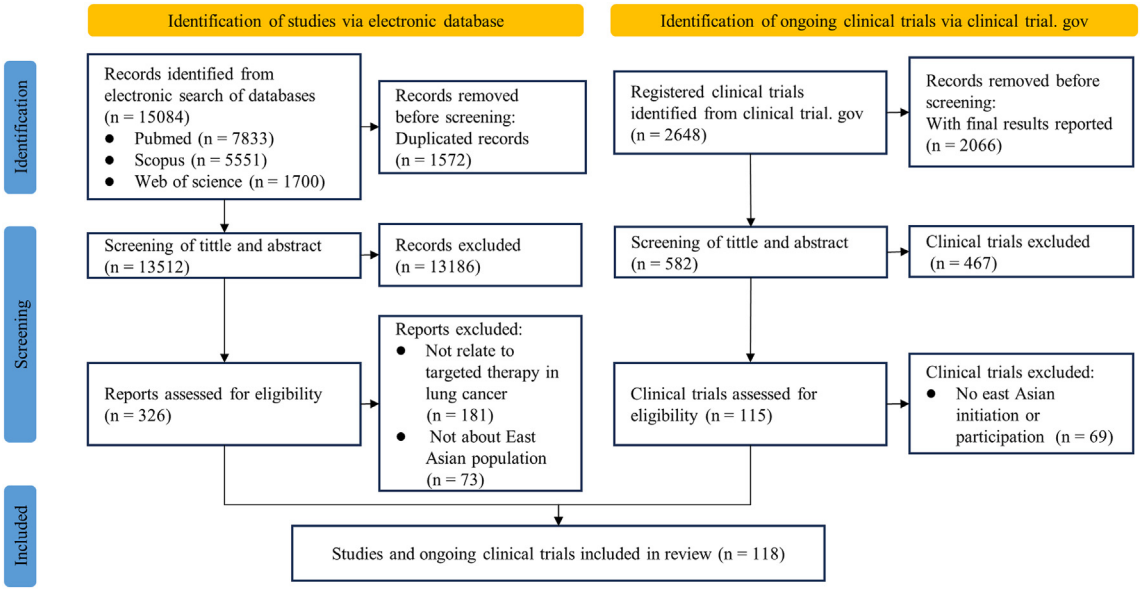

Fig. 1: Flow chart of references and ongoing trials selection.

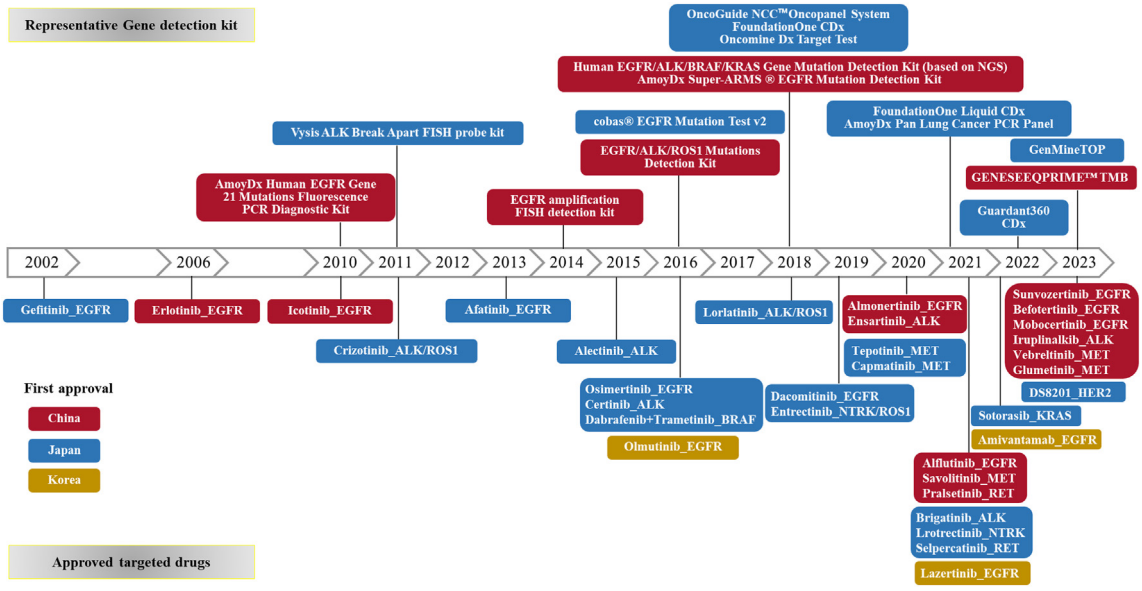

Fig. 2: The gene detection kit and targeted drugs approved in Eastern Asia.

In Japan, the Cancer Genomic Medicine (CGM) Promotion Consortium was established in 2017. A total of 233 hospitals were qualified as CGM institutes in 2022. The Pharmaceuticals and Medical Devices Agency (PMDA) and MHLW (Ministry of Health, Labour and Welfare) officially approved and reimbursed one small NGS panel and five large comprehensive genomic profiling panels: OncomineDXTT, OncoGuide NCC Oncopanel, FoundationOne CDx, FoundationONE Liquid, Guardant360, and GenMineTOP.[14] The OncomineDXTT (46 gene NGS) has been approved and reimbursed before the first line treatment of non-small cell lung cancer as one of companion diagnostic tests. The Centre for Cancer Genomics and Advanced Therapeutics (C-CAT) has collected comprehensive genomic profiling and clinical data of 36,340 patients with cancer as of June 30, 2022. It has released that 5.8% of the first 25,991 patients had lung cancer.[14] Furthermore, the database has been widely used by other hospitals, academia, and industry. The National Cancer Centre in Japan launched the "SCRUM-Japan (Cancer Genome Screening Project for Individualized Medicine in Japan)" project in 2015.[15] This project has supported the regulatory approval of 11 new drugs (13 indications) and 7 *in-vitro* diagnostics, contributing to the early delivery of effective therapeutic drugs and diagnostics to patients nationwide. "LC-SCRUM-Asia" expands the screening platform for lung cancer to Eastern Asia in 2021 and will realize individualized medicine by introducing the latest analysis techniques that shortens testing times. MONSTAR-SCREEN-2" performs molecular profiling based on multi-omics analysis, including RNA and protein expression, to elucidate the nature of cancer and promote the development of new treatments based on these findings (http://www.scrum-japan.ncc.go.jp/).[16]

South Korea initiated the K-MASTER program to collect and characterize the complex genomes of Korean patients with advanced solid tumours in 2017.[17] In total, 4028 Korean patients with advanced solid tumours have been subjected to prospective clinical sequencing, and all data have been made accessible to the public (https://kmportal.or.kr).

The Asia–Pacific Oncology Drug Development Consortium (APODDC) provided recommendations for the use of NGS for patients with metastatic cancer in the Asia–Pacific region. Given the expanding list of actionable alterations in NSCLC, a small-panel, multiplex-gene NGS assay with adequate coverage of key alterations may be considered for NSCLC. This approach would save costs and lead to shorter turnaround times compared to comprehensive genomic profiling NGS.[18]

Genetic testing for clinical trials

Large-panel NGS with at least 100 genes could serves for patients screening, particularly for clinical trials with multiple targets and multiple drugs. Several umbrella trials use NGS for screening with the advantage of saving sample, saving time, and saving patients. In China, learning from the small umbrella CLUSTER trial, the Chinese Thoracic Oncology Group (CTONG) initiated a large phase II umbrella trial and real-word study, using a large NGS panel with at least 400 genes aimed at all-comer recruitment in the advanced NSCLC patients.[19] This screening platform provides an essential infrastructure for precision medicine studies.

In the past two years, ultra-deep sequencing was used to detect molecular residual disease (MRD) for postoperative NSCLC patients in clinical trials and for research. Potentially cured patients were identified by dynamic monitoring with longitudinal negative MRD.[20] An increasing number of observational and interventional clinical trials were initiated to confirm the negative predictive value and the feasibility of using MRD-guided drug treatment in lung cancer patients after curative therapy in Eastern Asia. The CTONG2105 trial explored adjuvant treatment based on the dynamic MRD for resectable non-squamous NSCLC with *EGFR* mutations.[21] When MRD is positive, patients will be treated with EGFR-TKI, and when it turns to negative, patients enter into the period of drug holiday. This novel treatment paradigm is a type of adaptive de-escalation targeted therapy, which has the aim to ensure efficacy, reduce drug toxicity, and reduce cost.[22]

New targets and drugs

NSCLC patients in Eastern Asia demonstrated an ethnically unique characteristic on driver gene profile.[23,24] With the continuous development of targeted drugs, the treatment paradigm in Eastern Asia has shifted from classical driver genes (the first two targets with approved targeted agents: *EGFR* mutation and *ALK* fusion), to rare genetic alterations (the frequency in lung cancer is less than 5%), which include *KRAS* mutations, *EGFR* exon 20 insertions (*EGFR* 20ins), *RET* fusion, *NTRK* fusion, and *HER2* mutation. The new targets and drugs approved in Eastern Asia in 2021–2023 are summarized in Table 1.

EGFR *exon 20 insertion*

EGFR 20ins accounts for approximately 12% of *EGFR* mutations and 1.8% of the genetic variations in NSCLC.[32] The gene insertion represents a heterogeneous group of variants. Different insertion types have different effects on drug kinetics and binding, leading to differences in clinical characteristics and sensitivity to EGFR-TKIs.[33] Unlike common *EGFR* mutations, *EGFR* 20ins has limited efficacy to classical EGFR-TKIs. Three EGFR 20ins inhibitors have been approved for clinical use, including one bispecific antibody and two small molecule TKIs. Dr. Zhou and colleagues in Eastern Asian participated in or even led these international multi-centre clinical trials.[26,34]

Amivantamab is a bispecific IgG1 antibody that simultaneously targets EGFR and MET,[35] with a median progression free survival (PFS) of 8.3 months and a median OS of 22.8 months. It was approved by the FDA in May 2021 for NSCLC patients with *EGFR* 20ins who progress on platinum-based therapy.[36,37] In the phase III PAPILLON trial, Dr Zhou. and colleagues in Eastern Asian led this trial and contributed to 63% of the enrolled patients. The subgroup analysis reported that amivantamab plus chemotherapy achieved a median PFS of 11.5 months, compared with 5.6 months in the chemotherapy alone group in Asian patients.[25,34]

Drug	Targets	First approval in global	Regulatory authorities	First approval in Eastern Asia	Regulatory authorities in Eastern Asia	Efficacy in Asia
Amivantamab	*EGFR* 20 ins	2021/5/21	FDA	2022/2/14	MFDS	Participants (Asian/Total): 186/308; ORR: 70%; PFS: 11.5 months; 2-year OS: 76%[25]
Mobocertinib	*EGFR* 20 ins	2021/9/15	FDA	2023/1/10	NMPA	Participants (Asian/Total): 68/114; ORR: 30.9%[26]
Sunvozertinib	*EGFR* 20 ins	2023/8/22	NMPA	2023/8/22	NMPA	Participants (Asian/Total): 104/104; ORR: 61%[27]
Adagrasib	*KRAS* G12C mutation	2022/12/12	FDA	/	/	Participants (Asian/Total): 5/116
Sotorasib	*KRAS* G12C mutation	2021/5/28	FDA	2022/1/20	PMDA	Participants (Asian/Total): 21/171; PFS: 8.3 months[28]
Pralsetinib	*RET* fusion	2020/9/4	FDA	2021/3/23	NMPA	Participants (Chinese/Total): 68/233; ORR: 66.7% (pretreated), 83.3% (treatment naïve); PFS: 11.7 months (pretreated), 12.7 months (treatment naïve)[29]
Selpercatinib	*RET* fusion	2020/5/8	FDA	2021/9/27	PMDA/NMPA	Participants (Asian/Total): 76/129; PFS: NR[30]
Larotrectinib	*NTRK* fusion	2018/11/26	FDA	2021/3/23	PMDA/NMPA	
Trastuzumab deruxtecan	*HER2* mutation	2022/8/11	FDA	2023/8/23	PMDA	(5.4 mg/kg group) Participants (Asian/Total): 63/103; ORR: 50.8%; PFS: 10.8 months; 1-year OS: 71.3% (6.4 mg/kg group) Participants (Asian/Total): 31/50; ORR: 73.3%; PFS: 15.4 months; 1-year OS: 76.3%[31]
Telisotuzumab vedotin	MET overexpression	/	/	Priority review by PMDA		
Alectinib[a]	*ALK* fusion	/	/	Priority review by NMPA		
Garsorasib	*KRAS* G12C mutation	/	/	Priority review by NMPA		
Fulzerasib	*KRAS* G12C mutation	/	/	Priority review by NMPA		
Reporectinib	*ROS1* fusion	2023/11/15	FDA	Priority review by NMPA		
Taletrectinib	*ROS1* fusion	/	/	Priority review by NMPA		

[a]The indication for the adjuvant treatment of *ALK*-positive NSCLC patients after complete tumour resection was under priority review.

Table 1: **Targets and drugs approved by regulatory authorities.**

Mobocertinib irreversibly binds to and inhibits *EGFR* 20ins at lower concentrations than wild type *EGFR*. Based on data from a phase I/II EXCLAIM study (NCT02716116),[26,38] mobocertinib was granted accelerated approval by the FDA in September 2021 and approved by NMPA in January 2023,[39] with a median PFS of 7.3 months and a median OS of 20.2 months. However, it was declared that the phase III EXCLAIM-2 study, which evaluated mobocertinib vs. platinum-based doublet chemotherapy in treatment-naive patients, did not meet its primary endpoint; thus, mobocertinib has been withdrawal globally.

Sunvozertinib is an irreversible, potent, and selective EGFR-TKI that demonstrates activity against *EGFR* 20ins and other mutations. FDA granted breakthrough therapy designation (BTD) for sunvozertinib in January 2022, based on the data from the phase I/II clinical trials WU-KONG1 and WU-KONG2.[40] In August 2023, sunvozertinib received its first approval by the NMPA based on data from the WU-KONG6 study.[27,41] At the 2023 European Society for Medical Oncology (ESMO), results from WU-KONG1 and WU-KONG15 studies demonstrated that the objective response rate (ORR) was 78.6%, and the median PFS was 12.4 months for treatment-naïve patients.[42] Two global, phase III, multicentre, randomized, studies (NCT05668988; FURVENT, NCT05607550) are ongoing to assess the efficacy and safety of sunvozertinib and furmonertinib vs. platinum-doublet chemotherapy in treatment-naïve *EGFR* 20ins NSCLC.

KRAS *mutation*

KRAS mutation has long been considered undruggable. Asian NSCLC patients have a lower frequency of *KRAS* mutations i.e., 10%, compared with Caucasian NSCLC patients.[43] *KRAS G12C* mutation is the most prevalent subtype,[44] and significant targeted therapy breakthroughs directed at this mutation have been made in recent years. Sotorasib and adagrasib have been approved by the FDA. Until 2023, sotorasib was the only KRAS inhibitor approved in Eastern Asia. However, the efficacy of these two drugs appears to be unsatisfactory. In China, two KRAS G12C inhibitors, garsorasib and fulzerasib (IBI351), have been granted with accelerated approval pathway.

Garsorasib demonstrated anti-tumour activity with an ORR of 40.5% and a median PFS of 8.2 months in a phase I trial (NCT05383898).[45] Fulzerasib demonstrated encouraging efficacy with an unconfirmed ORR of 59.5%, a confirmed ORR of 46.6%, and a median PFS of 8.3 months in pretreated *KRAS G12C*-mutated NSCLC.[46] Both drugs have been granted in priority review for approval in China.

RET *fusion*

The *RET* gene was identified as a proto-oncogene in 1985.[47] Oncogenic *RET* alterations include point mutations, gene rearrangements or fusions, and copy number variations. *RET* fusions occur in approximately 1–2% of NSCLC cases. Recently, highly selective RET inhibitors are setting a new treatment paradigm for personalized treatment in *RET* fusion-positive NSCLC.

Selpercatinib is a highly selective, potent, brain-penetrant RET inhibitor that was approved by the FDA in May 2020 for the treatment of advanced *RET* fusion-positive NSCLC patients based on the phase I/II LIBRETTO-001 study.[48] In the global phase III LIBRETTO-431 trial, 212 patients with *RET* fusion were randomized to receive first-line selpercatinib or chemotherapy and pembrolizumab, among whom 116 patients were enrolled from Eastern Asia. A prolonged median PFS in the selpercatinib group (24.8 vs. 11.2 months, $P < 0.001$) was reported.[30] In September 2022, the NMPA approved selpercatinib for the treatment of NSCLC patients with *RET* fusions.

Pralsetinib is another selective inhibitor of the RET receptor tyrosine kinase that can provide durable relief for patients with *RET*-altered solid tumours. This drug was approved by the FDA for the treatment of NSCLC patients with *RET* fusions in September 2020, based on the results of the phase I/II ARROW study, with an ORR of 64%, and a median PFS was 16.4 months.[49,50] The drug was approved by the NMPA in March 2022 with a reported ORR of 75% in Chinese patients from ARROW trial.[29] The confirmatory phase III AcceleRET Lung study is ongoing.

NTRK *fusion*

The *NTRK* gene family includes *NTRK1, NTRK2,* and *NTRK3*, which encode three different transmembrane proteins in the tropomyosin receptor kinase family. *NTRK* fusion have been detected in several solid tumours with an incidence of <1% in NSCLC.[51]

Based on pooled analysis of several phase I and II solid tumour trial, larotrectinib and entrectinib, the first-generation TRK inhibitors, received tumour-agnostic approval by the FDA in 2018 and 2019, respectively, and approval by the NMPA in 2022 and 2023, respectively. The ORR and median PFS of larotrectinib were 73% and 35.4 months, respectively, for *NTRK* fusion-positive lung cancer,[52] which included 8 (40%) Asian patients. The efficacy is similar to the ORR of 79% and median PFS of 28.3 months, respectively, for *NTRK* fusion-positive solid tumours.[53] Entrectinib has also demonstrated durable systemic responses in *NTRK* fusion-positive NSCLC, with an ORR of 81%, and a median PFS of 30.3 months in the subset of Chinese patients with *NTRK* fusion-positive solid tumours from the STARTRK-2 trial.[54]

HER2 *mutation*

HER2 mutations occur in 2–4% of NSCLC patients. The *HER2* exon 20 insertion within tyrosine kinase domain is the most common type.[55] Therapies that target HER2

alterations, including monoclonal antibodies and TKIs, are effective for other cancers, such as breast cancer, but show conflicting results in NSCLC. Recently, promising data have been reported for anti-HER2 antibody-drug conjugates (ADCs).[56] Trastuzumab deruxtecan (DS-8201) was the first approved by the FDA for the treatment of unresectable or metastatic *HER2*-positive breast cancer in 2019. In August 2022, the FDA approved trastuzumab for previously treated patients with *HER2*-mutated metastatic NSCLC based on the results from DESTINY Lung01 and DESTINY-Lung02.[57,58] The updated results from the Asian subgroup analysis of DESTINY-Lung02 trial demonstrated that the ORR in the 6.4 mg/kg and 5.4 mg/kg treatment groups was 73.3% and 50.8%, respectively, and the median PFS was 15.4 months and 10.8 months, respectively, which was generally consistent with the overall population. In August 2023, DS-8201 was approved in Japan for the treatment of *HER2*-positive NSCLC. The approval in Korea and China is not far behind.

Limitations on targeted therapy in Asia still exist. Combination therapy will be widely used in targeted field for NSCLC. However, many targeted agents have only been approved in Asia, there are still significant challenges get indication as combined therapy in the European and American markets. Secondly, most compounds and trial designs are still "me too" style, although a trend towards "me better" seems to appear. There is still a huge gap for original innovative compounds. Standardized use according to NCCN or local guidelines still has a long way to go. Continues efforts have been made in this area to deepen the basic concept of precision treatment at the grassroots level.

New treatment paradigm for lung cancer

With the fast development of targeted therapy, the treatment paradigm for NSCLC patients with a driver gene mutation has shifted from chemotherapy to effective targeted therapy and combination therapy with targeted therapy and chemotherapy. Asian investigators are highly active in perioperative studies. We discuss several trials from 2021 to 2023 that have changed or will change the treatment paradigm in the future for lung cancer patients with early- and advanced-stage disease.

Adjuvant TKIs for early-stage NSCLC

Because the first biomarker-guided, adjuvant targeted therapy CTONG1103 trial achieved positive results for the DFS primary endpoint, many similar clinical trials were performed in Asia, particularly in China.[59–61] The EVIDENCE trial explored the effects of icotinib (a first-generation EGFR-TKI, China only) as adjuvant treatment in stage II-IIIA patients with resected *EGFR*-mutant NSCLC. After a median follow-up of 24.9 months, the median disease-free survival (DFS) was longer in the adjuvant icotinib group (47.0 vs. 22.1 months; $P < 0.0001$).[62] Despite a lack of data on OS, the NMPA approved icotinib as adjuvant treatment for *EGFR*-mutant NSCLC patients after complete resection in June 2021.

The ADAURA trial assessed the effects of osimertinib (a third-generation EGFR-TKI) in stage IB-IIIA patients with resected *EGFR*-mutant NSCLC.[63] Of 682 patients enrolled globally, 159 patients in China were included. The China subgroup analysis reported that osimertinib demonstrated clinically meaningful improvement in DFS in patients with completely resected *EGFR*-mutant NSCLC. The risks of disease recurrence and death were reduced by 77% in patients with stage II-IIIA disease and 71% in the overall Chinese population with stage IB-IIIA disease. The OS data was unmature with 13% maturity after a follow-up of more than 5 years.[64] Osimertinib has been approved by the FDA and 98 other regulatory authorities in the adjuvant setting for patients with resected *EGFR*-mutant stage IB-IIIA NSCLC since 2021.

The ALINA study was the first phase III trial to compare adjuvant alectinib with chemotherapy for patients with completely resected stage IB–IIIA NSCLC with an *ALK* fusion.[65] A subgroup analysis of the ALINA study for 140 Asia patients reported that adjuvant alectinib was associated with clinically meaningful DFS benefit compared with chemotherapy, with a reduced risk of disease recurrence and death of 61% in the ITT population, which is consistent with the global ALINA data.[66] Approval by regulatory authorities should occur soon. Asian investigators made great contributions in the ADAURA and ALINA trials.

New treatments for advanced-stage NSCLC

The FLAURA2 study is a phase III, international, open-label, randomized trial, to compare osimertinib with or without chemotherapy in previously untreated advanced *EGFR*-mutated NSCLC. With a median follow-up of 19.6 months, the median PFS was 29.4 vs. 19.4 months in combined and single agent group (HR = 0.62; $P < 0.001$). Favourable benefit was more significant in the subgroup of patients with brain metastasis and *EGFR* 21L858R mutation. In Asian Chinese and Asian non-Chinese, the HR was 0.49 (95% CI: 0.30–0.81) and 0.76 (0.53–1.09), respectively.[67] Although the successful result of FLAURA2, the editorial by Dr. Wu and Dr. Zhou hold the opinion that the combination is not yet considered to be standard therapy, but it will be a treatment option, especially for brain metastasis.[68]

The phase III MARIPOSA study was a head-to-head comparison of first-line amivantamab plus lazertinib with osimertinib or lazertinib for patients with advanced-stage *EGFR*-mutant NSCLC. After a median follow-up of 22.0 months, the median PFS was longer in the amivantamab plus lazertinib group than in the osimertinib group (23.7 vs. 16.6 months; HR = 0.70; $P < 0.001$).[69] Among Asian patients, amivantamab plus

lazertinib also demonstrated potent effects with a median PFS of 27.5 months compared to 18.3 months in the osimertinib group (HR = 0.65; P < 0.001).[70]

Because resistance to EGFR-TKIs is irreversible, there are many trials exploring immunotherapy-based treatment strategies for oncogene-positive NSCLC patients who progress on prior targeted therapy.[71] Two international trials, CheckMate 722 and KeyNote789, were failures, but two Asian trials (Orient 31 and ATTLAS/KCSG-LU19-04) achieved positive results.[72,73] The Orient 31 trial and the ATTLAS/KCSG-LU19-04 study compared the clinical efficacy of check-point blockers plus bevacizumab and chemotherapy (ABCP) with chemotherapy (PC) in patients with *EGFR*- or *ALK*-mutated NSCLC who failed prior targeted therapy. Orient 31 reported a median PFS of 7.2 months for the four-drug regime compared with 4.3 months for chemotherapy; however, the PFS benefit did not translate to an overall survival benefit.[72] ATTLAS reported that the median PFS was significantly better in the ABCP than PC arm (8.5 v 5.6 months, HR = 0.62, P = 0.004). The PFS benefit increased as PD-L1 expression increased with HRs of 0.47, 0.41, and 0.24 for PD-L1 ≥1%, ≥10%, and ≥50%, respectively. However, the median OS was similar between the ABCP and PC arms (20.6 vs. 20.3 months, HR = 1.01, P = 0.975).[73]

Ongoing lung cancer clinical trials in Eastern Asia

Unresectable stage III NSCLC studies

Patients diagnosed with stage III NSCLC demonstrated high heterogeneity and a 5-year survival rate ranging from 13% to 36%.[74] Stage III NSCLC can generally be classified as resectable or unresectable. In recent years, based on the results of the PACIFIC study, the standard treatment for unresectable stage III NSCLC patients has shifted to immune consolidation therapy following concurrent chemoradiotherapy (cCRT).[75,76] The phase III GEMSTONE-301 study demonstrated that after cCRT or sequential chemoradiotherapy (sCRT), there was an extended median PFS for all patients and patient subgroup.[77] Sugemalimab was approved in China for the treatment of unresectable stage III NSCLC patients with no progression after cCRT or sCRT in June 2022.

However, unresectable stage III NSCLC patients with driver gene mutations appear to have less benefit from maintenance immunotherapy.[78,79] The use of the PACIFIC treatment paradigm should be approached with caution.[80] It remains unclear whether targeted therapy could be applied to consolidation therapy after definitive chemoradiotherapy. The phase III LAURA trial is designed to compare the efficacy of osimertinib vs. placebo as consolidation therapy after chemoradiotherapy in unresectable stage III *EGFR*-mutant NSCLC patients. In China, ongoing clinical trials explore combinations of erlotinib or almonertinib and definitive chemoradiotherapy (NCT03074864 and NCT04951635). A global phase I-III umbrella study (NCT05170204) compares the efficacy and safety of different TKIs with durvalumab in unresectable stage III NSCLC according to biomarker status. We summarized the ongoing trial targets and patients with unresectable stage III NSCLC in Table 2.

With the promising efficacy of novel therapies in lung cancer, it was hypothesized that some portion of unresectable stage III NSCLC tumours could be changed into resectable tumours after induction therapy. Promising data was seen in a phase II trial (NCT04580498) with the use of SHR-1701 alone or plus with chemotherapy as induction therapy followed by surgery or definitive chemoradiotherapy in unresectable stage III NSCLC without driver gene mutation.[81] However, CTONG1103 only provides a MPR of 9.7% after neoadjuvant erlotinib for early-stage EGFR-mutant patients after erlotinib. Thus, it remains unclear if this treatment model is appropriate for patients with driver genes and if immunotherapy is more suitable than targeted therapy. We need to wait to see ongoing trial results, such as that of the LAURA trial.

MRD-related clinical trials

MRD refers to the molecular abnormalities of cancer origin that cannot be detected by conventional imaging (including PET/CT) or laboratory methods after treatment but are detected by liquid biopsy, representing the persistence and clinical progression of lung cancer.[82] Clinical trials on MRD can be mainly divided into two types, one includes trials that use MRD testing as an exploratory objective to assess the value of MRD testing, and the other includes interventional studies that use MRD testing to guide personalized targeted therapy. The tumour-informed approach, such as cancer personalized profiling by deep sequencing (CAPP-Seq) and tagged-amplicon deep sequencing (TAmSeq), is used to detect a single tumour-specific mutation or a limited panel of mutations known to be present in the primary tumour on the basis of prior genomic analysis of resection or biopsy specimens. These methods are more sensitive than non-targeted sequencing approaches, with ctDNA detection limits of <0.01%.[83] We summarized the ongoing trials in Table 3 and Fig. 3.

The Lumpcure I study was the first to define a potential curative localized NSCLC population. It was demonstrated that 96.8% of patients with longitudinal undetectable MRD did not relapse during the follow-up period. Further subgroup analyses reported that patients with undetectable MRD might not benefit from adjuvant therapy.[20] On this basis, the Lumpcure II observational study (NCT05457049) is planned to enrol 180 patients with stage IB-IIIA NSCLC. The primary endpoint is the two-year DFS rate for patients with longitudinal undetectable MRD.[84]

NCT/Name; Start date	Phase	Sample size	Classification; pathology	Agent type	Experimental arm (Control arm)	Primary endpoint	Country
NCT01015443 (INSPIRE); January 2009	III	285 (Actual)	Unresectable; NSCLC	therapeutic cancer vaccine	cCRT → Tecemotide (L-BLP25) + Single low dose cyclophosphamide (cCRT → Saline + Placebo)	OS	Asia
NCT00880971; 2009/2/18	III	394 (Actual)	Resectable (N2); NSCLC	radiotherapy	postoperative radiotherapy after postoperative chemotherapy (postoperative chemotherapy)	DFS	China
NCT03074864 (CTONG1704); 2017/2/27	II/III	90 (Estimated)	Unresectable; NSCLC	EGFR-TKI	erlotinib induction → local radiotherapy → erlotinib maintenance (/)	ORR	China
NCT03521154 (LAURA); 2018/7/19	III	216 (Actual)	Unresectable; NSCLC	EGFR-TKI	cCRT/sCRT → Osimertinib maintenance (cCRT/sCRT → Placebo maintenance)	PFS	Global
NCT04951635; 2021/3/18	III	150 (Estimated)	Unresectable; NSCLC	EGFR-TKI	cCRT/sCRT → Almonertinib maintenance (cCRT/sCRT → Placebo maintenance)	PFS	China
NCT05170204; 2022/11/1	III	121 (Estimated)	Unresectable; NSCLC	ALK-TKI ROS1-TKI RET-TKI	ALK-Positive: cCRT/sCRT → alectinib maintenance ROS 1-positive: cCRT/sCRT → entrectinib maintenance RET fusion-positive: cCRT/sCRT → pralsetinib maintenance (cCRT/sCRT → Durvalumab maintenance)	PFS	Global
NCT04841811 (APPROACH); 2022-6-20	III	192 (Estimated)	Unresectable; NSCLC	EGFR-TKI	Group A: Almonertinib induction → radical therapy (surgery or radiotherapy) → Almonertinib continuous treatment Group B: Almonertinib induction → radical therapy (surgery or radiotherapy) → MRD-guided treatment	ORR, EFS	China
NCT05338619 (PLATINUM); 2022-6-30	II	77 (Estimated)	Unresectable; NSCLC	EGFR-TKI	cCRT → lazertinib maintenance	PFS	Korea
NCT03884192 (CONSIST); 2018/12/12	III	162 (Estimated)	Unresectable; NSCLC	PD-1 inhibitor	cCRT → Sintilimab maintenance (cCRT → Observation)	PFS	China
NCT03728556 (GEMSTONE301); 2018/10/26	III	381 (Actual)	Unresectable; NSCLC	PD-L1 inhibitor	cCRT/sCRT → sugemalimab maintenance (cCRT/sCRT → Placebo maintenance)	PFS	China
NCT04325763; 2020/5/27	III	315 (Estimated)	Unresectable; NSCLC	PD-L1 inhibitor	Arm1: cCRT/sCRT → TQB2450 + Anlotinib maintenance Arm2: cCRT/sCRT → TQB2450 maintenance (cCRT/sCRT → Placebo maintenance)	PFS	China
NCT05157776; 2021/10/28	III	72 (Estimated)	Resectable; NSCLC	PD-1 inhibitor	Neoadjuvant Sintilimab + chemotherapy (4 cycles) before surgery (Neoadjuvant Sintilimab + chemotherapy (2 cycles) before surgery and adjuvant Sintilimab + chemotherapy (2 cycles, optional) after surgery)	pCR rate	China

cCRT, concurrent chemo-radiotherapy; EFS, event-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PFS, progression free survival; sCRT, sequential chemo-radiotherapy.

Table 2: **Clinical trials for resectable and unresectable stage III disease.**

Using MRD testing to guide personalized targeted therapy is under exploration in trials for oncogene-mutant NSCLC.[85] Chinese investigators have designed two innovative clinical trials for *EGFR*-mutant NSCLC, FATES and APPROACH. FATES is a phase II trial (NCT05536505) enrolling stage IB-IIIB NSCLC patients who receive peripheral blood MRD assessment within one week and one month after surgery followed by MRD assessment every 12 weeks. Adjuvant EGFR-TKI treatment or a drug holiday period would be dynamically determined by the MRD status.[86] The phase III APPROACH trial (NCT04841811) was the first designed to evaluate the efficacy and safety of almonertinib (a third-generation EGFR-TKI) induction therapy in *EGFR*-mutated patients with unresectable stage III NSCLC, and to evaluate the efficacy of dynamic MRD-guided maintenance therapy with almonertinib after local therapy (radical surgery or radiotherapy) determined by muti-disciplinary treatment discussion.[87] There are also studies on MRD-guided therapy in advanced NSCLC. In a de-escalation study, an exploratory component of the CTONG1602 trial (NCT03046316), patients with stage IIIB or IV *EGFR*-mutant oligo-residual disease were screened for MRD after local consolidative therapy following first-line targeted therapy, and the preliminary result reported that "drug holiday" based on MRD status was feasible for these patients.[22]

Clinical trial designs in personalized medicine

Rapid advances in precision oncology pose a challenge when designing clinical trials. Multiple innovative and flexible trial designs, including basket trials, umbrella trials, platform trials, and patient-centric trials, have been adopted in drug development, serving better acceleration of drug assessment and approval.[88]

Umbrella trials evaluate multiple treatments according to biomarker subsets for a single histology, which help to provide a concurrent evaluation of the efficacy of multiple distinct treatment regimens for a specific tumour type. Basket trials, identified as tissue-agnostic trials, assess the same treatment regimen across cancer types based on the same genetic variation. Platform trials are defined as randomized, adaptive trials, potentially without a scheduled termination date, making it

NCT (Name)	Title	Study Type (Phase)	Pathology	Sample size	Clinical stage	Primary endpoint	Country
NCT05079022	ctDNA-MRD based adjuvant targeted therapy in *EGFR* mutation-positive stage I lung adenocarcinoma patients after complete surgical resection	Interventional (Phase I/II)	*EGFR* Positive LUAD	50	I	Clearance of ctDNA at 6 months	China
NCT05536505 (CTONG2105/ FATES)	Adjuvant treatment based on MRD for resectable non-squamous NSCLC with *EGFR* mutations	Interventional (Phase II)	*EGFR* Positive nsq-NSCLC	180	IB–IIIB	DFS, 3 yeas DFS rate	China
NCT04841811 (APPROACH/ CTONG2101)	Effectiveness and safety of dynamic MRD guiding treatment after aumolertinib induction therapy of *EGFR*-mutation-positive unresectable stage III NSCLC in the MDT diagnostic model: an open-label, multicentre, randomized, Phase III Study	Interventional (Phase III)	*EGFR* Positive NSCLC	192	III	ORR, EFS rate	China
NCT04385368 (MERMAID-1)	A phase III, randomized, multicentre, double-blind, placebo-controlled study to determine the efficacy of adjuvant durvalumab in combination with platinum-based chemotherapy in completely resected stage II–III NSCLC	Interventional (Phase III)	NSCLC	332	II–III	Current: DFS in FAS; Primary: DFS in MRD+ analysis set	Global
NCT04642469 (MERMAID-2)	A phase III, randomized, multicentre, double-blind, placebo-controlled study of durvalumab for the treatment of stage II-III NSCLC patients with MRD following surgery and curative intent therapy	Interventional (Phase III)	NSCLC	284	II–III	Current: DFS in all randomized patients; Primary: DFS in PD-L1 TC $\geq$ 1%	Global
NCT05460195	Sintilimab combined with anlotinib for perioperative NSCLC based on MRD evaluation	Interventional (Phase II)	NSCLC	42	II–IIIA	MPR	China
NCT05286957 (Seagull)	MRD-guided adjuvant tislelizumab and chemotherapy in resected Stage IIA-IIIB NSCLC: a randomized controlled phase II study	Interventional (Phase II)	NSCLC	60	IIA–IIIB	Current: 2-year PFS rate; Primary: Percentage of patients changed from MRD+ to MRD- after treatment with 8 cycle Tislelizumab	China
NCT04976296 (NOTICE)	Dynamic MRD detection in stage I–IIIA NSCLC after radical resection	Observational	NSCLC	300	I–IIIA	The prognostic value of MRD	China
NCT05167604	Utility of ctDNA in predicting whether giving adjuvant chemotherapy in patients with stage IB–IIA resected NSCLC	Observational	NSCLC	150	IB–IIA	3-year DFS rate	China
NCT05441566	Dynamic monitoring and significance of MRD after surgery in driver gene-positive and driver gene-negative stage IB–IIA NSCLC	Observational	NSCLC	60	IB–IIA	Changes in ctDNA levels after surgery 2 years	China
NCT05457049 (CTONG 2201/ LUMPcure II)	Dynamic observational strategy for stage IB–IIIA NSCLC after complete resection based on longitudinal undetectable MRD: prospective, multicentre, single-arm study	Observational	NSCLC	180	IB–IIIA	2-year DFS for patients with longitudinal undetectable MRD	China
NCT06081777	A study evaluating MRD biomarker in patients with potentially resectable Stage III NSCLC	Observational	NSCLC	65	III	DFS	China
NCT05822284	The role of dynamic ctDNA-MRD testing in stage IIIB–C oncogene-negative NSCLC patients treated with induction chemoimmunotherapy in the MDT model of diagnosis and treatment	Observational	oncogene-negative NSCLC	50	IIIB–C	Predicting PFS, pCR, OS	China
NCT05965024 (LungMate016)	Exploration on the value of MRD based on ctDNA detection in predicting recurrence of resected NSCLC	Observational	NSCLC	377	IB–IIIB	2-year RFS rate	China

ctDNA, circulating tumour DNA; DFS, disease-free survival; MRD, molecular residual disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PFS, progression free survival; RFS, recurrence-free survival.

Table 3: **MRD-related clinical trials for early-stage NSCLC.**

possible to assess several treatments in a single pathology.[89] Expanding or terminating study arms while a trial is running is allowed according to pre-established rules. The design of platform trials is highly variable, bringing faster results at lower cost. There are many successful examples for these novel clinical trial design, such as the Lung-MAP trial led by the US National Cancer institute,[90] the CLUSTER trial in China, the CTONG1702 trial in China,[91–93] the LC-SCRUM trial in Japan and the National Lung Matrix Trial (NLMT) in the United Kingdom.[94]

In recent years, patient-centric clinical trial (PCT) proposed a design scheme that prioritizes the needs of patients of all stages in clinical trials, which helps to further accelerate the advancement of precision therapy.[95,96] In a patient-centric phase II trial, consisting of a criteria-fulfilled (CF) cohort and a compassionate use (CU) cohort under expanded eligibility criteria, and a prospective real-world study (RWS), 48 treatment-naive patients with advanced *HER2*-mutant NSCLC received pyrotinib (CF and CU cohorts) or physician's therapy of choice (RWS cohort). This study was the first to demonstrate the feasibility of a PCT design for NSCLC patients with rare genetic alteration, which should be encouraged in future trials for rare diseases.[92] Based on these results, another ongoing patient-centric phase II

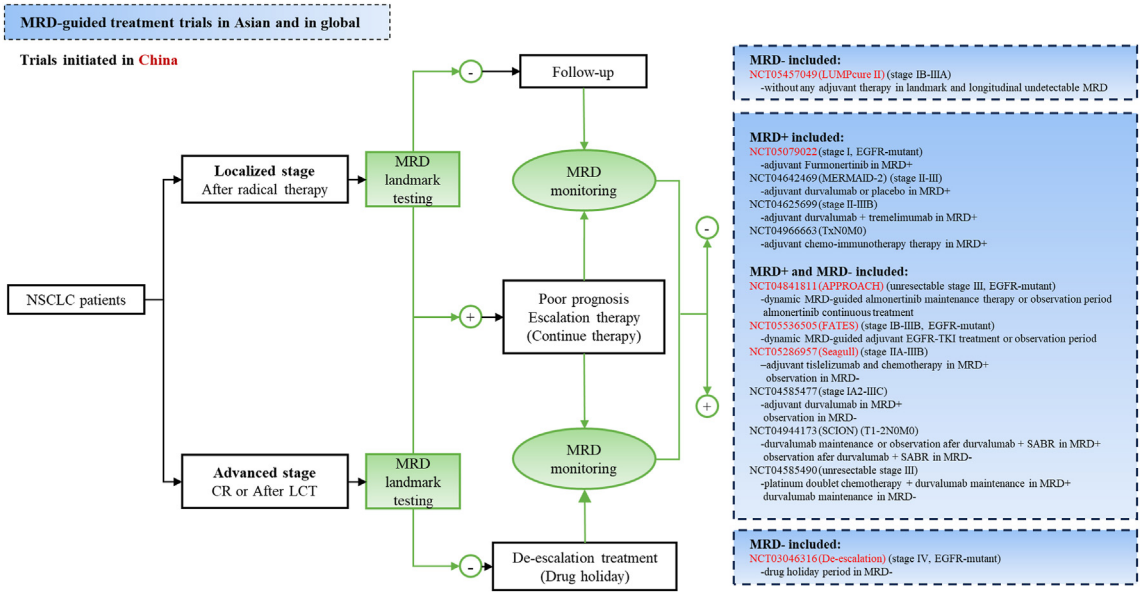

Fig. 3: Ongoing clinical trials using MRD as an exploratory objective or to guide personalized targeted therapy.

trial (CTONG2201/NCT06092086) was initiated in China to assess the effectiveness and safety of lorlatinib monotherapy in the three aforementioned cohorts as the first-line treatment in patients with advanced *ALK*-positive NSCLC.[97] This design created an efficient idea for the comprehensive collection of clinical data of patients with rare genetic alterations, and the exploration of the most reasonable treatment plan.

Novel agents with high potential to change clinical practice

In addition to phase III studies, some phase I and II trials with novel drugs have presented promising preclinical data or limited clinical outcome. Bispecific antibodies have specific constructs that recognize two epitopes or antigens, and these are aimed at improving clinical efficacy and drug tolerance. This modality is regarded as a new generation of cancer treatment, with the prospect to significantly improve the prognosis of cancer patients.[98]

Zenocutuzumab, is a HER2xHER3 bispecific antibody, that has been shown to be effective for tumours driven by NRG1 gene rearrangements in preclinical data. This drug inhibits HER3 and AKT phosphorylation, induces the expression of apoptosis markers, and inhibits tumour growth.[99] At the 2023 ESMO, data of zenocutuzumab efficient from an ongoing pivotal phase II study were released. The confirmed ORR was 34% (22/64; 95% CI 23–47), and 78% (50/64) of patients had target lesion reduction. The median DOR was 12.9 months with responses ongoing in 50% (11/22) of patients. Among 85 patients treated with zenocutuzumab, Grade ≥ 3 TRAEs occurred in <4% of patients, and no patients discontinued the drug for a TRAE.[100]

The technology developed for ADC drugs by Japanese companies, is currently attracting global attention. The ADCs have become a new therapeutic approach to overcome resistance to EGFR-TKIs. The HERTHENA-Lung01 study is an international, multicentre, open-label, phase II trial aimed at evaluating the safety and efficacy of Patritumab Deruxtecan (HER3-DXd, a type of HER3 ADC) in treating *EGFR*-mutated advanced NSCLC patients who have disease progression on previously received EGFR-TKI and platinum-based chemotherapy. Asians contributed 46.7% of the enrolment. The confirmed ORR was 29.8%. The median PFS was 5.5 months and the median OS period was 11.9 months.[101] According to BICR assessment, an intracranial ORR was 33.3% in a subgroup of 30 patients with baseline brain metastases. The results indicated that HER3-DXd is a promising therapeutic approach to overcome EGFR-TKI resistance and HERTHENA-Lung02, a phase III study is ongoing.[102]

The TROPION-Lung01 study is the first phase III study for ADC drug in the field of lung cancer, aimed at evaluating the efficacy and safety of Dato-DXd (a type of TROP2 ADC) monotherapy compared to docetaxel in previously treated advanced NSCLC patients with or without targeted genomic alterations (AGA).[103] 2023 ESMO ASIA showed that in the ITT population, Dato-DXd monotherapy significantly improved median PFS compared to docetaxel (4.4 months vs. 3.7 months; HR = 0.75, 95% CI 0.62–0.91, P = 0.004), and the confirmed ORR of Dato-DXd group was nearly doubled compared to the docetaxel group (26.4% vs. 12.8%). The median DOR was 7.1 months and 5.6 months, respectively. Asians contributed 46.7% of the enrolment in the

TROPION-Lung01 study. The TROPION-Lung05 study is a single arm, open-label phase II study, to evaluate the efficacy and safety of Dato-DXd in advanced NSCLC patients with positive driver gene mutation who have progressed on at least one line of targeted therapy and platinum-based chemotherapy.[104] Of 137 patients enrolled globally, 66 were from Asia with the ORR of 42.4% and the DCR of 80.3%. The median PFS was 5.4 months, and the median DOR was 4.4 months. Efficacy seems to be better in EGFR mutant subgroup with a ORR of 48.9%.[105] All of these provide a solid evidence-based foundation for further research on Dato-DXd in the field of NSCLC.

Regulatory authorities for drug approvals in Eastern Asia

Regulatory approval processes in China, Korea, and Japan

Drug approval processes for different types of compounds can vary by country in Eastern Asia, including the NMPA for China, MHLW for Japan, and MFDS for Korea, but there are general similarities in the steps involved. The regulatory approval process always involves preclinical studies, clinical trials (phase I, II, and III), and submission of a new drug approval application to the regulatory authorities.[106] In China, the drug approval should evaluate toxicity and efficacy in phase I to phase III clinical trials. In recent years, China has been working on streamlining its drug approval process and has implemented reforms to accelerate the approval timeline. The acceptance of global clinical trial data has been increasing, making it somewhat easier for multinational pharmaceutical companies to conduct global clinical trials and seek approval in China based on international data.[107]

In Japan, the drug approval process is relatively complex and is the responsibility of the PMDA and MHLW.[108] The combination of stringent clinical data requirements, unique regulatory standards, and a focus on post-marketing surveillance contributes to the complexity of the drug approval process in Japan.[108] Because drug approval is linked to national health insurance reimbursement,[109] Japan tends to have a rigorous and conservative regulatory approach, emphasizing the need for thorough safety and efficacy data from trials conducted within the country. However, Japan has recently set to overhaul its regulations for clinical trials for new drugs developed overseas.

New drug approval process in South Korea is relatively streamlined. Traditionally, local clinical trial data have been required for approval. However, recently, South Korea has been making an effort to expedite its regulatory processes but may still have a more conservative approach compared to China.

In general, the new drug approval process in all three countries includes drug clinical trials and application materials review, but the specific approval process and institutions are different.

As precision medicine continues to evolve, the need for robust ethical guidelines and regulatory frameworks will become more apparent. Striking a balance between innovation and safeguarding patient rights and privacy will be crucial. Governments and regulatory bodies are likely to play an active role in developing and enforcing ethical standards in the field.

Important progress made by regulatory authorities in Eastern Asia

Cooperation and exchange among Asian regulators, the European Medicines Agency (EMA) and the US FDA are becoming increasingly important in the global drug approval process. These collaborations aim to facilitate the exchange of scientific and technical information, harmonize regulatory standards, and streamline drug approval procedures. Several important measures have significantly improved and accelerated the drug approval process, including the following:

Participating in the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)

The International Coordination Meeting was developed for harmonized guidance on technical issues to ensure the development and registration of high-quality, safe and effective medicines in the most efficient and cost-effective manner. Since its inception in 1990, ICH has gradually evolved in response to the growing globalization of the pharmaceutical industry.[110] ICH brings together regulatory agencies and the pharmaceutical industry to develop uniform guidelines for drug quality, safety and effectiveness. Increasing numbers of national regulators are joining the ICH and applying ICH guidelines, which provides a framework for regulatory standards accepted in many countries, including countries in Asia, Europe, and the United States. This harmonization has greatly facilitated the global development and registration of medicines. China and other Eastern Asian countries have growing involvement in global health and managing processes of change.[111]

Cooperation and mutual trust in drug inspection between national regulators

National regulatory agencies have reached a Mutual Recognition Agreement (MRA) to recognize the results of drug quality supervision inspections conducted by their regulatory counterparts within their respective countries, achieving mutual recognition of inspections and avoiding duplicate inspections. MRA is a trade agreement aimed at promoting market access and encouraging more international coordination of compliance standards while protecting consumer safety, which benefits regulatory agencies by reducing duplicate inspections within each other's borders.[112]

MRAs between regulatory agencies allow for mutual recognition of inspections and regulatory decisions, reducing duplicate work and accelerating the approval process. For example, the EMA has signed an MRA with Japan.

Participating in information sharing and collaboration

The International Coalition of Medicines Regulatory Authorities (ICMRA) is composed of 29 drug regulatory agencies from countries and regions such as the United States, the European Union, Japan, Canada, Australia, and the United Kingdom. China's drug regulatory authorities became a member in 2015. ICMRA is a new international cooperation mechanism positioned at the level of heads of drug regulatory agencies in various countries. The purpose of ICMRA is to strengthen strategic planning, innovate regulatory measures, improve the management efficiency of international cooperation, effectively utilize resources, promote drug regulatory cooperation, and promote regulatory mechanism convergence throughout the entire lifecycle of drugs. The ICMRA actively promotes regulatory mutual trust, believing that through regulatory mutual trust, management procedures can be optimized, duplicate work can be minimized, the regulatory capabilities of various countries can be strengthened, national and international health systems and drug supply can be improved, and the public can accelerate access to high-quality drugs with favourable cost-effectiveness ratios.

Add priority review and fast track channels

Similar to the EMA and FDA, priority review projects and fast track channels for innovative drugs to address unmet medical needs, rare diseases, and public health emergencies in some countries of Eastern Asia have been established. These projects aim to accelerate the evaluation and approval of important therapies, enabling patients to obtain new therapies earlier. These measures have greatly improved the drug approval process and accelerated approval speed by promoting the convergence of regulatory requirements, promoting collaboration, and accelerating the review and approval of innovative drugs. Therefore, patients can benefit from timely access to new effective therapies while maintaining high standards of safety and quality.

Important progress on drug accessibility and reimbursement

Some general measures by regulatory authorities in Eastern Asia may have been taken or considered to address the difficulties on drug accessibility and reimbursement, such as drug price controls, health insurance reforms and generic medicines encouragement. National Healthcare Security Administration (NHSA) plays a crucial role in overseeing China's healthcare system, including drug reimbursement policies, drug prices regulation and cost-effective healthcare promotion. In Japan and Korea, the health insurance system, which covers the majority of the population, plays a central role in ensuring drug accessibility. The system is characterized by a universal health insurance scheme that provides coverage for various medical services, including prescription medications.

Perspectives and conclusion

Targeted therapy based on precision medicine in Asia stands at a breakthrough point poised for even greater advancements in the coming years. Several key factors contribute to the promising future prospects in the region. In the future, genomic sequencing including DNA, RNA, and methylation sequencing will be widely used and provide researchers and clinical practitioners with a rich resource for studying genetic variations, understanding disease mechanisms, and tailoring treatments. Advancements in molecular biomarkers will lead to the development of novel therapeutic modalities. Tailored treatment plans based on individual molecular profiles will become more commonplace, improving treatment efficacy while minimizing adverse effects. Liquid biopsy for MRD monitoring is promising for clinical practice to realized adaptive de-escalation treatment and the trial design.

For perspective trials, more and more unique driver gene alterations will be discovered. With increased understanding of rare genetic disorders and the development of targeted therapies, individuals with previously untreatable conditions may find new hope through personalized and effective interventions. The future of precision medicine will witness a paradigm shift towards increased patient engagement. Empowered by personalized health information, individuals will actively participate in decision-making processes regarding their healthcare. This shift is expected to result in more patient-centric approaches, emphasizing preventive strategies and lifestyle interventions.

International collaborations and knowledge-sharing initiatives are likely to expand. Collaborative efforts will accelerate the pace of research, allowing for the pooling of resources, expertise, and diverse datasets, decreasing disparity in Asian countries, which ultimately benefits patients worldwide. As precision medicine continues to evolve, the need for robust ethical guidelines and regulatory frameworks will become more apparent. Striking a balance between innovation and safeguarding patient rights and privacy will be crucial. Governments and regulatory bodies are likely to play an active role in developing and enforcing ethical standards in the field.

In conclusion, the future of targeted therapy and research in Asia holds immense promise. The synergy of technological advancements, collaborative efforts, ethical considerations, and a patient-centric approach will propel the field forward, ultimately reshaping the landscape of healthcare delivery and improving outcomes for individuals across the region and beyond.

Search strategy and selection criteria.

References for this review were identified through searches of PubMed, Scopus, and Web of Science from January 2010 and December 2023, with the terms of "targets", "targeted therapy", "targeted drugs", "precision medicine", "drug approval", "next-generation sequencing", and "lung cancer". We did not restrict our search by language, but restrict the research from the Eastern Asia region. Articles were also identified through searches of the authors' own files. All studies meeting the following criteria were included in the current review: 1) studies conducted on or involved Eastern Asian participants; 2) studies focused on the drug development and evidence for lung cancer targeted therapy in Eastern Asia; 3) published in peer-reviewed journals or conference proceedings. The general exclusion criteria were: 1) not relate to targeted therapy in lung cancer; 2) not about Eastern Asian population; 3) unavailable full texts or not a peer-reviewed research article or review, except for conference abstract reporting the updated results of clinical trials.
We also searched clinical trial. gov for ongoing studies as of December 2023, with the terms "unresectable stage III", "resectable stage III", "molecular residual disease", "umbrella trial", "basket trial", and "lung cancer". We included ongoing trials about evidence for lung cancer targeted therapy in Eastern Asia. Clinical trials were excluded if they studied not related to our topic, or if they lacked sufficient regional relevance. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Contributors

The authors conceived and designed the detailed outline: Yi-Long Wu, Yangqiu Li, Myung-Ju Ahn, Hidehito Horinouchi and Si-Yang Maggie Liu; the authors directed and performed the literature search and data collection: Si-Yang Maggie Liu, Zhen-Yi Jin, and Jia-Yi Deng; the authors complete the figures and tables: Si-Yang Maggie Liu, Jia-Yi Deng and Si-Min Zhong. All authors were involved in writing, revision, and critical review of the article, and have approved the submitted version.

Declaration of interests

Prof. Yi-Long Wu reports grants and personal fees from AstraZeneca, BMS, Pfizer; and personal fees from Boehringer Ingelheim, Eli Lilly, Hengrui, MSD, Sanofi, Roche, outside the submitted work. Prof. Hidehito Horinouchi reports grants from AstraZeneca, Roche/Chugai, MSD, Abbvie, BMS/Ono and Daiichi-Sankyo; and personal fees from AstraZeneca, Roche/Chugai, MSD, BMS/Ono and Abbvie. The other authors have no competing interests to declare.

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