Deutsche Bank
Research

Rating
Buy

Asia
China

Health Care
Pharmaceuticals / Biotechnology

Company
TYK Medicines

Reuters	Bloomberg	Exchange	Ticker
2410.HK	2410 HK	HSI	2410

Date
16 May 2025

Initiation of Coverage

Price at 15 May 2025 (HKD)	25.40
Price target - 12mth (HKD)	31.60
52-week range (HKD)	55.50 - 13.70
Unavailable	23,453

Incubating strategically differentiated small-molecule drugs. BUY

Valuation & Risks

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Initiate with BUY and PT of HK$31.6. Core Product and potential blockbuster, Asandeutertinib (TY-9591, KARDORISSO) is a differentiated third-generation EGFR-TKI for advanced EGFR mutated non-small cell lung cancer (NSCLC) treatment, which is expected to start generating revenue in 2026E. We believe the product could rapidly gain market share through addressing unmet medical needs. Our PT is based on 10-year DCF model (WACC: 12.2%, terminal growth: 1.5%).

Risks: (1) Delay or failure in developing pipeline candidates, (2) market acceptance of products, (3) intensifying market competition, (4) pricing pressure from government guidance, (5) lack of experience in commercialization of products, (6) intellectual property rights, (7) potential government supportive policies, (8) expanding into new markets, (9) potential collaboration agreements

Demonstrated improved efficacy over Osimertinib in NSCLC patients with brain metastases. The Company recently announced that it has submitted a Pre-NDA (Pre-New Drug Applicationton) the Center for Drug Evaluation (CDE) of National Medical Products Administration (NMPA) in China for Asandeutertinib (TY-9591) and the Company expects the drug to become the world's first 3rd generation EGFR TKI targeting NSCLC patients with brain metastases. The submission is based on results of TYKM1601202 study (ESAONA), which aimed to evaluate the efficacy and safety of asandeutertinib compared to osimertinib in first-line treatment of NSCLC patients with brain metastases. As of this submission, the study has enrolled 224 NSCLC patients with EGFR-sensitive mutations and brain metastases. The results showed that asandeutertinib demonstrated a superior intracranial objective response rate (assessed by IRC) compared to Osimertinib, the primary endpoint of the study. Additionally, the drug exhibited good safety and tolerability, with no new safety risks identified.

Detailed study data is included in an oral presentation session of the upcoming ASCO meeting on 30 May. (A phase II study of asandeutertinib (TY-9591) in advanced NSCLC patients with EGFR-positive mutations and brain metastases).

Strategically focused on lung cancer and CDK inhibitors. The Company's research and development of pipeline products focuses on two aspects: (1) developing a portfolio of differentiated therapies to treat lung cancer patients with different driver gene mutations and resistance mechanisms; and (2) CDK inhibitors, with the potential to treat oncology indications.

Executive summary

TYK Medicines is a clinical-stage biopharmaceutical company committed to the discovery, development and commercialization of differentiated targeted therapies to address unmet medical needs in cancer treatment. TYK Medicines is currently conducting a pivotal Phase II clinical trial of TY-9591 monotherapy as first-line treatment of brain metastases from epidermal growth factor receptor ("EGFR") mutated non-small cell lung cancer ("NSCLC") in China, as well as a registrational Phase III clinical trial of TY-9591 monotherapy as first-line treatment in locally advanced or metastatic NSCLC with EGFR L858R mutation in China.

Since its inception in 2017, the Company has built a pipeline with 11 drug candidates, including Core Product TY-9591, Key Product TY-302, its internally developed Key Product TY-2136b, four other innovative clinical products and four products in preclinical stage.

Figure 1: Drug candidates of TYK Medicines

	Product[1]	Target	Indication	Regimen	Preclinical / IND-Enabling / Ph I/Ia / Ph Ib/II / Pivotal/ Registrational Ph II/Ph III	Current Status/ Upcoming Milestone	Commercial Rights/Partner
Clinical Stage	★ TY-9591	3rd-Generation EGFR-TKI	NSCLC with brain metastasis (1L)	Mono	Pivotal Phase II trial ongoing in China	NDA submission in Q2 2025	China
			EGFR L858R LC (1L)	Mono	Registrational Phase III trial ongoing in China	NDA submission in 2026	
			NSCLC (1L)	Combo	Phase II trial ongoing in China	Ph II ongoing	
	☆ TY-302	CDK4/6	Breast cancer (2L+)	Combo	Phase II trial ongoing in China	Enter Registrational Trial in 2026	China
			Prostate cancer (1L)	Combo	Phase II trial ongoing in China	Enter Ph II in Q2 2025	
	☆ TY-2136b	ROS1/NTRK	ROS1/NTRK-mutant solid tumor	Mono	Phase Ib study ongoing in China	Ph Ib ongoing	Livzon (Greater China)[2]
			ROS1/NTRK-mutant NSCLC	Mono	Phase I trial ongoing in the U.S.	Ph I ongoing	Ex-Greater China
	TY-2699a	CDK7	Breast cancer, Pancreatic cancer, Head and neck squamous cell carcinoma	Mono/Combo	Phase Ib/II trial ongoing in China	Ph Ib/II ongoing	Global
					IND approval in the U.S.	IND approved	
	TY-0540	CDK2	Breast cancer, Ovarian cancer, Metastatic castration-resistant prostate cancer	Mono/Combo	Phase Ia/Ib trial ongoing in China	Ph Ib/II ongoing	Global
					IND approval in the U.S.	IND approved	
	TY-1091	RET	RET-fusion positive solid tumor, RET-mutation medullary thyroid cancer	Mono	Phase I trial ongoing in China	Ph I ongoing	Global
					IND approval in the U.S.	IND approved	
	TY-4028	EGFR Exon 20	EGFR exon 20 insertion NSCLC	Mono	IND approval in China	IND approved	Global
					IND approval in the U.S.	IND approved	
	TY-1054	YAP-TEAD	Solid tumor	-	IND approval in China	IND approved	Global
					IND approval in the U.S.	IND approved	
Preclinical Stage	CDK4	CDK4	Solid tumor	-		Enter IND-enabling in 2025	Global
	EGFR (PROTAC)	EGFR (PROTAC)	NSCLC	-		Enter IND-enabling in 2025	Global
	PI3Kα	PI3Kα	Solid tumor	-		Enter IND-enabling in 2026	Global
	CDK4/2	CDK4/2	Solid tumor	-		Enter IND-enabling in 2026	Global

★ Core Product ☆ Key Product

Abbreviations: 1L = first line; 2L+ = third- or later-line; EGFR = epidermal growth factor receptor; CDK = cyclin-dependent kinase; ROS1 = ROS proto-oncogene 1; NTRK = neurotrophic tyrosine receptor kinase; RET = rearranged during transfection; YAP = yes associated protein; TEAD = transcriptional enhanced associate domain; PROTAC = proteolysis-targeting chimera; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; TNBC = triple-negative breast cancer; Ph = Phase; NDA = new drug application; 2H = second half; Q1 = first quarter.

Note: (1) The relevant intellectual property rights for TY-9591 and TY-302 were acquired from Changzhou Runnuo and Guangzhou Boji, and Tetranov Pharmaceutical, respectively. TYK Medicines has developed these two drug candidates at their own costs since preclinical stage. Except for these two drug candidates, all other drug candidates were internally discovered and developed by the Company.
(2) TYK Medicines has out-licensed the rights to develop, manufacture and commercialize TY-2136b in the Greater China to Livzon. The Comany maintains the rights to develop and commercialize this drug candidate in the rest of the world.

Source: Company data

An improved third-generation EGFR-TKI (TY-9591) to address significant market demand

EGFR is the most common driver of gene mutation in NSCLC, accounting for 50.2% of non-small cell lung cancer (NSCLC) incidence in China in 2023, according to Frost & Sullivan. As EGFR-TKI has become the dominant treatment option for EGFR

mutation-positive patients with NSCLC, the EGFR-TKI market in China increased at a CAGR of 29.3%, from RMB3.1 bn in 2017 to RMB14.5bn in 2023, and it is forecast to grow further to reach RMB20.1bn and RMB28.4bn in 2027 and 2033, respectively, according to the same source.

TY-9591 was modified by H/D exchange of Osimertinib, the top-selling EGFR-TKI globally, according to Frost & Sullivan. The product not only retains the advantages of Osimertinib, but it also shields metabolic soft-spots of Osimertinib, resulting in a potentially broadened therapeutic window. A higher dose of TY-9591 can therefore be administered to patients to achieve improved efficacy, leading to a higher level of blood-brain entry. Due to the potential better efficacy over existing EGFR-TKIs, the Company is progressing via:

(1) a pivotal Phase II clinical trial of TY-9591 monotherapy as a first-line treatment in brain metastases from EGFR-mutated NSCLC, for which TYK Medicines expects to complete patient enrollment in the third quarter of 2024 and submit an application to the NMPA for conditional marketing approval in 2Q25.

(2) a registrational Phase III clinical trial of TY-9591 monotherapy as a first-line treatment in locally advanced or metastatic NSCLC with EGFR L858R mutation, for which TYK Medicines expects to complete patient enrollment in the fourth quarter of 2024 and submit a NDA in the second half of 2026.

(3) TYK Medicines applied for and obtained the IND approval for conducting Phase II and Phase III clinical trials of TY-9591 in combination with chemotherapy as first-line treatment in EGFR mutated advanced or metastatic NSCLC in March 2024. The Company started the preparation for Phase II trial in November 2024 and officially initiated the site in February 2025. The Company expected to complete the patient enrollment for the Phase II trial in 2H25, and to communicate with CDE for confirmatory clinical study in the 1Q26.

Strategically focused on lung cancer and CDK inhibitors

The Company's research and development of pipeline products focus on two aspects, to develop: (i) products that can improve the outcome of lung cancer, which is a cancer that involves significant medical needs, and (ii) products that aim to better explore the mechanism of action of inhibitors of the CDK family in cancer treatment.

Lung cancer therapies: In addition to TY-9591 mentioned above, the Company is developing a portfolio of differentiated therapies to treat lung cancer patients, with different driver gene mutations and resistance mechanisms, targeting some of the key kinases, including EGFR, ROS1, NTRK and RET:

(1) **TY-2136b, one of the Company's key products, is an internally developed, oral ROS1/NTRK inhibitor for the treatment of solid tumors.** The Company's current primary focus lies in NSCLC with ROS1 or NTRK mutation, a demographic estimated to reach 56.2 thousand new cases worldwide in 2033, according to Frost & Sullivan.

TY-2136b has demonstrated an encouraging safety profile in preclinical trials. Its preliminary efficacy against ROS1 and NTRK mutations has been demonstrated across multiple animal models, showcasing its potential to

address drug resistance against existing ROS1/NTRK drugs. In September 2023, TYK Medicines received the Orphan Drug Designation of TY-2136b from the FDA. With FDA's IND approval in November 2021, TYK Medicines is currently conducting a Phase I trial of TY-2136b in the US. TYK Medicines has out-licensed the rights to develop, manufacture and commercialize TY-2136b in the Greater China to Livzon. Currently, Livzon is conducting a Phase Ib clinical trial of TY-2136b in China.

(2) TY-4028. EGFR exon 20 insertion TKI. According to Frost & Sullivan, approximately 7.7% EGFR-mutated NSCLC patients have EGRFR exon 20 insertion. Patients with exon 20 insertion mutations are associated with primary resistance to targeted EGFR-TKIs and correlate with a poor patient prognosis. TY-4028 presents an innovative, targeted therapy for this specific subset of NSCLC patients. The Company received IND approvals from both the FDA and NMPA in April 2023 and June 2023, respectively. TYK Medicines plans to initiate a Phase I trial of TY-4028 in NSCLC with exon 20 insertion mutation in China in 2024.

(3) TY-1091. RET inhibitor. The drug is intended for the treatment of advanced NSCLC with RET gene fusion, advanced MTC with RET mutation and other advanced solid tumors with RET alterations. TYK Medicines received IND approvals from both the FDA and NMPA in August 2022 and December 2022, respectively. TYK Medicines is currently conducting a Phase I clinical trial of TY-1091 in RET fusion-positive solid tumors in China.

Pipeline targets CDK family: TYK Medicines has built a pipeline of innovative CDK inhibitors, with potential as monotherapies or combination therapies to treat oncology indications including lung cancer, breast cancer and prostate cancer, with the aim of tackling clinical pain points and addressing unmet needs.

(1) TY-302. CDK4/6 inhibitor. TY-302, one of the Company's key products, is a potent, selective oral CDK4/6 inhibitor developed for the treatment of breast cancer and prostate cancer. Based on preliminary safety data collected through the Company's current Phase I/II clinical trial in breast cancer, TY-302 achieved an improved safety profile with regard to adverse events (AEs) in general. In addition, TY-302 has achieved encouraging efficacy in breast cancer. TYK Medicines observed that TY-302 achieved a disease control rate (DCR) of 71.4 % among the 14 recruited breast cancer patients who had failed the two or more lines of treatments.

TYK Medicines also plans to commence a Phase II clinical trial of TY-302 in prostate cancer in the 1H25, exploring TY-302 in combination with Abiraterone for the treatment of mCRPC, an advanced prostate cancer that is challenging to treat, with no response to the standard-of-care treatment, endocrine therapy.

(2) TY-0540, a novel selective CDK2/4/6 inhibitor intended for the treatment of advanced/metastatic solid tumors. According to Frost & Sullivan, approximately 20% of patients exhibit primary resistance to CDK4/6 inhibitors, rendering initial therapy ineffective, while others develop resistance within approximately 25 months. Once resistance occurs, treatment options often entail higher toxicity and limited clinical benefit, such as mammalian targeting of rapamycin inhibitors, leading to the emergence of CDK2/4/6 inhibitors as a novel therapeutic avenue to curb

cancer cell proliferation. In preclinical studies conducted on mouse models, TY-0540 exhibited excellent tolerance of up to 40mg/kg (BID) and displayed preliminary efficacy in breast cancer and pancreatic cancer at this dosage level. TYK Medicines received IND approvals from the FDA and NMPA in June 2023 and September 2023, respectively. TYK Medicines is currently conducting a Phase I clinical trial of TY-0540 monotherapy or combination therapy in solid tumors in China.

(3) TY-2699a is a selective CDK7 inhibitor intended for the treatment of advanced/metastatic solid tumors. The Company's preclinical studies showed that TY-2699a may have an improved safety window with blood-brain barrier penetration capability. TNBC has the worst prognosis among the subtypes of breast cancer, with no targeted therapy available. With studies showing that CDK7 expression is correlated with poor prognosis in TNBC, TYK Medicines is conducting a Phase I clinical trial to evaluate the safety and efficacy of TY-2699a in TNBC. TY-2699a has demonstrated preliminary efficacy in TNBC in the Company's preclinical studies in mice.

End-to-end capabilities from R&D to manufacturing

TYK Medicines has developed end-to-end capabilities that encompass key drug development functionalities from R&D to manufacturing. The Company's in-house R&D capabilities cover the entire R&D cycle, including early-stage drug discovery, chemical synthesis and selection, and clinical development and regulatory affairs.

In anticipation of the commercialization of TY-9591 and TY-302, TYK Medicines is in the process of establishing a cGMP-compliant manufacturing facility in Changxing Economic Development Zone, Huzhou, Zhejiang Province, which has completed construction and is expected to commence trial operations, and commence commercial-scale manufacturing by the end of 2025. With a GFA of approximately 38,000 sq.m., such a manufacturing facility is expected to have a designed annual production capacity of approximately 150 million tablets or capsules. After the commencement of manufacturing by the end of 2025, TYK Medicines may continue to rely on CDMOs to manufacture drug candidates or a portion of the approved drugs when necessary.

Initiate BUY and PT of HK$31.6

Core Product and potential blockbuster, Asandeutertinib (TY-9591, KARDORISSO) is a differentiated third-generation EGFR-TKI for advanced EGFR mutated non-small cell lung cancer (NSCLC) treatment, which is expected to start generating revenue in 2026E. We believe the product could rapidly gain market share through addressing unmet medical needs. Our PT is based on 10-year DCF model (WACC: 12.2%, terminal growth: 1.5%).

Risks

(1) Delay or failure in developing pipeline candidates, (2) market acceptance of products, (3) intensifying market competition, (4) pricing pressure from government guidance, (5) lack of experience in commercialization of products, (6) intellectual property rights, (7) potential government supportive policies, (8) expanding into new markets, (9) potential collaboration agreements

TY-9591 – An improved third-generation EGFR-TKI

TY-9591 is a third-generation EGFR-TKI, which was modified by H/D exchange of the best-selling third-generation EGFR-TKI, Osimertinib. TY-9591 retains the advantages of Osimertinib, and it is anticipated to present a broadened therapeutic window, which could result in a higher dose that can be administered to patients, translating into potentially better efficacy. From Phase I and II clinical studies, TY-9591 has shown promising efficacy for NSCLC treatment-naïve patients with brain metastases and EGFR mutated (L858R) NSCLC patients. The product shows better efficacy than current third-generation EGFR-TKI in these two areas. The Company is conducting a pivotal Phase II clinical trial of TY-9591 monotherapy as 1L treatment for brain metastases from EGFR mutated NSCLC and a registrational Phase III trial of TY-9591 monotherapy as 1L treatment for locally advanced or metastatic NSCLC with EGFR exon 21 L858R mutation. Both are head-to-head studies against Osimertinib. We believe TY-9591 has the potential to be an improved third-generation EGFR-TKI.

The Company has recently submitted a Pre-NDA to the CDE of NMPA in China for Asandeutertinib (TY-9591) and the Company expects the drug to become the world's first 3rd generation EGFR TKI targeting NSCLC patients with brain metastases. ***Detailed study data is included in an oral presentation session of the upcoming ASCO meeting on 30 May. (A phase II study of asandeutertinib (TY-9591) in advanced NSCLC patients with EGFR-positive mutations and brain metastases).***

Lung cancer – the most common malignant tumor in the world. Lung cancer is the most common malignant tumor in the world in terms of incidence and death rate. About 90% of lung cancer cases are caused by smoking and the use of tobacco products. However, other factors such as exposure to air pollution and chronic infections can also contribute to lung carcinogenesis. In addition, multiple inherited and acquired mechanisms of susceptibility to lung cancer have been proposed. Lung cancer is highly heterogeneous and can arise in many different sites in the bronchial tree, presenting highly variable symptoms and signs depending on its anatomic location. 70% of patients diagnosed with lung cancer present with advanced-stage (stage III or IV) disease.

Based on pathologic and histomorphologic features, lung cancer can be classified as non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). NSCLC is any type of epithelial lung cancer other than SCLC. The most common types of NSCLC are adenocarcinoma (40%), squamous-cell carcinoma (25%) and large-cell carcinoma (10%). All types can occur in unusual histologic variants and develop as mixed-cell-type combinations. Symptoms of more advanced NSCLC cases include bone pain, headache, weakness and vomiting. The five-year survival rate can be as low as 9% for NSCLC patients and is less than 7% at all seven stages combined for SCLC patients. Treatment options for lung cancer include surgery, radiation therapy, chemotherapy and targeted therapy. Therapeutic-modalities recommendations depend on several factors, including the type and stage of cancer. Despite the improvements in diagnosis and therapy during the past 25 years, the prognosis for patients with lung cancer is still unsatisfactory. Responses to current standard therapies are poor except for the most localized cancers.

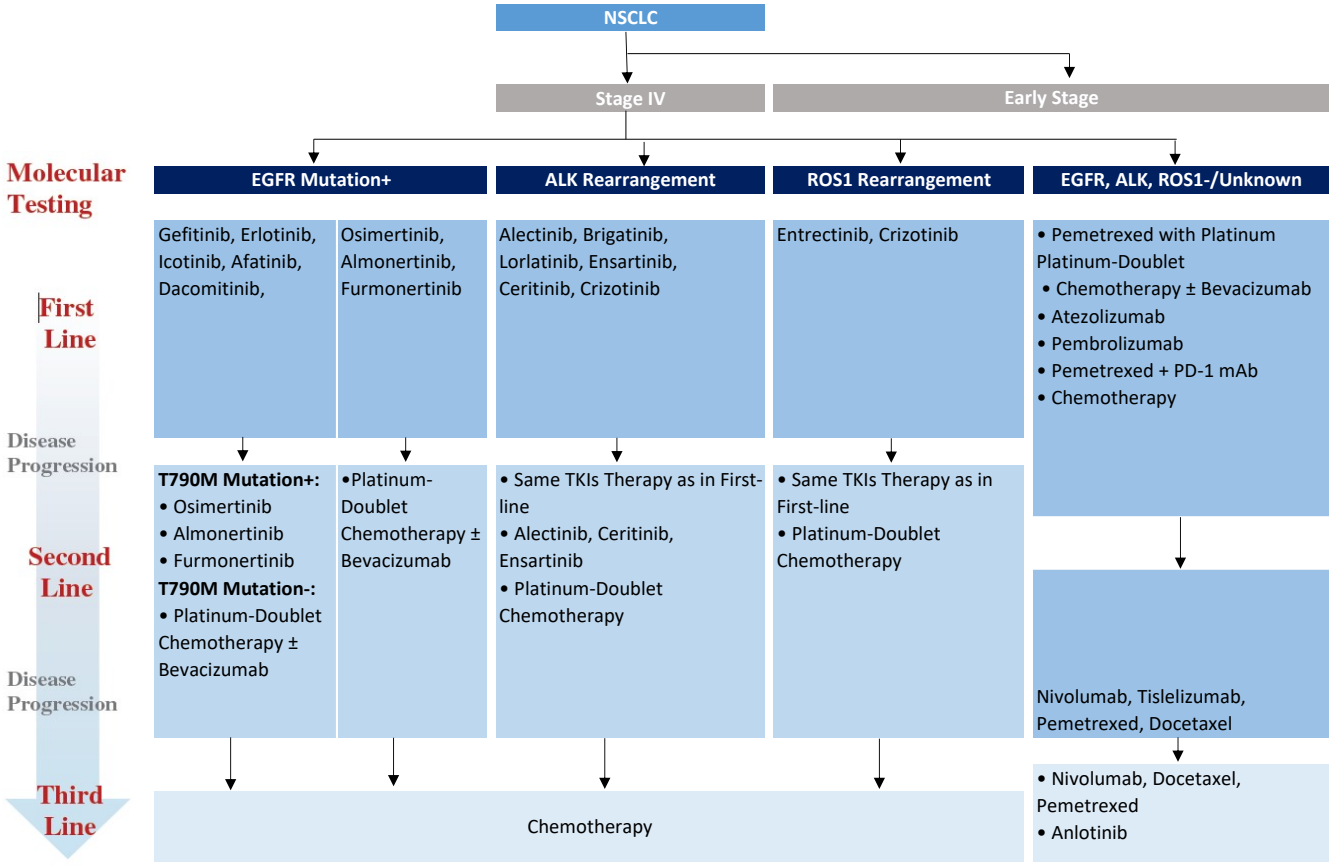
Lung cancer is one of the leading causes of cancer-related mortality in China

NSCLC is the most prevalent lung cancer and accounts for around 85% of all lung cancer cases. According to Frost & Sullivan, NSCLC incidence in China increased from 0.71mn in 2017 to 0.86mn in 2023, and is expected to grow to 1.13mn in 2033. There were 0.70mn NSCLC death cases in China in 2023.

EGFR mutation accounts for over 50% of NSCLCs in China

According to Frost & Sullivan, among NSCLCs driven by gene mutations, EGFR mutation accounted for 50.2% in China in 2023. Among these, exon 19 deletion and L858R mutation account for 85% of EGFR mutations, with exon 19 deletion accounting for 44.8% and L858R accounting for 39.8% of the overall EGFR mutation profile.

Figure 2: Treatment paradigm of stage IV NSCLC



Source : CSCO NSCLC Treatment Guideline 2023, Frost & Sullivan

Robust growth potential for EGFR-TKIs in China

EGFR is a cell-surface receptor tyrosine kinase for EGF. Activation of EGFR can lead to a series of downstream signaling activities that activate tumor-cell growth, survival, invasion, metastasis and inhibition of apoptosis. Tumor-cell division can happen uncontrollably when the pathway is abnormally activated through EGFR mutations, gene amplification of wild-type EGFR or over-expression of wild-type EGFR.

EGFR-TKIs inhibit the activation of the EGFR intracellular tyrosine kinase domain by competing with ligands such as EGF for binding to the EGFR receptor, blocking the downstream cascade by inhibiting the upstream signaling pathway.

In China, the EGFR-TKI market increased from RMB3.1bn in 2017 to RMB14.5bn in 2023, representing a CAGR of 29.3%. Driven by increasing demand for targeted therapies and new approaches to address drug resistance, the EGFR-TKI market in China is expected to reach RMB20.1bn and RMB28.4bn in 2027 and 2033, respectively, growing at a CAGR of 8.5% from 2023 to 2027 and a CAGR of 5.9% from 2027 to 2033. EGFR-TKIs target EGFR exon 19 deletion, and EGFR exon 21 L858R mutations dominate the market, with a market share of 94.6% in 2023.

Figure 3: EGFR-TKI market in China (RMB bn)

Source : Frost & Sullivan

There are three generations of EGFR-TKIs that have been approved for marketing. First-generation EGFR-TKIs include Gefitinib, Erlotinib and Icotinib, of which Gefitinib was the first approved first-generation EGFR-TKI, approved in Japan in 2002. With the deepening understanding of the drug mechanism of EGFR targets, there has been more and more drug research around EGFR and its resistance targets.

Figure 4: Development path of EGFR-TKIs

	1st Generation EGFR-TKI	2nd Generation EGFR-TKI	3rd Generation EGFR-TKI
Drugs	Gefitinib, Erlotinib, Icotinib	Afatinib, Dacomitinib	Osimertinib, Almonertinb, Furmonertinib, Befotertinib
Mechanism	Competitive inhibition of ATP binding to EGFR tyrosine kinase activation region sites	Irreversible binding to EFGR tyrosine kinase activation region	Covalently binding to Cys797 of tyrosine kinase binding domain
Inhibition mode	Reversible	Irreversible	Irreversible
Targeting mutations	Exon19 del, Exon 21 L858R	Exon19 del, Exon 21 L858R	Exon19 del, Exon 21 L858R, Exon 20 T790M
BBB permeability	Weak	Weak	Ordinary

Source : Literature Review, Frost & Sullivan

Third-generation EGFR-TKIs overcome acquired resistance to first- and second-generation EGFR-TKIs

First-generation EGFR-TKIs, including Erlotinib, Gefitinib and Icotinib, are reversible inhibitors that can inhibit EGFR activity by reversibly binding to the ATP-binding site in the tyrosine kinase domain. They were effective for patients with EGFR mutated NSCLC in the first-line setting. Unfortunately, despite the initial benefit, most patients develop acquired resistance to them within one year, driven in approximately 50% of cases by a second-site EGFR point mutation, the T790M mutation occurring within exon 20. Second-generation EGFR-TKIs Afatinib and Dacomitinib irreversibly inhibit all four ErbB receptors including EGFR. As such, they were designed to be more potent inhibitors of EGFR, aiming to improve ORR

and PFS, but at the cost of increased toxicity. Nevertheless, Afatinib failed to extend OS compared to first-generation EGFR-TKI Afatinib (according to the LUX-Lung 7 study, the overall survival (OS) of Afatinib vs Gefitinib was 27.9 vs 24.5 months), and the T790M mutation remains the major resistance mechanism to first- and second-generation TKIs in EGFR-mutant NSCLC.

The T790M mutation increases the competition between ATP and reversible EGFR-TKIs by exerting effects on both steric hindrance and increased ATP affinity to mutant EGFR receptor, thereby decreasing the efficacy of first- and second-generation EGFR-TKIs. Third-generation EGFR-TKIs, including Osimertinib, Befotertinib, Furmonertinib and Almonertinib, have satisfactory efficacy in overcoming acquired resistance to first- and second-generation EGFR-TKIs mediated by T790M mutation. These mutant-selective EGFR-TKIs could represent a promising approach to overcoming T790M-mediated resistance in NSCLC patients. For example, Osimertinib has been classed as a breakthrough compound for fast-track development and received its first global approval by the FDA in November 2015 for patients with metastatic EGFR T790M-positive NSCLC who had progressed on prior systemic therapy, including an EGFR-TKI. In addition, third-generation EGFR-TKIs exhibited selectivity against EGFR mutations over wild-type EGFR. This favorable property resulted in an improved safety profile.

The three generations of EGFR-TKIs demonstrate distinct PFS outcomes for exon 19 deletion and exon 21 L858R. **While third-generation EGFR-TKIs have enhanced PFS for exon 19 deletion, there remains a need for improvement in the progression-free survival (PFS) for exon 21 L858R.**

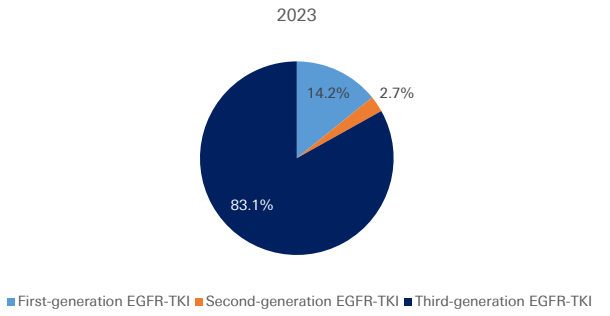
Figure 5: PFS of the three generations of EGFR-TKIs

				Indications		
Drug Name	Brand Name	Generation	Clinical trial	19del	21 L858R	Overall
Befotertinib	Surmana	3rd-generation	IBIO-103	NE	17.9	22.1
Furmonertinib	Ivesa	3rd-generation	FURLONG	Undisclosed		20.8
Almonertinib	Ameile	3rd-generation	AENEAS	20.8	13.4	19.3
Osimertinib	Tagrisso	3rd-generation	FLAURA	21.4	14.4	18.9
Dacomitinib	Vizimpro	2nd-generation	ARCHER 1050	16.5	12.3	14.7
Afatinib	Gilotrif	2nd-generation	Lux-Lung 7	12.7	10.9	11.0
Icotinib	Conmana	1st-generation	CONVINCE	11.2	11.1	11.2
Erlotinib	Tarceva	1st-generation	ENSURE	11.1	8.3	11.0
Gefitinib	Iressa	1st-generation	IPASS	11.0	9.2	9.5

Source : Literature Review, Frost & Sullivan

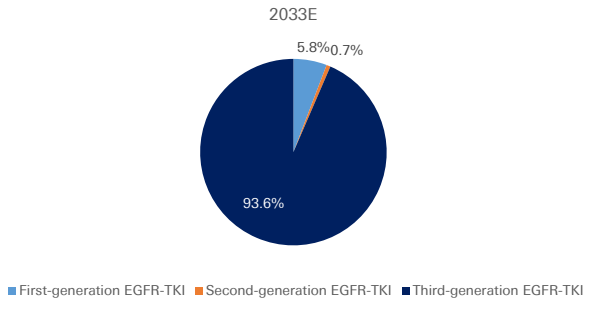
In 2023, third-generation EGFR-TKIs dominated the EGFR-TKI drug market, accounting for 83.1% of the China market share. The market share of third-generation EGFR-TKIs will likely keep increasing and account for 93.6% of China's EGFR-TKI market in 2033.

Figure 6: Breakdown of China's EGFR-TKI market, 2023



Source : Frost & Sullivan

Figure 7: Breakdown of China's EGFR-TKI market, 2033E



Source : Frost & Sullivan

Competitive landscape of third-generation EGFR-TKIs in China

As of the latest practicable date, there were four third-generation EGFR-TKIs approved for NSCLC with EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M in China, including Befotertinib, Furmonertinib, Almonertinib and Osimertinib. None of these drugs were indicated for brain metastases from lung cancer.

Figure 8: Competitive landscape of marketed third-generation EGFR-TKIs for NSCLC in China

Drug Name	Brand Name	Target	Generation	Company	Indications	mPFS(month)			Line	Approval Date	2022 Global sales (million USD)
						Ex19del	L858R	Overall			
Befotertinib	Surmana	EGFR	3rd-generation	Betta Pharma	NSCLC	NE	17.9	22.1	1st line	5/31/2023	NA
Furmonertinib	Ivesa	EGFR	3rd-generation	Allist Pharmaceutical	NSCLC	Undisclosed		20.8	1st line	3/3/2021	Undisclosed
Almonertinib	Ameile	EGFR	3rd-generation	Hansoh Pharma	NSCLC	20.8	13.4	19.3	1st line	3/17/2020	117.3
Osimertinib	Tagrisso	EGFR	3rd-generation	Astrazeneca	NSCLC	21.4	14.4	18.9	1st line	3/22/2017	5,444.0

Source : NMPA, Frost & Sullivan

As of the latest practicable date, 10 third-generation EGFR-TKI candidates were in clinical development for NSCLC and two of them were indicated for NSCLC with brain metastases, among which TY-9591 was the most clinically advanced EGFR-TKI candidate. Meanwhile, TY-9591 is the only EGFR-TKI currently undergoing head-to-head pivotal trials directly comparing its efficacy with Osimertinib's, which is by far the most effective third-generation EGFR-TKI.

Figure 9: Competitive landscape of clinical-stage third-generation EGFR-TKIs for NSCLC in China

Drug Name/Code	Target	Mutation subtype	Company	Control	Clinical Stage	Indications	First Posted Date
TY-9591	**EGFR**	**Ex19del, L858R, T790M**	**TYK Medicines, Inc**	**Osimertinib**	**III** **II (Pivotal)**	**NSCLC** **NSCLC with Brain Metastases**	**5/19/2022** **11/16/2021**
Abivertinib	BTK, EGFR	Ex19del, L858R, T790M	Sorrento/Essen Pharmaceutical	Gefitinib	III	NSCLC	4/9/2019
FHND9041	EGFR	Ex19del, L858R, T790M	Chia Tai Fenghai Pharmaceutical	Afatinib	III	NSCLC	8/31/2021
Oritinib	EGFR	Ex19del, L858R, T790M	Sanhome Pharmaceutical	Gefitinib	III	NSCLC	3/3/2020
Rezivertinib	EGFR	Ex19del, L858R, T790M	Shanghai Beta Pharma	Gefitinib	III	NSCLC	3/7/2019
Limertinib	EGFR	Ex19del, L858R, T790M	Aosaikang Pharmaceutical	Gefitinib	III	NSCLC	8/29/2019
Kenitinib	EGFR	Ex19del, L858R	Suzhou Teligene	NA	II	NSCLC with Brain Metastases	5/12/2020
TQB3456	EGFR	Ex19del, L858R, T790M	Chia Tai-tianqing Pharmaceutical	NA	I	NSCLC	8/31/2018
QLH11811	EGFR	Ex19del, L858R, T790M	Qilu Pharmaceuticals	NA	I	NSCLC	9/22/2022
YZJ-0318	EGFR	Ex19del, L858R, T790M	Yangtze River Pharmaceutical	NA	I	NSCLC	1/28/2018

Source : CDE, Frost & Sullivan

The EGFR-TKI market focusing on exon 21 L858R mutation increased from RMB1.4bn in 2017 to RMB5.6bn in 2023, representing a CAGR of 26.2%, and is projected to grow to RMB11.9bn in 2033, at a CAGR of 7.8% from 2023 to 2033, according to Frost & Sullivan.

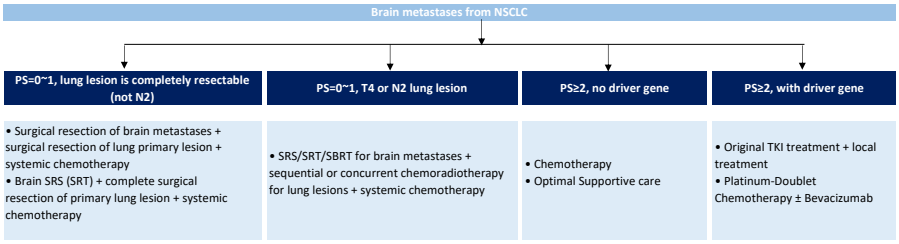
Brain metastases from lung cancer: urgent and unmet medical needs

Brain metastases occur when cancer cells spread from their original site to the brain. Any cancer can spread to the brain, but the types most likely to cause brain metastases are cancers of the lung, breast, colon and kidney and melanoma. Brain metastases may form one tumor or many tumors in the brain. As metastatic brain tumors grow, they create pressure on and change the function of surrounding brain tissue. This causes signs and symptoms such as headaches, personality changes, memory loss and seizures.

Brain metastases, prevalent in a high percentage of advanced NSCLC cases, pose a grave prognosis with a brief average survival period. The incidence of brain metastases in patients with advanced NSCLC can be nearly 25% at diagnosis; approximately 30% to 55% of NSCLC patients develop brain metastases during treatment, and the incidence of brain metastases increases year by year during the survival period. The incidence of brain metastases in NSCLC patients with EGFR mutation is higher than in those without EGFR mutation. The natural average survival of NSCLC patients with brain metastases is only one to two months, and the prognosis is poor, seriously jeopardizing patients' lives and quality of life. The absence of globally approved drugs for this indication underscores the urgent and unmet medical needs in this critical area.

The number of new patients with brain metastases from lung cancer worldwide increased from 0.33mn in 2017 to 0.39mn in 2023. According to Frost & Sullivan, it is estimated that the number of new patients with brain metastases from lung cancer worldwide will reach 0.51mn in 2033. The number of new patients with brain metastases from lung cancer in China was 0.14mn in 2017 and it is estimated that the number will increase to 0.22mn in 2033.

Figure 10: Treatment guidelines for brain metastases from NSCLC



Abbreviations: SRS = Stereotactic Radiosurgery; SRT = Stereotactic Radiation Therapy; SBRT = Stereotactic BodyRadiotherapy
Source: CSCO NSCLC Treatment Guideline 2023, Frost & Sullivan

Unmet clinical needs of NSCLC treatment

- *Targeted drugs with better blood-brain barrier permeability.* Currently, patients with brain metastases have a poor prognosis. BBB is a complex and unique semi-permeable membrane that serves as a protective structure to maintain homeostasis within the brain. Due to the poor blood-brain barrier permeability of targeted drugs, the concentration of drugs in the cerebrospinal fluid is lower than that in peripheral blood at standard doses, resulting in a poor effect of targeted therapy. Therefore, it is important to develop targeted drugs with better blood-brain barrier permeability for the treatment of patients with brain metastases.
- *New-generation targeted drugs or better treatment solutions to overcome acquired resistance.* Acquired resistance is categorized into on-target resistance and off-target resistance. On-target resistance refers to mutations of the kinase domain, which lead to steric hindrance changes or conformational changes to prevent TKI binding. Off-target resistance may result from activation of bypass signaling, reactivation of downstream signaling pathways or histological phenotypic shifts. To overcome on-target resistance, researchers are developing a new generation of targeted therapy against tumor cells with drug-resistant mutations. Different treatment solutions are often required for different off-target resistance. In some instances, combination therapy is more effective than monotherapy, and new drug modalities show more benefits than those existing drugs.
- *More effective targeted drugs for EGFR exon 21 L858R mutated patients.* Exon 19 deletion and exon 21 L858R mutation are the two most common EGFR mutation subtypes, but the OS and PFS of patients with exon 21 L858R mutation treated with EGFR-TKI were significantly lower than of those with exon 19 deletion. This is because the molecular characteristics of exon 21 L858R enable it to bind TKI drugs with a lower affinity than exon 19 deletion. Increased drug dosage has the potential to elevate the affinity for the drug, thereby improving the drug's inhibition of the enzyme. Therefore, EGFR-TKI with lower toxicity may become a more effective targeted drug for EGFR exon 21 L858R mutated patients, as it is safer to increase drug dosage with this.

Trends in China's EGFR-TKI market

- *Filling the treatment vacuum.* Although targeted therapies including EGFR-TKI have significantly improved the treatment of NSCLC patients, due to the influence of the blood-brain barrier, the concentration of targeted drugs and chemotherapeutic agents in the cerebrospinal fluid is often lower than that in peripheral blood, making it relatively difficult to treat NSCLC patients with brain metastases, and the survival period is shorter. EFGR-TKI with better blood-brain barrier permeability will likely be developed in the future, to broaden the therapeutic window of EGFR-TKI, increasing the efficacy of

treatment for patients with brain metastases.

- *Precise targeted therapy indicated for EGFR mutation subtypes.* Exon 19 deletion and exon 21 L858R mutations are two of the most common subtypes of EGFR mutations. Several large randomized controlled trials have found that first-, second- and third-generation EGFR-TKIs show different efficacy in treating patients with exon 19 deletion and exon 21 L858R mutations. Overall, patients with exon 19 deletion have significantly higher PFS and OS benefits than patients with exon 21 L858R mutation. Currently, EGFR exon 21 L858R patients still lack effective treatment. Continued research and innovation may lead to the emergence of targeted drugs exhibiting superior clinical efficacy for specific mutation subtypes, surpassing the currently available options. Such advancement would enable doctors to select distinct drugs tailored to the various EGFR mutation subtypes, paving the way for a more precise and effective EGFR-targeted therapy.
- *Increasing market share of third-generation EGFR-TKIs.* EGFR-TKIs have occupied an absolutely dominant position in the treatment paradigm of NSCLC patients with EGFR mutation, and targeted therapy has become one of the most important NSCLC therapeutic methods. The utilization rate and penetration rate of EGFR-TKI are expected to continue to rise. Since the price of Osimertinib has been reduced and Osimertinib has entered the NRDL, patients' access to third-generation EGFR-TKIs has greatly improved. With the successful exploration of combination therapy with third-generation EGFR-TKIs and other drugs in the future, the scope of application of third-generation EGFR-TKIs would continue to expand and the market share of third-generation EGFR-TKIs would continue to increase.
- *Continue addressing drug resistance.* The next generation of the EGFR-TKIs-based regimen is currently in development to combat on-target resistance. New EGFR-TKIs are poised to directly address emerging mutations such as EGFR C797S. Simultaneously, combining EGFR-TKIs with other therapies presents a strategy to counter off-target resistance. For instance, the investigation of combining MET inhibitors with EGFR-TKIs addresses MET amplification-induced resistance to drugs such as Osimertinib. Moreover, in cases where resistance mechanisms remain unknown, researchers are exploring the amalgamation of targeted agents with chemotherapy or immune checkpoint inhibitors. These tailored development efforts would effectively tackle new challenges in cancer treatment in the future.
- *Combination therapy improves clinical outcome.* Combination therapy can introduce a synergistic antitumor effect, significantly improving the clinical outcome. For example, the FLAURA2 study in Asia showed that the combined
therapy of Osimertinib and chemotherapy improved efficacy more than did Osimertinib monotherapy. It can irreversibly bind to certain EGFR mutants including L858R mutation, exon 19 deletion, L858R/T790M mutation and exon 19 deletion/T790M mutation, inhibiting the downstream signaling cascade by blocking the phosphorylation of tyrosine kinases and intracellular signaling pathways, such as the Ras/Raf/MEK/ERK or PI3K/AKT pathway, ultimately inhibiting the proliferation and metastasis of cancer cells.

TY-9591 – An improved third-generation EGFR-TKI

TY-9591 was modified by H/D exchange of Osimertinib. It not only retains the advantages of Osimertinib, but also shields the metabolic soft spots of Osimertinib, which can significantly reduce the formation of the metabolite TY-9591-D1 (AZ5104).

TYK Medicines is currently conducting a pivotal Phase II clinical trial of TY-9591 monotherapy as a first-line treatment for brain metastases from EGFR mutated NSCLC. It expects to complete patient enrollment for this clinical trial in the third quarter of 2024 and to submit an application to the NMPA for conditional marketing approval in the first quarter of 2025. It is also conducting a registrational Phase III clinical trial of TY-9591 monotherapy as a first-line treatment for locally advanced or metastatic NSCLC with EGFR L858R mutation. TYK Medicines expects to complete patient enrollment for this clinical trial in the fourth quarter of 2024 and to submit an NDA in the second half of 2026. To fully explore the potential of TY-9591, it also applied for a registrational Phase III clinical trial of TY-9591 in combination with chemotherapy as a first-line treatment for EGFR mutated NSCLC in January 2024 and expects to obtain IND approval in the first quarter of 2024. It expects to commence this clinical trial in the second half of 2024 and to complete patient enrollment in the first half of 2026.

TY-9591 has the advantage of a third-generation EGFR-TKI

Despite the remarkable clinical responses observed in EGFR-mutated advanced/metastatic NSCLC patients treated with first-generation EGFR-TKIs, acquired resistance to these compounds inevitably develops within 12 months, principally due to the section of resistant clones harbouring the secondary EGFR-T790M mutation. Second-generation EGFR-TKIs, like first-generation EGFR-TKIs, also failed to overcome resistance in T790M-mutant lung cancer patients, because the dosage required to achieve the complete inhibition of T790M-mutant tumors is associated with unacceptable toxicity. As such, third-generation EGFR-TKIs have been developed to overcome EGFR T790M-mediated resistance. Osimertinib, the third-generation EGFR-TKI, irreversibly and selectively targets the EGFR T790M mutation. It was approved by the FDA in 2015 for the treatment of patients with metastatic EGFR-mutant NSCLC who have acquired the EGFR T790M resistance mutation and was approved by the FDA as a first-line therapy for advanced EGFR-mutated NSCLC in 2018. Clinical trials have demonstrated that Osimertinib has superior efficacy compared to chemotherapy and previous generations of EGFR-TKIs. For example, the Phase III FLAURA trial explored the efficacy and safety of Osimertinib as a first-line therapy for EGFR-mutant advanced/metastatic NSCLC in comparison with Gefitinib and Erlotinib. First-line treatment with Osimertinib was associated with a significantly longer progression-free survival (18.9 months vs 10.2 months). Despite a longer duration of exposure, patients treated with Osimertinib had lower rates of serious adverse effects than patients who received first-generation EGFR-TKIs (34% vs 45%).

TY-9591 potentially demonstrates a better safety profile than that of Osimertinib

Improving the safety of Osimertinib is expected to broaden its therapeutic window, which could be beneficial for higher exposure of Osimertinib and lead to the increased shrinkage of brain tumors. After oral administration of Osimertinib, there are two main pharmacologically active metabolites: AZ5104 and AZ7550. Metabolite AZ5104 has lower mutation selectivity, poor tumor-tissue selectivity and no blood-brain barrier penetration, and causes side effects that do not relate to treatment

efficacy.

TY-9591 was modified by H/D exchange of Osimertinib. It not only retains the advantages of Osimertinib, but also shields the metabolic soft spots of Osimertinib, which can significantly reduce the formation of metabolite TY-9591-D1 (AZ5104). By reducing the production of TY-9591-D1, TY-9591 is expected to be safer than Osimertinib and can be administered at a higher dose level, leading to improved antitumor efficacy and a higher level of blood-brain entry. As such, a higher dose of TY-9591 could be administered to patients to achieve improved efficacy, leading to a higher level of blood-brain entry. TYK Medicines conducted a head-to-head study in mice to analyze the PK profiles of TY-9591 and AZD9291 (Osimertinib). Each mouse received 25mg/kg of either TY-9591 or AZD9291 through oral administration. The findings revealed that under identical conditions, Osimertinib generated five times more AZD5104 than TY-9591. Furthermore, the ratio between AZD9291 and AZD5104 was 2.3:1, while the ratio between TY-9591 and TY-9591-D1 was 13:1.

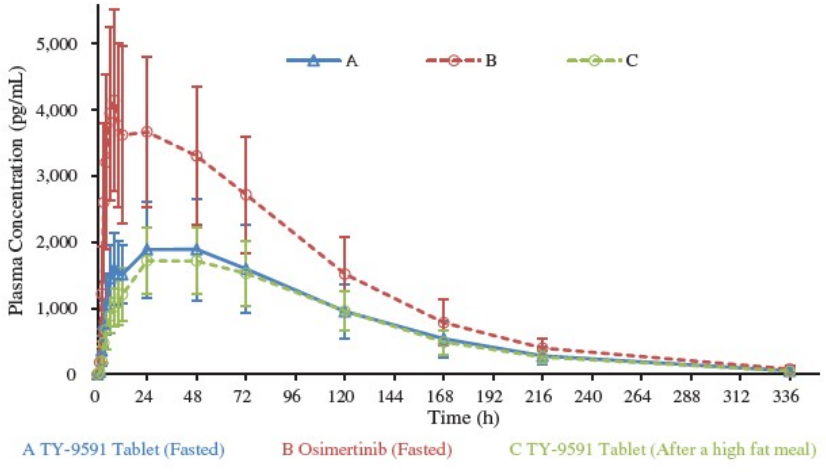
The Company's clinical studies also support a similar conclusion. In a Phase I clinical trial, it investigated the mean drug metabolite concentration-time profiles after a single oral dose of 80mg of TY-9591 and Osimertinib in healthy subjects. Compared to Osimertinib, the results showed an approximately 50% reduction in metabolite TY-9591-D1 exposure levels after TY-9591 administration, indicating that TY-9591 may have a superior safety profile than that of Osimertinib.

Figure 11: PK profiles of TY-9591 and AZD9291 (osimertinib)

PK profile	Unit	AZD9291	AZ5104 (TY-9591-D1)	TY-9591	TY-9591-D1 (AZ5104)
Cmax	**ng/ml**	549	181	507	37
AUClast	**h*ng/ml**	2128	859	1939	152
T1/2	**h**	3.7	21.6	3.3	10.5

Source: Company data

Figure 12: Plasma concentration of TY-9591-D1 (AZ5104) in healthy subjects



Source: Company data

In addition, in the Phase I study in healthy adult subjects, 10 out of 16 subjects

experienced AEs, all of which were Grade 1 or 2 in severity. Only four were likely related to the study drug. TYK Medicines observed no SAEs occurring during the trial, and no subjects withdrew from the trial due to AEs.

Moreover, TY-9591 demonstrated a favorable safety profile among advanced NSCLC patients. In a Phase I study in advanced NSCLC, TYK Medicines evaluated the safety of TY-9591 in a total of 105 patients who received 20mg to 200mg TY-9591 QD. The results showed that no DLT was observed during the observation period (starting from receiving the first treatment until the end of one cycle with continuous dosing). The overall incidence of SAEs was 19.0%, with only 7.6% of these events being treatment-related. Most patients experienced SAEs due to their poor overall condition at enrollment. In addition, most treatment-related SAEs lead to symptom disappearance after either reducing the dosage or temporarily discontinuing the drug. Only one patient withdrew from the trial due to a decrease in white blood cell count, neutrophil count, and platelet count. Data collected from the below-detailed clinical trials showed that TY-9591 is safer than Osimertinib according to data from the Phase III FLAURA trial and its drug label.

As of May 17, 2023, a total of 134 subjects were exposed to TY-9591 in two clinical studies (TYM1601101, TYM1601201) in patients with NSCLC, of which 38, 39 and 50 were in the three extended dose groups of 80mg, 120mg and 160mg, respectively. The median treatment duration was approximately 22.5 months for 105 patients in the Phase I dose escalation and expansion studies and 8.5 months for 29 patients in the Phase II study.

In general, the incidence of TEAEs and SAEs in the dose expansion groups of 80mg TY-9591 QD was lower than that of 80mg Osimertinib QD in the FLAURA study in the Chinese population. The incidence of Grade 3 TEAEs and SAEs in the dose expansion groups of 160mg TY-9591 QD was comparable to that of 80mg Osimertinib QD in the FLAURA study in the Chinese population. In addition, no deaths were led by the administration of TY-9591,whereas Osimertinib recorded 4% study-drug related death.

According to the data available from the drug label of Osimertinib and the Phase III FLAURA trial, TY-9591 generally achieved a more favorable safety profile than Osimertinib. Specifically, the incidence of skin and subcutaneous tissue and gastrointestinal system adverse reactions was lower with the 160mg dose of TY-9591 than with the 80mg dose of Osimertinib.

AEs associated with administration of 160mg TY-9591 QD were similar to the types of AEs common to EGFR-TKIs, with no new safety concerns identified. The incidence and severity of common skin and subcutaneous and diarrhea AEs, as well as the incidence of SAEs, were lower compared to those of 80mg Osimertinib QD.

In addition, TYK Medicines investigated the safety profile of TY-9591 in NSCLC patients with brain metastases, which showed that the drug candidate was well tolerated among the patients, consistent with previous safety observations. In this study, a total of 24 NSCLC patients with brain metastases received at least one single dose of 160mg TY-9591 once daily (cut-off date December 21, 2022). The incidence of Grade 3 and above ADRs was less than 5%. The overall incidence of SAEs was 8.3% and treatment-related SAEs was 8.3%. The study drug-related SAEs were primarily nasal inflammation and cerebral infarction. The nasal inflammation resolved without requiring a dosage adjustment, while the cerebral infarction showed improvement after temporarily discontinuing the drug. We note

that there were no deaths related to the study drug observed in this study.

Figure 13: Adverse events summary table (TY-9591 vs. osimertinib) in Chinese population

	TY-9291			Osimertinib
	80mg (N=38) n(%)	120mg (N=39) n(%)	160mg (N=50) n(%)	80mg (N=71) n(%)
All TEAE	38 (100.0)	39 (100.0)	49 (98.0)	70 (99)
≥ Grade 3 TEAE	10 26.3)	19 (48.7)	22 (44.0)	38 (54)
Study drug related TEAE	37 (97.4)	35 (89.7)	47 (94.0)	66 (93)
Study drug related ≥ Grade 3 TEAE	5 (13.2)	16 (41.0)	19 (38.0)	18 (25)
TEAE leading to death	4 (10.5)	2 (9.1)	2 (4.0)	7 (10)
Study-drug related TEAE leading to death	0	0	0	3 (4)
All SAE	9 (23.7)	10 (25.6)	9 (18.0)	25 (35)
Study-drug related SAE	3 (7.9)	5 (12.8)	3 (6.0)	9 (13)
TEAE leading to dose reduction	0	3 (7.7)	7 (14.0)	0
Study-drug related TEAE leading to dose reduction	0	3 (7.7)	7 (14.0)	0
TEAE leading to dose interruption	12 (31.6)	14 (35.9)	16 (32.0)	15 (21)
Study-drug related TEAE, leading to doe interruption	4 (10.5)	14 (35.9)	12 (24.0)	/
TEAE leading to discontinuation	2 (5.3)	2 (5.1)	2 (4.0)	9 (13)
Study-drug related TEAE leading to discontinuation	1 (2.6)	2 (5.1)	1 (2.0)	6 (9)

Source : Literature Review, Company data

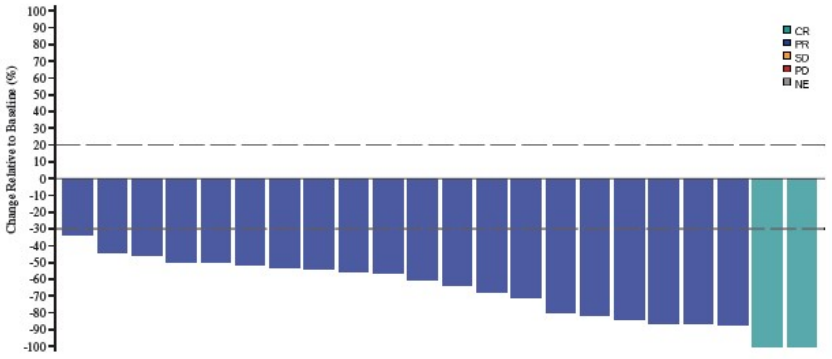
TY-9591 demonstrates potentially better efficacy than Osimertinib

TY-9591 monotherapy for brain metastases in NSCLCs

Because the molecular design of TY-9591 improves Osimertinib's safety profile, a higher dose of TY-9591 can be safely used in humans compared to Osimertinib – i.e., 160mg vs. 80mg. As such, the therapeutic window of TY-9591 is expanded and its efficacy, especially efficacy in patients with brain metastases, can be potentially improved.

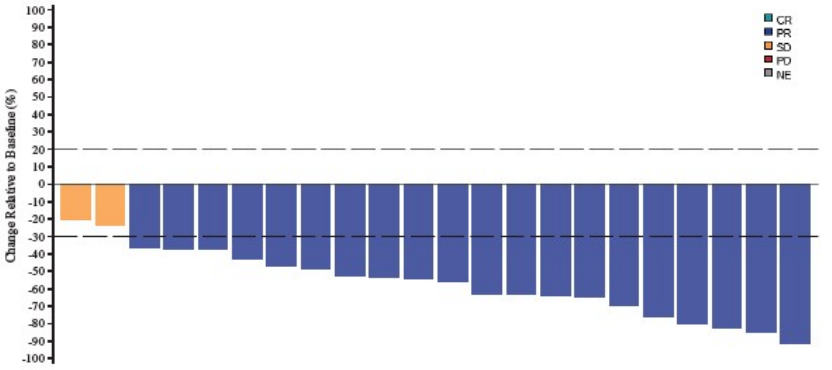
In a Phase II clinical study conducted by the Company, of the 22 patients with brain metastases from lung cancer (cut-off date of March 10, 2023), 20 (90.9%) experienced partial responses (PRs) intracranially and two experienced complete responses (CRs), with a confirmed intracranial objective response rate (ORR) of 100%. Systemic PR occurred in 20 cases (90.9%) and stable diseases (SDs) occurred in two cases, with a systemic ORR of 90.9%. After six-week treatment, intracranial tumor lesions were significantly reduced. The median depth of response was 62.0%.
Based on this encouraging efficacy data as well as the favorable safety profile, in April 2023, the NMPA agreed to allow the Company to conduct a pivotal Phase II clinical trial of TY-9591 monotherapy as a first-line treatment in brain metastases from EGFR mutated NSCLC to obtain conditional marketing approval.

Figure 14: Waterfall plots of changes in total longest diameter of intracranial target lesions relative to baseline



Note: Best efficacy determined as of March 2023.
Source: Company data

Figure 15: Waterfall plots of changes in total longest diameter of systemic target lesions relative to baseline



Note: Best efficacy determined as of March 2023.
Source: Company data

TY-9591 monotherapy for 1L EGFR mutants

According to information available to the public, the median PFS of Osimertinib reached 18.9 months, according to its Phase III FLAURA study. For NSCLC patients with EGFR mutation of exon 19 deletion, the PFS can be as long as 21.4 months, and for NSCLC patients with EGFR exon 21 L858R mutation, the PFS is 14.4 months.

As of cut-off date May 18, 2023, among the 78 evaluable patients with EGFR mutations enrolled in the Phase Ib study, the result showed that when TY-9591 was received as first-line treatment, the median PFS reached 21.5 months, including 25.7 months for exon 19 deletion patients and 19.3 months for exon 21 L858R mutation patients. The investigator-confirmed ORR was 85.9%, including 85.7% for exon 19 deletion patients and 86.1% for L858R mutation patients. Accordingly, TY-9591 was more effective in patients with exon 19 deletion and L858R mutation compared to Osimertinib, and the efficacy against L858R mutation patients was significantly improved.

In addition, according to preliminary efficacy data from the Phase Ib study, TY-9591 demonstrated improved efficacy. For example, according to public information such as drug labels, the median PFSs of Erlotinib, Afatinib, Almonertinib and Furmonertinib are 10.4, 11.2, 19.3 and 20.8 months, respectively. The median PFS of TY-9591 was 21.5 months, significantly better than that of Erlotinib (a first-generation EGFR-TKI) and Afatinib (a second-generation EGFR-TKI), and improved compared to other third-generation EGFR-TKIs, including Almonertinib and Furmonertinib. Although no head-to-head data are available at this stage, TYK Medicines believes the following comparisons with Erlotinib, Afatinib, Osimertinib, Almonertinib and Furmonertinib shed light on the differentiated features and advantages of TY-9591 from an efficacy perspective:

Figure 16: Efficacy data of EGFR TKIs for first-line treatment of EGFR mutated NSCLC

			Afatinib (2)		Osimerinib (3)-(5)			
	TY-9591 (Phase Ib)	Erlotinib (1) (EURTAC)	Global (LUX-Lung3)	Asia (LUX-Lung6)	Global Cohort (FLAURA)	China Cohort (FLAURA)	Almonertinib (6) (AENEAS)	Furmonertinib (7) FURLONG)
Sample size (N)	78	86	230	242	279	71	214	178
Del19	43	66%	48.70%	51.20%	62.70%	50.70%	65.40%	51%
L858R	36	34%	39.60%	38%	37.30%	49.30%	34.60%	49%
mPFS (months)	21.5	10.40%	11.2	11	18.9	17.8	19.3	20.8
Del19	25.7	(vs control group) HR=0.27*	13.8	13.1	21.4	/	20.8	(vs control group) HR=0.346*
L858R	19.3	(vs control group) HR=0.52*	10.8	9.6	14.4	/	13.4	(vs control group) HR=0.537*

Notes:
(1) First- and second-generation EGFR-TKIs were selected to list representative data for Erlotinib and Afatinib respectively;
(2) Symbol "/" refers to "not available"; and
(3) Symbol "" refers to "no PFS data according to historical data"*

Source:
[1] Tarceva (Erlotinib) _FDA Label 2016;
[2] Afatinib Maleate Tablets (JXHS1600008~11)_CDE Specification;
[3] Osimertinib Mesylate Tablets (JXHS2000150)_Marketed Drug Announcement Report;
[4] Tagrisso-H-C-4124-II-0019: EPAR -Assessment Report-Variation;
[5] Literature Review;
[6] Almonertinib Mesylate Tablets (CXHS2101017)_Application for Marketing Technical Review Report; and
[7] Furmonertinib Mesylate Tablets (CXHS2101055)_Application for Marketing Technical Review Report

Based on the encouraging efficacy data collected from the Phase I clinical trial, in March 2022, the NMPA approved the Company's progression to conduct a registrational Phase III trial of TY-9591 monotherapy as a first-line treatment in locally advanced or metastatic NSCLC with EGFR exon 21 L858R mutation and EGFR exon 19 deletion mutation. With the aim of addressing urgent, unmet medical needs, TYK Medicines subsequently initiated communications with the NMPA to focus on NSCLC patients with EGFR exon 21 L858R mutation only, and in November 2023, the NMPA approved the Company's revised clinical trial protocol.

Strategic indication selection

To fully explore the potential of TY-9591, TYK Medicines has adopted a comprehensive strategy for its clinical development, exploring different regimens of monotherapy and combination therapy to address current unmet medical needs and to compete with available treatments aimed at improving the outcome of NSCLC patients.

Monotherapy

TYK Medicines will continue exploring TY-9591 monotherapy as a first-line treatment for brain metastases from NSCLC. Currently, there is no approved or marketed drug for NSCLC brain metastases indications in the world, and there is a significant unmet medical need. According to Frost & Sullivan, the annual incidence of lung cancer in China was 1,015.5 thousand in 2023, and the incidence of brain metastases in patients with advanced NSCLC can be nearly 25% at diagnosis; approximately 30-55% of NSCLC patients develop brain metastases during treatment, and the incidence of brain metastases in NSCLC patients with EGFR mutation is higher than those without EGFR mutation. Clinical treatment of brain metastases can be difficult, not only because the brain is an important, delicate organ, encompassed by the skull, but also because the brain is protected by the blood-brain barrier. Thus, it can be difficult for drugs to penetrate this natural filter and enter the brain. It has been reported that the blood-brain barrier penetration of 160mg of Osimertinib is eight times higher than that of 80mg, and as a deuterated compound of Osimertinib with an expanded therapeutic window, the brain exposure of TY-9591 is expected to reach an increased level at the dosage of 160mg. Consistent with this expectation, the Company's clinical data revealed that TY-9591 exhibited a strong ability to penetrate the blood-brain barrier, showcasing promising efficacy, with an intracranial ORR of up to 100%.

EGFR exon 19 deletion and exon 21 L858R are the two most common mutations in EGFR, and they are sensitive to treatment with EGFR-TKIs, accounting for approximately 85% of observed EGFR mutations in NSCLC, according to Frost & Sullivan. However, in retrospective studies and subgroup analyses, it was found that they may have different sensitivities to EGFR-TKIs. We note that patients with L858R mutation can be less sensitive to EGFR-TKI treatment than patients with exon 19 deletion, underscoring unmet medical needs for effective treatment. For example, it has been demonstrated that an increased dose of Icotinib (250mg, TID) in exon 21L858R patients achieved similar efficacy to that of patients with exon 19 deletion at the conventional dose (125mg, TID), with median respective PFSs of 12.9 and 12.5 months, significantly longer than the mPFS in the exon 21 L858R group that received the conventional dose (a median PFS of 9.2 months). Osimertinib also showed a similar trend, with a median PFS of 21.4 months for exon 19 deletion and 14.4 for exon 21 L858R mutation for NSCLC patients receiving 80mg of Osimertinib.

160mg TY-9591 monotherapy was shown to be effective in NSCLC patients with EGFR L858R mutation with an mPFS of 19.3 months, which is expected to improve clinical efficacy in L858R patients. It showed superior efficacy compared to 80mg of Osimertinib, which has a PFS of 14.4 months for EGFR exon 21 L858R mutation, according to the Phase III FLAURA study.

Combination therapy

The clinical efficacy of TY-9591 in NSCLC with EGFR L858R mutation and exon 19

deletion can be further enhanced by combining it with chemotherapy.

In the treatment-naïve setting of EGFR mutated advanced NSCLC, Osimertinib, when combined with Platinum-Pemetrexed, demonstrated encouraging efficacy with an ORR of 90.9% and a median PFS of 31.0 months in the Phase II OPAL study, conducted in Japan. The interim findings from the Phase III FLAURA 2 study revealed a statistically significant and clinically meaningful improvement in PFS for first-line treatment of EGFR mutated advanced NSCLC with Osimertinib in combination with Platinum-Pemetrexed, compared to Osimertinib monotherapy. The combination therapy group exhibited a prolonged median PFS of 25.5 months, surpassing the monotherapy group by 8.8 months (25.5 months vs. 16.7 months), as evaluated by the principal investigator.

Given that TY-9591 was modified by H/D exchange of Osimertinib, and the Phase III FLAURA 2 clinical trial demonstrated a synergistic antitumor effect with Osimertinib in combination with chemotherapy, TYK Medicines anticipates that TY-9591 combined with chemotherapy will similarly enhance antitumor efficacy compared to its monotherapy. Considering the potential safety and efficacy advantages of TY-9591 over Osimertinib in monotherapy, TYK Medicines believes its combination therapy has the potential to further improve efficacy and benefit NSCLC patients with EGFR L858R mutation and exon 19 deletion.

TY-302 – selective oral CDK4/6 inhibitor

TY-302 is a potent, selective oral CDK4/6 inhibitor developed for the treatment of advanced solid tumors, including breast cancer and prostate cancer. TY-302 acts as an inhibitor of CDK4/6, a key regulator of the cell cycle. It suppresses the phosphorylation of the Rb, preventing proliferation of cancer cells. TY-302 was modified by H/D exchange of Palbociclib, the best-selling CDK4/6 inhibitor in the world. Because TY-302 has a better PK profile than Palbociclib (based on data from the Company's Phase I clinical trial), and it demonstrated preliminary safety and antitumor efficacy in the same trial, TYK Medicines believes that TY-302 is a potentially improved CDK4/6 inhibitor.

TYK Medicines is currently conducting a Phase I/II clinical trial of TY-302 in breast cancer. TYK Medicines also plans to commence a Phase II clinical trial of TY-302 in prostate cancer in 1H25, and the Company expects to commence a registrational Phase III clinical trial of TY-302 in combination with Abiraterone as a first-line treatment in the second half of 2026.

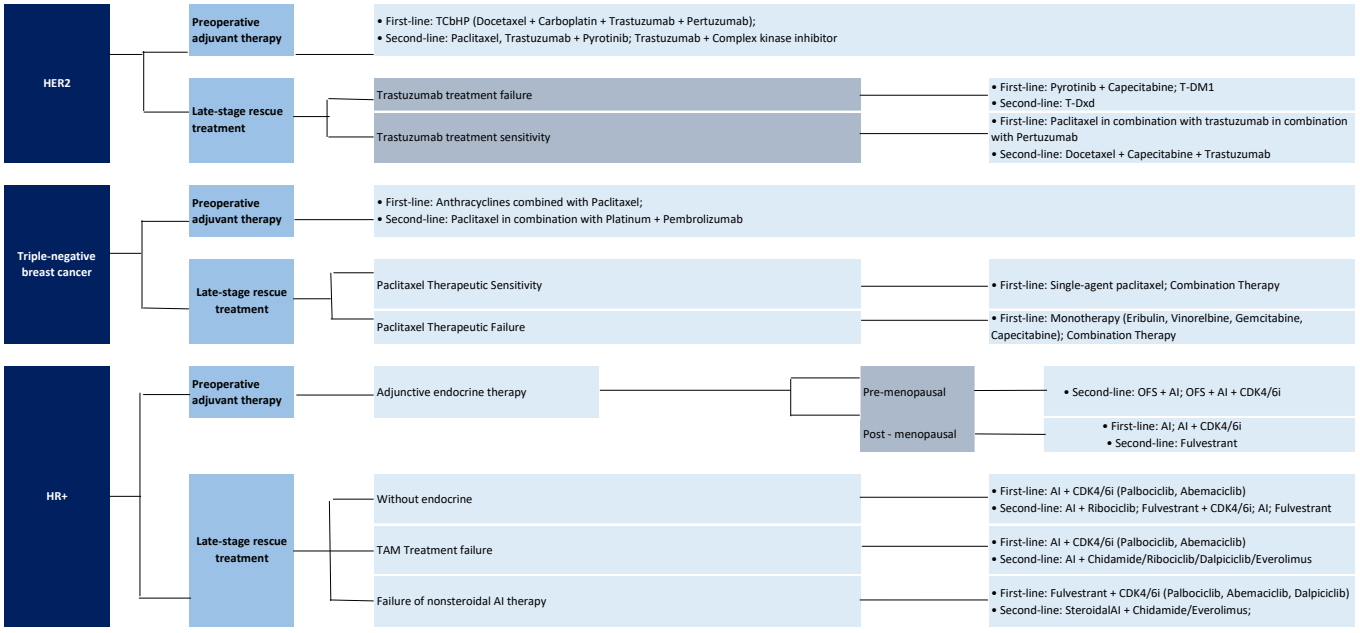
Breast cancer – The most common cancer in women

Breast cancer is the most common cancer in women, and its incidence rises with age, increasing year by year as women age. It mostly occurs in women of age 50. Developing from breast tissue, breast cancer may present as a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, a newly inverted nipple, or a red or scaly patch of skin.

The global number of new breast cancer cases increased from 2,045.0 thousand in 2017 to 2,394.8 thousand in 2023, and it is expected to reach 2,865.8 thousand in 2033. The number of new breast cancer cases in China increased from 315.2 thousand in 2017 to 345.5 thousand in 2023, and it is projected to reach 376.9 thousand in 2033, according to Frost & Sullivan.

CDK4/6 inhibitors are novel targeted therapeutic agents, which are mainly applied to HR+/HER2– breast cancer patients. They are making a breakthrough in related endocrine treatment modalities. Compared to traditional endocrine therapy alone, CDK4/6 inhibitors combined with endocrine therapy have significantly prolonged the progression-free survival of breast cancer patients, and they were well tolerated. The treatment paradigm for breast cancer in China is shown below.

Figure 17: Treatment paradigm for breast cancer in China



Source : CSCO(2023), Frost & Sullivan

HR+/HER2− breast cancer

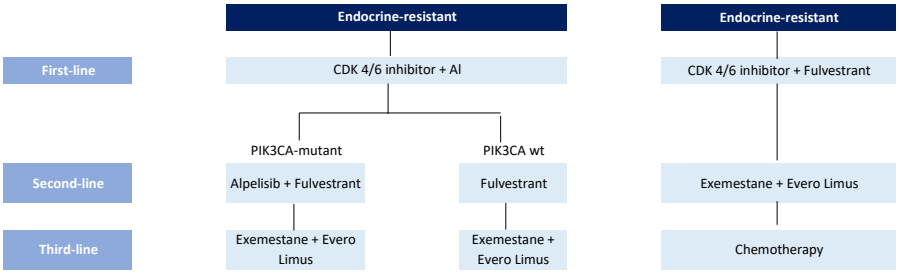
HR+/HER2− breast cancer is a tumor that has tested positive for estrogen and progesterone receptors and negative for HER2. This subtype accounts for most cases of breast cancer. Results of related studies have shown that CDK4/6 inhibitors in combination with endocrine therapy have extended preferred indications for endocrine therapy and provided benefits for HR+/HER2− patients. There are four main female breast cancer subtypes (in order of prevalence): HR+/HER2−, HR−/HER2−, HR+/HER2+, and HR−/HER2+. The breast cancer subtype HR+/HER2− is the most common subtype, as around 60% of breast cancers are HR+/HER2−.

ER+/HER2− indicates specific molecular characteristics of breast cancer cells. Estrogen receptor positive or "ER+" means that the breast cancer cells express estrogen receptors, indicating sensitivity to antiestrogen. "HER2−" signifies that these breast cancer cells do not overexpress human epidermal growth factor receptor 2 (HER2), distinguishing them from other breast cancer types in which HER2 is overexpressed. ER+/HER2− breast cancer is a relatively common subtype. HR+ includes both ER+ and progesterone receptor positive (PR+). In HR+ breast cancer, it typically involves the simultaneous expression of both estrogen receptors and progesterone receptors. About 80% of all HR+ breast cancers are ER+ or ER/PR +.

According to Frost & Sullivan, the global number of new HR+/HER2− breast cancer cases increased from 1,267.9 thousand in 2017 to 1,484.8 thousand in 2023, and this is expected to reach 1,776.8 thousand in 2033. In China, the number of new HR+/HER2− breast cancer cases increased from 189.1 thousand in 2017 to 207.3 thousand in 2023, and this is expected to reach 226.1 thousand in 2033.

According to the treatment guidelines for HR+/HER2– breast cancer, the antitumor treatment regimen for resectable breast cancer is surgery plus systemic therapy. Once the disease progresses and becomes locally advanced or metastatic breast cancer, the first-line recommended therapy is endocrine therapy combined with CDK4/6 inhibitors. The treatment paradigm for HR+/HER2– breast cancer in China is shown below.

Figure 18: Treatment paradigm for HR+/HER2– breast cancer in China



Source : CSCO(2023), JCO Oncology Practice, Frost & Sullivan

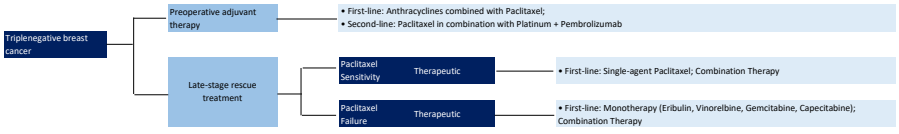
TNBC

TNBC is characterized by a lack of estrogen and progesterone receptor expression, and it lacks HER2 over-expression or gene amplification. It accounts for approximately 15% of the total breast cancer population globally. TNBC is typically diagnosed more frequently in younger and premenopausal women. It is a biologically aggressive tumor, characterized by moderate/high-grade and highly proliferative cancer cells, which, together with limited treatment options, leads to the poorest prognosis among breast cancer subtypes.

According to Frost & Sullivan, the number of new TNBC cases has historically shown steady growth, and this is anticipated to continue in the future. Globally, the number of new TNBC cases increased from 306.8 thousand in 2017 to 359.2 thousand in 2023. The number is forecasted to reach 387.6 thousand in 2027 and 429.9 thousand in 2033. The number of new TNBC cases in China increased from 47.3 thousand in 2017 to 51.8 thousand in 2023. The number is forecasted to reach 54.2 thousand in 2027 and 56.5 thousand in 2033.

TNBC is a highly aggressive subtype of breast cancer. Chemotherapy is the primary treatment for TNBC, but its effectiveness is limited. In recent years, various targeted treatment strategies have emerged, based on specific molecules and signaling pathways expressed in TNBC.

Figure 19: Treatment paradigm for TNBC in China



Source : CSCO(2023), Frost & Sullivan

Unmet clinical needs of breast cancer treatment

- *Recurrence/metastatic diseases for HR+/HER2– patients.* Although outcomes for patients with breast cancer have improved in the past years, with disease-free survival increasing to a much higher rate, unmet needs remain. 30% of HR+/HER2– BC patients develop metastatic (incurable) disease at some point. The goal of treatment is to prolong life, while limiting the impact of side effects on patients' quality of life. While survival for metastatic breast cancer has improved, patients eventually need chemotherapy, which results in additional side effects. More advances are required to delay disease progression and to enable the continuation of day-to-day living.
- *Limited treatment options in the late-stage setting.* CDK4/6 inhibitors have dramatically changed the therapeutic landscape for HR+/HER2– advanced breast cancer. A combination of CDK4/6 inhibitors with endocrine therapy significantly improves patients' PFS and OS, and it reduces the risk of disease progression and death. Despite the effectiveness of current therapeutic strategies, drug resistance remains a great challenge, and there is no effective treatment for HR+/HER2– metastatic breast cancer. There is a significant need for new and effective HR+/HER2– therapeutics that can be administered to patients.
- *Addressing drug resistance in breast cancer therapy.* Currently, CDK4/6 inhibitors in combination with endocrine therapy are the standard of care in patients with HR+/HER2– metastatic breast cancer. Although the approval of CDK4/6 inhibitors has changed the treatment landscape for these patients, 10-20% of the patients turn out to be primarily resistant to this therapy, and acquired resistance eventually occurs in virtually all patients. Therefore, the mechanisms underlying resistance to CDK4/6 inhibitors and the development of new therapeutic strategies to circumvent such resistance is a hot topic in cancer research.
- *Limited treatment options for TNBC patients.* TNBC is widely recognized as an aggressive breast cancer subtype with high rates of recurrence and metastatic spread. Although targeted therapies have benefited patients with other subtypes of breast cancer, sequential single-agent chemotherapy remains the standard of care for patients with TNBC.

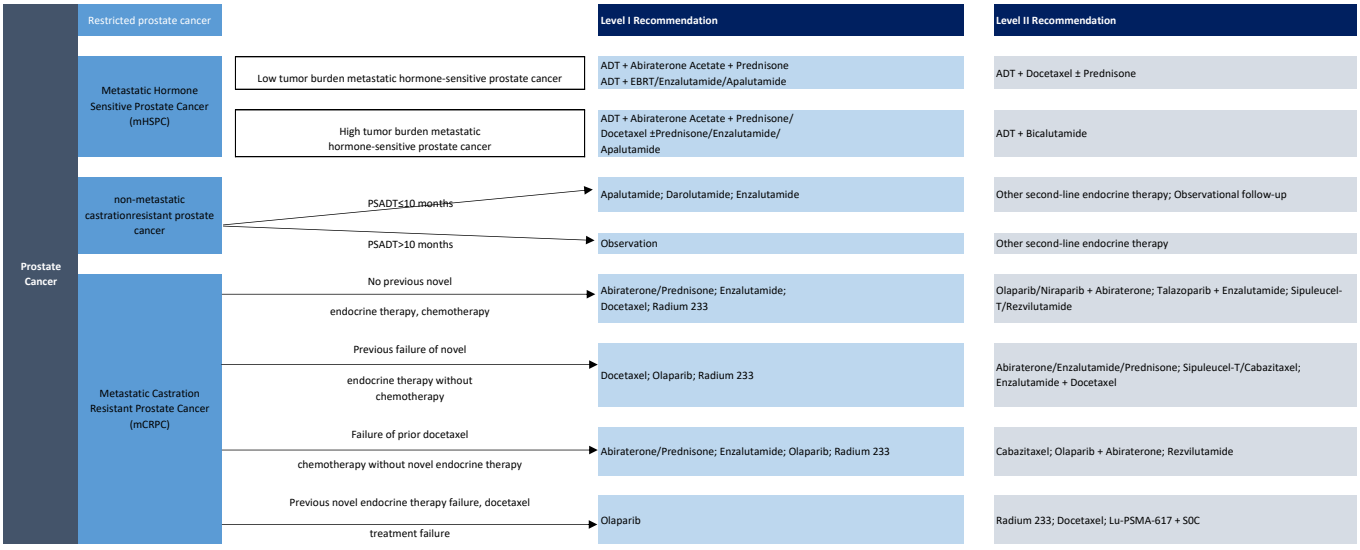
Prostate cancers

Prostate cancer is an epithelial malignant tumor that occurs in the prostate. It is the most common malignant tumor of the male genitourinary system, and it mostly occurs in people over 65 years of age. Early prostate cancer usually has no clear symptoms, often similar to those of benign prostatic hyperplasia. Metastatic prostate cancer (especially bone metastases) can cause symptoms, such as difficulty in maintaining the stream of urine, frequent urination, bone pain, dysuria (painful urination), hematuria and erection difficulty.

According to Frost & Sullivan, the number of new prostate cancer cases globally grew from 1,237.9 thousand in 2017 to 1,543.8 thousand in 2023 at a CAGR of 3.8%. This number is expected to grow and reach 2,049.6 thousand in 2033, representing a CAGR of 2.8%. The number of new prostate cancer cases in China grew from 97.3 thousand in 2017 to 132.7 thousand in 2023 at a CAGR of 5.3%. This number is expected to grow, potentially reaching 189.1 thousand in 2033.

Currently, national guidelines unanimously recommend Abiraterone Acetate for first-line treatment of patients with metastatic desmoplasia-resistant prostate cancer. Prostate cancer is an androgen-sensitive tumor, and androgens play a key role in prostate carcinogenesis through their interaction with the androgen receptor. Abiraterone is an endocrine therapeutic agent that blocks androgen synthesis, but an increasing number of preclinical and clinical studies have revealed that the signaling pathway is frequently disregulated and resistant in prostate cancer after Abiraterone treatment, and new therapeutic options are urgently needed in clinics. Studies have demonstrated that CDK4/6 inhibitors inhibit tumor growth and reverse drug resistance in preclinical models such as prostate cancer, and CDK combined with abiraterone may have potential synergistic antitumor efficacy in prostate cancer.

Figure 20: Treatment paradigm for prostate cancer in China



Source : CSCO, Frost & Sullivan

mCRPC

Almost all advanced prostate cancer patients eventually progress to CRPC after undergoing hormonal therapy, with mCRPC being the primary cause of patient death. The main goal for treating mCRPC is to control symptoms and slow progress. Even though ADT or hormone therapy may no longer work completely to stop prostate cancer from growing, most men with mCRPC remain on ADT because some prostate cancer cells continue to respond to it. Other cells require additional treatment to keep the cells from forming.

According to Frost & Sullivan, in 2017, global mCRPC incidence was 121.3 thousand, growing to 151.3 thousand in 2023 at a 3.8% CAGR. Predictions indicate further growth to 170.4 thousand in 2027 and 200.9 thousand in 2033, at CAGRs of 3.0% and 2.8%, respectively. In China, mCRPC incidence was 48.7 thousand in 2017, reaching 66.4 thousand in 2023 at a 5.3% CAGR. Projections suggest that it will reach 76.6 thousand in 2027 and 94.6 thousand in 2033, at CAGRs of 3.6% and 3.6%, respectively.

Figure 21: Treatment paradigm for mCRPC in China

Therapy Regimen	Level 1 recommendation	Level 2 recommendation
No prior novel endocrine therapy or chemotherapy	• Abiraterone/Prednisone • Enzalutamide • Docetaxel • Radium 233	• Olaparib/Niraparib + Abiraterone • Talazoparib + Enzalutamide • Sipuleucel-T/Rezvilutamide
Previous failure of novel endocrine therapy without chemotherapy	• Docetaxel • Olaparib • Radium 233	• Abiraterone/Enzalutamide/Predn sone • Sipuleucel-T/Cabazitaxel • Enzalutamide + Docetaxel
Failure of prior docetaxel chemotherapy without novel endocrine therapy	• Abiraterone/Prednisone • Enzalutamide • Olaparib • Radium 233	• Olaparib + Abiraterone • Cabazitaxel • Rezvilutamide
Failure of prior novel endocrine therapy and docetaxel chemotherapy	• Olaparib	• Radium 233 • Docetaxel • Lu-PSMA-617+S0C

Source : CSCO, Frost & Sullivan

Drug treatments are becoming less available. Hence, there is an urgent need for prolonged survival. The current approved primary treatment option for adult patients with mCRPC who have failed prior therapy is chemotherapy with a combination of novel endocrine agents or Paclitaxel on top of depot therapy. mCRPC patients who have progressed on novel endocrine agents often lack an effective treatment regimen.

CDK inhibitor drug market

CDKs are a group of serine/threonine kinases whose activity is regulated by both cell cycle proteins and CDK inhibitors. They play crucial roles in governing cell cycle checkpoints and DNA transcription, acting as pivotal regulators during cell division and proliferation. By forming heterodimers with cell cycle proteins in response to diverse internal and external cell signals, CDKs regulate cell division. In humans, the CDK and cell cycle protein family is extensive, comprising 29 cell cycle proteins and 20 CDK proteins identified so far. While CDKs 1, 2, 3, 4, and 6 directly influence cell cycle transitions and division, CDKs 7-11 primarily govern DNA transcription.

Early development efforts focused on the development of nonselective CDK inhibitors, with activities against multiple CDKs. For example, Alvocidib, which inhibits CDK1, 2, 4, 6, 7 and 9, and Seliciclib, which inhibits CDK1, 2, 5, 7 and 9, have entered clinical trials and been assessed for various types of tumors. However, these drugs have shown limited clinical activity. This is because many CDK proteins are critical for the function of normal tissues, and the nonselectivity of these compounds likely limits their ability to discern cancer cells from normal cells, resulting in a narrow therapeutic window and associated toxicities, including fatigue, diarrhea, nausea and hyperglycemia.

More recent efforts have focused on developing selective CDK inhibitors, including CDK4/6, CDK2/4/6 and CDK7 inhibitors. CDK4/6, CDK2/4/6, and CDK7 are all selective CDKs, but they have different roles and functions in the cell cycle. The CDK4/6 inhibitor, the pioneer approved in 2015, remains the sole CDK inhibitor authorized for marketing in the world. Nevertheless, patients receiving CDK4/6 inhibitor treatment eventually develop progressive disease due to intrinsic or acquired drug resistance. It has been found that when CDK4/6 activity is inhibited, tumor cells can leverage CDK2-CDK2 Cyclin E activation as a complementary

compensatory pathway to facilitate the proliferation of tumor cells. To combat resistance stemming from CDK4/6 inhibitors, one ongoing development effort is focusing on the CDK2/4/6 inhibitor to address this challenge. In addition, efforts are being made to explore CDKs' role in regulating DNA transcription. Recently developed, highly specific inhibitors of CDK7 have been instrumental in revealing the potential of CDK7 as a cancer drug target. Studies in mice have shown that CDK7 inhibitors are well tolerated and effective at reducing tumor growth *in vivo*, making CDK7 inhibitors promising candidates for cancer treatment.

As of the Latest Practicable Date, there were five CDK inhibitors approved and marketed globally, namely, Palbociclib, Abemaciclib, Dalpiciclib, Trilaciclib and Ribociclib, all of which targeted CDK4/6, with the main therapeutic areas focusing on solid tumors, such as breast cancer. The global CDK4/6 inhibitors market grew from US$3.2bn in 2017 to US$10.7bn in 2023 at a CAGR of 22.2%. With an increasing number of CDK4/6 inhibitors coming to market, the market size will likely continue to expand in the future, and the global CDK 4/6 inhibitors market is expected to reach approximately US$16.1bn and US$26.2bn in 2027 and 2033, respectively, at a CAGR of 10.6% from 2023 to 2027 and a CAGR of 8.5% from 2027 to 2033, according to Frost & Sullivan,.

Competitive landscape of CDK inhibitors globally and in China

As of the Latest Practicable Date, there were 34 CDK inhibitor candidates under clinical development globally, among which the most clinically advanced candidates were CDK4/6 inhibitors in the Phase III clinical stage, and all CDK2/4/6 inhibitor candidates were in Phase I clinical trials. Among the 34 CDK inhibitor candidates, there were seven candidates selectively targeting CDK7, with the most clinically advanced candidate in the Phase II stage. TYK Medicines is the only company developing multiple candidates targeting different members within the CDK family.

Figure 22: Competitive landscape for the global CDK4/6, CDK7 and CDK2/4/6 inhibitor pipeline

Drug Name/ Code	Company	Indications	Target	Clinical Stage	First Posted Date
Dalpiciclib	Jiangsu HengRui Medicine	HR+/HER2-Breast Cancer	CDK4/6	III	2023/05
BPI-16350	Betta Pharmaceuticals	HR+ and HER2-Breast Cancer	CDK4/6	III	2022/06
TQB3616	Chia Tai Tianqing Pharmaceutical	Breast Cancer	CDK4/6	III	2023/03
Lerociclib	Genor Biopharma	HR+/HER2-Breast Cancer	CDK4/6	III	2023/04
XZP-3287	Xuanzhu Biopharmaceutical	HR+/HER2-Breast Cancer	CDK4/6	III	2022/02
HS-10342	Jiangsu Hansoh Pharmaceutical	HR+/HER2-Breast Cancer	CDK4/6	II	2021/09
SPH4336	Shanghai Pharmaceuticals	HR+/HER2-Breast Cancer	CDK4/6	II	2023/05
BPI-1178	Beta Pharma (Suzhou)	Advanced Solid Tumor, HR+/HER2-Breast Cancer	CDK4/6	I/II	2020/02
GLR2007	Gan & Lee Pharmaceuticals	NSCLC, Glioblastoma Multiforme	CDK4/6	I/II	2020/06
TY-302	**TYK Medicines, Inc**	**Breast Cancer, Prostate Cancer, Solid Tumor**	**CDK4/6**	**I**	**2020/06**
UCT-03-008	1200 Pharma	Advanced Solid Tumor	CDK4/6	I	2021/10
BEBT-209	BeBetter Med	HR+/HER2-Breast Cancer	CDK4/6	I	2023/09
PRT3645	Prelude Therapeutics	Breast Cancer	CDK4/6	I	2022/09
Samuraciclib	Carrick Therapeutics/Pfizer	HR+/HER2-Breast Cancer	CDK7	II	2023/08
TY-2699a	**TYK Medicines, Inc**	**Solid Tumors**	**CDK7**	**I**	**2023/05**
EOC237	Shanghai Yiteng Jingang Biopharmaceutical Technology	Advanced Solid Tumor	CDK7	I	2023/05
GTAEXS617	GT Apeiron Therapeutics	Advanced Solid Tumor	CDK7	I	2023/07
Q901	Qurient/Merck Sharp & Dohme	Solid Tumor	CDK7	I	2022/05
XL102	Exelixis	Neoplasm Malignant, Epithelial Ovarian Cancer, HR+/HER2-Breast Cancer, TNBC, Metastatic Castration-resistant Prostate Cancer	CDK7	I	2021/01
SY 5609	Syros Pharmaceuticals	Advanced Solid Tumor, Breast Cancer, SCLC, Pancreatic Cancer	CDK7	I	2020/01
TY-0540	**TYK Medicines, Inc**	**Advanced solid tumors**	**CDK2/4/6**	**I**	**2024/01**
RGT-419B	Regor Therapeutics	HR+/HER2-Breast Cancer	CDK2/4/6	I	2022/02
SYH2043	CSPC Ouyi Pharmaceutical	Advanced Malignant Tumors	CDK/2/4/6	I	2023/01

Source : clinicaltrials.gov, Frost & Sullivan

As of the Latest Practicable Date, there were 26 CDK inhibitor candidates under development in China. TY-302 was the only CDK4/6 inhibitor indicated for prostate cancer. In addition, TY-2699a and TY-0540 were the most clinically advanced CDK7 inhibitor and CDK2/4/6 inhibitor, respectively. TYK Medicines is the only company developing multiple candidates targeting different members within the CDK family.

Figure 23: Competitive landscape for the CDK4/6, CDK7 and CDK2/4/6 inhibitor pipeline in China

Drug Name/ Code	Company	Indications	Target	Clinical Stage	First Posted Date
BPI-16350	Betta Pharmaceuticals	HR+/HER2-Breast Cancer	CDK4/6	III	2022/05
BEBT-209	BeBetter Med	HR+/HER2-Breast Cancer	CDK4/6	III	2022/02
TQB3616	Chia Tai TianQing Pharmaceutical	HR+/HER2-Breast Cancer	CDK4/6	III	2022/01
FCN-437c	Fosun Pharma	HR+/HER2-Breast Cancer	CDK4/6	III	2021/12
XZP-3287	Xzenith/Sihuan Pharmaceutical	HR+/HER2-Breast Cancer	CDK4/6	III	2021/09
SPH4336	Shanghai Pharmaceuticals	HR+/HER2-Breast Cancer	CDK4/6	II	2023/05
BPI-1178	Beta Pharma, Inc. (Suzhou)	HR+/HER2-Breast Cancer	CDK4/6	I/II	2020/02
GLR2007	Gan & Lee Pharmaceuticals	Glioblastoma	CDK4/6	I/II	2021/10
TY-302	**TYK Medicines, Inc**	**HR+/HER2-Breast Cancer, Prostate Cancer**	**CDK4/6**	**I**	**2020/06**
YZJ-2440	Yangtze River Pharmaceutical	HR+HER2-Breast Cancer, Solid Tumor	CDK4/6	I	2020/12
XH-30002	JinRui Foundation Biotechnology	HR+/HER2-Advanced Breast Cancer, Advanced Colorectal Cancer, Advanced Esophageal Cancer, or Advanced Gastric Cancer	CDK4/6	I	2020/12
HS-10342	Hansoh Pharma	Breast cancer, solid tumor	CDK4/6	I	2021/09
QHRD110	Changzhou Qianhong Biopharma	Malignant tumors of the central nervous system	CDK4/6	I	2023/11
SDT-101	Suzhou Splendustx Pharmaceutical	Advanced malignant solid tumor	CDK4/6	I	2020/03
TY-2699a	**TYK Medicines, Inc**	**TNBC, ER+HER2-Breast Cancer, PDAC**	**CDK7**	**I**	**2023/05**
EOC237	EOC Biopharma (Shanghai)	Solid tumor	CDK7	I	2023/05
TY-0540	**TYK Medicines, Inc**	**Advaned solid tumor**	**CDK/2/4/6**	**I**	**2023/11**
WXWH0240	Cisen Pharmaceutical	HR+HER2-Breast Cancer, Recurrent/Refractory Ovarian Cancer	CDK2/4/6	I	2021/10
SYH2043	CSPC Pharmaceutical	Breast cancer	CDK2/4/6	I	2023/02

Source : CDE, Frost & Sullivan

Future trends in the CDK inhibitor market

- *Overcoming drug resistance.* The main mechanisms of CDK4/6 inhibitor resistance include aberrant activation of upstream oncogenic signals and alterations in key cell cycle regulators. Cell cycle protein E1, encoded by the CCNE1 gene, activates CDK2 and promotes cell cycle progression. High expression of cell cycle protein E1 not only predicts poor prognosis in breast cancer patients, but also promotes resistance to endocrine therapy and CDK4/6 inhibitors. Previous studies have shown that cell cycle protein E1 may play a key role in CDK4/6 inhibitor resistance, and direct targeting of cell cycle protein E1 may be an effective way to overcome drug resistance. Meanwhile, CDK2 and CDK4 are protein kinases in cell cycle regulation, and they are closely related to tumorigenesis and progression. By interfering with the activities of CDK2 and CDK4, proliferation and survival of cancer cells can be affected, which is expected to help overcome certain types of drug resistance.
- *The development of selective CDK inhibitors is promising.* CDK has a wide range of physiological activities, and it has broad application prospects in the treatment of breast, pancreatic, prostate, ovarian and small-cell lung cancers. As technology has advanced, CDK inhibitor research has made some progress, but there are still major technical challenges in terms of subtype selectivity, combination therapy development and multi-target inhibitor development. Pan-CDK inhibitors have inherent problems, such as low specificity. Compared to pan-CDK inhibitors, selective CDK inhibitors have higher levels of safety and specificity, and the prospects for future development are more promising.

- *Expansion of Indications.* In the future, indications for CDK4/6 inhibitors in cancer treatment may not be limited to breast cancer. Currently, the state of research and the clinical pipeline show significant effects of CDK4/6 inhibitors in the treatment of other cancers, including recurrent/metastatic ovarian cancer, K-RAS mutated NSCLC, prostate cancer, hematoma and other advanced solid tumors. We believe that companies could achieve more progress/breakthroughs in the field of CDK4/6 inhibitor research, benefiting more cancer patients.
- *CDK4/6 inhibitors, combined with endocrine therapy, should further optimize antitumor regimens.* Combined endocrine therapies are effective in antitumor treatment, and they are a trend in terms of future clinical trials. CDK4/6 inhibitors have made great progress so far, especially for patients with hormone-receptor-positive advanced breast cancer. Considering that endocrine therapy is an effective treatment with fewer and more reversible side effects, CDK4/6 in combination with endocrine therapy may yield an improved safety and efficacy profile. We believe it is likely that the direction of future drug development will broaden further, potentially combining antitumor therapies in order to develop better oncological solutions. In the meantime, research is being actively directed toward identifying biomarkers (other than the estrogen receptor) that might be suggestive of the efficacy of CDK4/6 inhibitors, helping to achieve individualized precision.
- *Optimization of prostate cancer regimens.* Abiraterone serves as an endocrine therapeutic agent by blocking androgen synthesis. Despite its intended efficacy, an increasing number of both preclinical and clinical studies have uncovered frequent disregulation and resistance within the signaling pathway in prostate cancer after Abiraterone treatment. Consequently, there is urgent demand for novel therapeutic alternatives in the clinical setting to overcome the challenges associated with the development of resistance during Abiraterone treatment. Research findings have shown that CDK4/6 inhibitors effectively restrain tumor growth and that they can reverse drug resistance in preclinical models, including prostate cancer. The combination of CDK inhibitors with Abiraterone is generally believed to hold significant potential for synergistic antitumor efficacy in the context of prostate cancer.

TY-302: mechanism of action

The cyclin-dependent kinase, CDK4/6, is a key regulator of the cell cycle, and by forming a complex with cyclin D, it phosphorylates Rb and then releases transcription factor E2F, which facilitates the transcription of cell-cycle-related genes and allows cells to enter the S-phase. CDK4/6 inhibitors efficiently block the progression of tumor cells from the G1 phase to the S-phase.

The CDK-RB1-E2F pathway targeted by CDK4/6 inhibitors is essential for progression through the cell cycle, and it is disrupted in the majority of cancers. In breast cancer, the activation of estrogen receptors, as well as other proliferation-inducing signals, stimulates the complexation of CDK4/6 with cyclin D1. Binding of CDK4/6 to cyclin D1 induces phosphorylation of the Rb tumor suppressor protein, releasing its inhibitory effect and thereby providing the starting signal for cell division. Normally, CDK4 and CDK6 are inhibited by protein p16. However, in cancer, this mechanism of cell cycle control is often disrupted. Furthermore, cyclin D1, the binding partner of CDK4/6, is often overexpressed in patients with HR+/HER2– breast cancer, leading to continuous activation of the cyclin D1-CDK4/6 complex. Inhibition of CDK4/6 induces complete dephosphorylation of Rb,

resulting in sequestration of transcription factor E2F and subsequent inhibition of cell cycle progression.

In prostate cancer, the androgen receptor serves as a pivotal driver in the cancer's progression and development. The androgen receptor is a ligand-dependent transcription factor, and in prostate cancer, ligand activation of androgen receptors initiates the cell cycle, and androgen receptor signaling interacts with the cell cycle and controls receptor-dependent cell proliferation. Alterations in the cyclin D-CDK4/6-Rb pathway axis cause cell cycle abnormalities, leading to uncontrolled G1-S phase transition, one of the most frequent pathway variants in prostate cancer. Intervention in these molecular functions could be a molecular target for prostate cancer therapy. As in breast cancer, CDK4/6 inhibitors inhibit prostate tumor growth by inhibiting cyclin D1-CDK4/6 activity and promoting inactivation of Rb tumor suppressors, resulting in cells undergoing G1-phase blockade.

As a CDK4/6 inhibitor, TY-302 can inhibit CDK4/6 activity, down-regulate the level of phosphorylated Rb and effectively block the progression of tumor cells from the G0/G1 phase to the S phase in a dose-dependent manner, thereby blocking the cell cycle and leading to apoptosis of tumor cells.

Competitive advantages

Validated mechanism of action

CDK4/6 inhibitors may retard cancer progression through diverse mechanisms (in addition to cell-cycle regulation). The *in vivo* functions of CDK4/6 inhibition are likely to extend beyond simply enforcing reversible cytostasis. Some studies have shown that some Rb-positive cells undergo quiescence and others undergo senescence when treated with CDK4/6 inhibitors, depending on the cell type and the transforming event. It is known that senescent cells are characterized by metabolic changes and elaboration of cytokines that modulate the immune response. Thus, the ability of CDK4/6 inhibitors to drive tumor cells into senescence may lead to changes in the immune response and cellular metabolism, yielding a unified mechanistic cellular response.

TY-302 was modified by H/D exchange of Palbociclib. Palbociclib in combination with aromatase inhibitors has been approved for the treatment of advanced breast cancer in the US, the European Union and China (under the trade name IBRANCE). The safety and efficacy of Palbociclib have been widely validated in HR+/HER2– breast cancer patients. Namely, according to PALOMA-1, Palbociclib and Letrozole demonstrated a median PFS of 20.2 months in HR+/HER2– untreated advanced breast cancer. In PALOMA-2, treatment-naive patients with HR+/HER2– advanced breast cancer who received Palbociclib and Letrozole achieved a median PFS of 24.8 months. In PALOMA-3, women of any menopausal status with HR+/HER2– advanced breast cancer whose disease had progressed on prior endocrine therapy or recurred within 12 months of stopping adjuvant endocrine therapy were randomized to receive either Palbociclib and Fulvestrant or placebo and Fulvestrant. Approximately half of the patients had received two or more lines of endocrine therapy in the metastatic setting, and approximately one-third had received chemotherapy in the metastatic setting. Final analysis demonstrated a median PFS of 9.5 months in the Palbociclib and Fulvestrant group, compared to 4.6 months in the placebo and Fulvestrant group.

Encouraging clinical data

According to Phase I clinical data, TY-302 obtained a favorable PK portfolio. In the Phase I single-agent dose escalation phase, patients were given 25mg, 50mg, 75mg, 100mg or 125mg TY-302 once daily, 28 days as a cycle. In the Phase II combination therapy dose escalation and expansion phase, patients were given TY-302 in combination with 60mg of Toremifene Citrate for the 28-day cycle. PK characters of TY-302 were evaluated after receiving single or multiple dosing, respectively. The main PK parameters of TY-302 in Phase I were presented as follows:

After a single oral administration of 25mg, 50mg, 75mg, 100mg or 125mg of TY-302, the median time to peak plasma concentration of TY-302 was four to seven hours, and the mean half-life was more than 29 hours at all dose levels. The exposure of TY-302 (Cmax and AUC) demonstrated a direct correlation with the escalating dose. After repeated dosing to a steady state, TY-302 showed mild to moderate accumulation in patients. Compared to single-agent administration in the Phase I study, TY-302 combination therapy in dose escalation and extension phases showed similar PK profiles, indicating that Toremifene had no significant effect on the PK of TY-302, and the risk of drug-drug interactions was low.

Palbociclib was evaluated in a Phase I trial (NCT01684215, A5481010) in Japanese patients as monotherapy for solid tumors (part 1) and combined with Letrozole as a first-line treatment of postmenopausal patients with ER+/HER2– advanced breast cancer (part 2). Part1 evaluated Palbociclib 100 and 125mg once daily (3 weeks on/1 week off) to determine the maximum tolerated dose and preliminary efficacy of Palbociclib in patients. Part 2 evaluated the overall safety and preliminary efficacy of the combination of the MTD of 125mg of Palbociclib, plus 2.5mg of Letrozole. PK samples were collected after single or multiple doses to investigate the combinations' PK behavior in humans. The main parameters were listed as follows.

Figure 24: Summary of Plasma Palbociclib PK Parameter Values Following Single and Multiple Dosing

	Single Dose						Multiple Doses			
Dose	N	T_{max} (1) h	C_{max} ng/mL	AUC_{0-24h} h*ng/mL	$AUC_{0-\infty}$ h*ng/mL	$t_{1/2}$ (2) h	N	$T_{ss,max}$ h	$C_{ss,max}$ ng/mL	$AUC_{0-\tau}$ h*ng/mL
100mg	6	5.0	41.4	547.5	1039	25.7	6	4.0	77.4	1276
125mg	6	4.0	104.1	1322	2483	23.9	6	4.0	185.5	2838

(1) Data expressed as median;
(2) Data expressed as arithmetic mean.
Source: Literature Review

Compared to the PK data of Palbociclib in Japanese patients, the exposure of TY-302 in Chinese patients was significantly higher than that of Palbocilib after single and multiple administrations of the same dosage level of 100mg. In addition, in the Company's Phase I study, TYK Medicines also observed that exposure of TY-302 at 100mg was comparable to Palbociclib at 125mg in the Phase I trial (NCT01684215, A5481010) in Japan.

Compared to Palbociclib, based on preliminary safety data collected through the Company's Phase I/II clinical trial, TY-302 achieved a comparable safety profile. Among 23 solid tumor patients evaluated in the Phase I/II trial, TYK Medicines observed an encouraging safety profile.

TY-302 also showed encouraging preliminary efficacy, according to the data collected from the Phase I/II trial. Among 14 breast cancer patients who received one or more lines of antitumor treatments, eight patients achieved SD and two achieved PR, with a DCR of 71.4%.

Strategic clinical development plan

Later-line ER+/HER2− breast cancer

TYK Medicines adopts a differentiated clinical development strategy for breast cancer, targeting patients with third- or later-line ER+/HER2− breast cancer that has progressed after second-line endocrine therapy (i.e., Aromatase inhibitors or Fulvestrant). These patients have many options for treatment, but no standard of care exists for the next line of systemic therapy. Possible strategies include switching to different classes of endocrine therapy, switching to chemotherapy (as a single agent or in combination) or utilizing novel targeted agents. The optimal sequencing of the options above is not well established.

TYK Medicines is exploring TY-302 in combination with Toremifene for the treatment of third- or later-line ER+/HER2− breast cancer that has progressed after second-line endocrine therapy. Toremifene is a selective estrogen receptor modulator. That is, it is a selective mixed agonist–antagonist of the ERs, with estrogenic actions in some tissues and anti-estrogenic actions in other tissues. It is approved for the treatment of metastatic breast cancer in post menopausal women with ER+ or unknown-status tumors. Approved almost 30 years ago, Toremifene has a well established safety and efficacy profile in breast cancer patients.

Palbociclib in combination with Letrozole was approved by the FDA in 2015 for the treatment of 1L HR+/HER2− breast cancer. According to the Phase III PALOMA-2 clinical trial, Palbociclib in combination with Letrozole achieved a significantly improved mPFS compared to the control group (24.8 vs 14.5 months). Considering that TY-302 was modified by H/D exchange of Palbociclib and that it might have better safety and efficacy, and given that Letrozole and Toremifene are both estrogen receptor modulators that have similar mechanisms of action, TYK Medicines believes that TY-302 in combination with Toremifene will also achieve synergistic antitumor effects in ER+/HER2− patients.

1L mCRPC

Clinically, for androgen-sensitive prostate cancer, endocrine therapy via androgen receptor-androgens is a standard treatment, with Abiraterone treatment (to hinder androgen synthesis) being an important modality throughout the course of the disease. Abiraterone tablets, which effectively block androgen production from testicular, adrenal, and intra-tumoral sources by inhibiting the activity of CYP17, a key enzyme in the androgen synthesis pathway, reduce testosterone levels in the blood and bone marrow of prostate cancer patients to the lower limits of detection. Although Abiraterone significantly prolongs patient survival, many patients remain resistant to it after a period of treatment.

With the success of CDK4/6 inhibitors in the treatment of breast cancer, CDK4/6 inhibitors are expanding to other indications. Their mechanisms of action support a potential synergistic effect of TY-302 combined with Abiraterone to strongly regulate the cell cycle in prostate cancer. As such, TYK Medicines believes that the combination could delay disease progression and prolong survival of mCRPC patients. TYK Medicines has chosen to use Abiraterone Acetate tablets as a combination drug, expecting the combination of Abiraterone Acetate and TY-302 to produce a synergistic antitumor effect, potentially providing more therapeutic approaches for Chinese patients with mCRPC.

TY-2136b – selective oral ROS1/NTRK inhibitor

TY-2136b is an internally developed, selective oral inhibitor of ROS1/NTRK for the treatment of advanced cancer. It was designed to efficiently bind with active kinase conformation and avoid steric interference from a variety of clinically resistant mutations. The compact structure is believed to allow TY-2136b to precisely and efficiently bind to the ATP binding pocket of kinase, potentially circumventing the steric interference that results in resistance to bulkier kinase inhibitors. As an innovative ROS1/NTRK inhibitor, TY-2136b is effective against ROS1/NTRK oncogenic gene mutations. It also exhibits high selectivity of ROS1 and NTRK mutations, such as the ROS1 G2032R mutation and NTRK G595R, which commonly contribute to resistance against existing ROS1/NTRK drugs.

TYK Medicines received IND approval for conducting Phase I and Phase II clinical trials of TY-2136b for the treatment of solid tumors from the FDA in November 2021. Livzon received IND approval for conducting Phase I and Phase II clinical trials of TY-2136b for the treatment of solid tumors from the NMPA in February 2022. In September 2023, TYK Medicines received the Orphan Drug Designation of TY-2136b for the treatment of ROS1-positive, NTRK fusion-positive, ALK-positive or LTK-positive NSCLC from the FDA. Livzon is currently conducting a Phase Ib clinical trial of TY-2136b in China, and TYK Medicines is conducting a Phase I clinical trial in the US. Leveraging Phase I clinical data collected in China and the US, TYK Medicines plans to communicate with the FDA and carefully design the Company's future clinical development plan of TY-2136b in the US.

Mechanism of action

ROS1 is a pivotal transmembrane receptor protein tyrosine kinase that regulates several cellular processes, like apoptosis, survival, differentiation, proliferation, cell migration and transformation. There is increasing supportive evidence that ROS1 plays an important role in different malignancies, including glioblastoma, colorectal cancer, gastric adenocarcinoma, inflammatory myofibroblastic tumor, ovarian cancer, angiosarcoma and NSCLC. Recurrent gene fusions are oncogenic drivers of various cancers. ROS1 fusions include a kinase domain containing three regions of ROS1, fusing to various partners, of which CD74 is the most common. The resultant oncoprotein is characterized by constitutive kinase activation, increased downstream signaling and, ultimately, tumor growth. Typically, ROS1 fusions do not overlap with other canonical drivers in NSCLCs, including neurotrophin tyrosine receptor kinase (NTRK) fusions. According to Frost & Sullivan, up to 36% of patients with ROS1 fusion-positive NSCLCs have brain metastases upon diagnosis of advanced disease, and many others subsequently develop intracranial metastases. This fact highlights the need for novel ROS1 inhibitors in clinical therapy.

Fusions involving the NTRK gene family, including NTRK1, NTRK2 and NTRK3, lead to the expression of chimeric rearrangements in tropomyosin receptor kinases (TRKs) A, B and C, respectively, with constitutively active kinase function. NTRK fusions were observed in 0.31% of adult tumors and 0.34% of pediatric cancers, mostly in NTRK3 (0.16% of adult tumors) and NTRK1 (0.14% of pediatric tumors). So far, a total of two small NTRK-targeting inhibitors have been approved by the FDA, including Larotrectinib and Entrectinib.

Accordingly, TKIs can be used for the treatment of ROS1/NTRK mutated NSCLCs, and several products, such as Crizotinib and Entrectinib, have received marketing approvals worldwide. These ROS1/NTRK inhibitors have demonstrated encouraging antitumor activities in patients with NSCLC harboring ROS1/NTRK mutations. For example, Entrectinib (an oral pan-NTRK, ROS1 and ALK inhibitor approved by the FDA in 2019) has demonstrated an respective ORR, intracranial ORR and medium PFS of 67.1%, 79.2% and 15.7 months in locally advanced or metastatic ROS1 fusion-positive NSCLC. While current treatments have demonstrated effectiveness, the development of the next generation of ROS1/NTRK inhibitors aims to enhance their efficacy, simultaneously targeting the oncogene and combating drug-resistant mutations.

ROS1/NTRK-TKI market

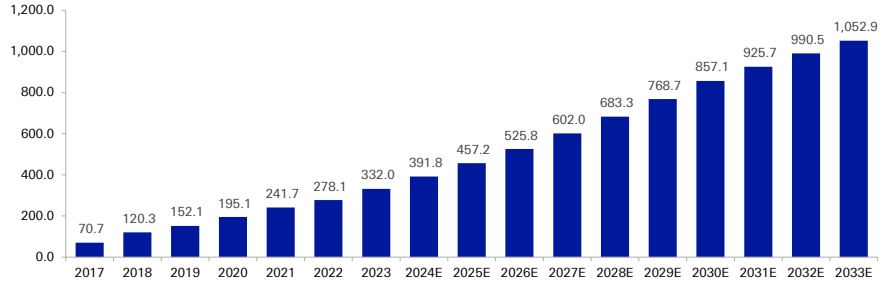
The ROS1 protein consists of three parts: the intracellular kinase domain, the transmembrane domain and the extracellular domain. The extracellular domain of the ROS1 protein binds to specific ligands, activating the intracellular kinase domain through the transmembrane domain. Activation of ROS1 leads to autophosphorylation of specific tyrosine residues within the cell, serving as docking sites for various adapter proteins. If the ROS1 gene undergoes oncogenic mutations, it activates downstream signaling pathways, causing excessive cell growth and proliferation, driving tumor development. ROS1 inhibitors can suppress the activation of the ROS1 tyrosine kinase domain, thereby inhibiting downstream signaling pathways and exerting antitumor effects.

TRK protein is a neurotrophic receptor kinase, belonging to the tyrosine kinase family. The TRK family comprises three highly homologous proteins – TRKA, TRKB and TRKC. They are encoded by the NTRK1, NTRK2 and NTRK3 genes, respectively. TRK proteins are associated with cellular processes such as proliferation, differentiation, metabolism and apoptosis. Due to gene fusion in NTRK, the extracellular domain of the TRK protein is lost, making it challenging for monoclonal antibodies to bind to the extracellular domain of the TRK protein. Therefore, small molecule NTRK-TKIs have a distinct advantage in clinical applications.

In China, ROS1 mutation accounts for approximately 1.5% of all NSCLC patients, while NTRK mutation accounts for approximately 1.0% of all NSCLC patients. From 2017 to 2023, the number of new cases of NSCLC with ROS1 or NTRK mutation worldwide increased from 36.8 thousand to 43.3 thousand, representing a CAGR of 2.7%. It is estimated that the number of new patients of NSCLC with ROS1 or NTRK mutation worldwide will reach 56.2 thousand in 2033, according to Frost & Sullivan. From 2017 to 2023, the number of new cases of NSCLC with ROS1 or NTRK mutation in China increased from 17.9 thousand to 21.6 thousand, representing a CAGR of 3.2%. It is estimated that the number of new patients with ROS1 or NTRK mutation in China will reach 28.3 thousand in 2033, according to the same source.

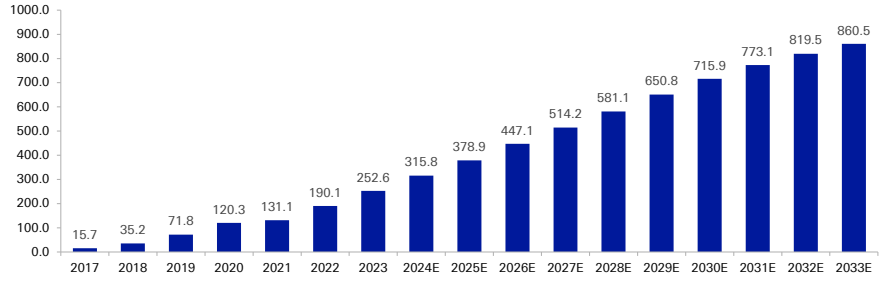
The global ROS1/NTRK-TKI market grew from US$70.7mn in 2017 to US$332.0mn in 2023, reflecting a CAGR of 29.4%. According to Frost & Sullivan, the global ROS1/NTRK-TKI market is forecast to reach US$602.0mn in 2027 and, ultimately, US $1,052.9mn in 2033, representing a CAGR of 16.0% from 2023 to 2027 and a CAGR of 9.8% from 2027 to 2033. The ROS1/NTRK-TKI market in China has developed at a faster pace, increasing from RMB15.7mn in 2017 to RMB252.6mn in 2023, demonstrating a CAGR of 58.8%. According to Frost & Sullivan, the ROS1/NTRK-TKI market in China is projected to grow further to RMB514.2mn in 2027 and RMB860.5mn in 2033, at a CAGR of 19.4% from 2023 to 2027 and a CAGR of 9.0% from 2027 to 2033.

Figure 25: Global ROS1/NTRK-TKI market (USD mn)



Source : Frost & Sullivan

Figure 26: ROS1/NTRK-TKI market in China (RMB mn)



Source : Frost & Sullivan

Competitive landscape of ROS1/NTRK-TKIs

As of the Latest Practicable Date, four ROS1/NTRK-TKIs had secured approval from the FDA, including Entrectinib by Roche, Rizotinib by Pfizer, Repotrectinib by BMS and Larotrectinib by Bayer. Except for Repotrectinib, all of the other three ROS1/NTRK-TKIs had also secured approval from the NMPA. Entrectinib targets NTRK, ROS1 and ALK, and it is indicated for NSCLC and NTRK-positive solid tumors. Crizotinib targets ALK, MET and ROS1, and it is approved for ALK-positive or ROS1-positive metastatic NSCLC, ALK-positive systemic anaplastic large cell lymphoma and ALK-positive unresectable inflammatory myofibroblast tumors. Repotrectinib targets NTRK, ROS1, ALK, JAK2, SRC and FAK, and it is approved for locally advanced or metastatic ROS1-positive NSCLC. Larotrectinib exclusively targets NTRK, and it is indicated for NTRK-positive solid tumors. Publicly available data showed that Crizotinib recorded global sales of US$374mn in 2023, according to Frost & Sullivan.

As of the Latest Practicable Date, 29 ROS1/NTRK-TKI candidates are under development globally. Among them, four candidates simultaneously target ROS1 and NTRK, with the most clinically advanced candidate in the Phase II clinical stage.

Figure 27: Four candidates that simultaneously target ROS1 and NTRK, with the most clinically advanced candidate in the Phase II clinical stage

Drug Name/ Code	Target	Company	Clinical Stage	Indications	First Posted Date
Taletrectinib	NTRK/ROS1	AnHeart Therapeutics Inc.	II	NSCLC	6/9/2021
XZP-5955	NTRK/ROS1	Xuanzhu Biopharmaceutical Co., Ltd.	I/II	Locally Advanced/Metastatic Solid Tumor/NSCLC	8/9/2021
TY-2136b	NTRK/ROS1	TYK Medicines, Inc	I	Locally Advanced/Metastatic Solid Tumor	3/15/2023
SIM1803-1A	NTRK/ROS1/ALK	Jiangsu Simcere Pharmaceutical Co., Ltd.	I	Advanced/Metastatic Solid Tumors With NTRK, ROS1 or ALK Gene Fusion	12/17/2020

Source : clinicaltrials.gov, Frost & Sullivan

Competitive advantages of TY-2136b

Potential superior safety

Although it was developed to bind to multiple targets, TY-2136b was preliminarily found to be well tolerated, based on multiple preclinical studies. This is because TY-2136b is highly potent against ROS1 and NTRK, moderately potent against ALK and LTK and only weakly potent against ABL1(H396P), JAK1, JAK2, JAK3 (collectively denoted as JAK1/2/3 hereafter) and SRC kinases.

First, TY-2136b does not confer inhibitory activity toward Ba/F3 cells overexpressing ABL1 (H396P) mutant kinase. TYK Medicines carried out a head-to-head comparison of inhibitory activities of TY-2136b with Repotrectinib (TPX-0005) and Rebastinib. As shown in the table below, TY-2136b was more than 20-fold less active than Rebastinib (an ABL1-specific inhibitor), and it showed less activity than Repotrectinib (a ROS1/NTRK/ALK inhibitor).

Figure 28: Inhibitory Activities Against Kinase ABL1 (H396P)

	TY-2136b	TPX-0005	Rebastinib	Selectivity Index	
				TY-2136b/TPX-0005	TY-2136b/Rebastinib
IC_{50}(nM)	87.13	49.98	4.32	1.74	20.12

Source : Company

Second, TY-2136b does not disrupt JAK/STAT signaling pathways in lung cancer cell line models. As summarized in the table below, TY-2136b was the least potent agent compared to the selected reference compounds inhibiting the activity of JAK1, JAK2 or JAK3. The selectivity index suggested that TY-2136b was 37-fold less active than Ruxolitinib (a JAK1/JAK2 inhibitor) toward JAK1, 124-fold less active than Ruxolitinib toward JAK2 and more than 221-fold less active than Tofacitinib (a JAK3 inhibitor) toward JAK3. TY-2136b is also similar or less potent than Repotrectinib.

Last, TY-2136b does not disrupt SRC kinase activity. To verify if TY-2136b confers any pharmacological activity against SRC kinase, TYK Medicines carried out a head-to-head comparison of TY-2136b's inhibitory activities against two other SRC inhibitors, Repotrectinib (TPX-0005) and Dasatinib. Repotrectinib is an ALK/ROS1/TRK inhibitor as well as a potent SRC inhibitor. Dasatinib is a potent inhibitor that targets ABL, SRC and c-Kit. The SRC kinase assay results showed that TY-2136b was approximately 12-fold less active than Repotrectinib over SRC, and more than 1,100-fold less active compared to Dasatinib, suggesting that TY-2136b bears much weaker inhibitory activity in disrupting SRC activation.

Considering that TY-2136b possesses a favorable *in vitro* safety profile (along with other factors), the FDA granted the Orphan Drug Designation of TY-2136b for the treatment of ROS1-positive, NTRK fusion-positive, or LTK-positive NSCLC in September 2023.

Potential superior efficacy

As TY-2136b is less likely to be captured by targets other than ROS1 and NTRK, more TY-2136b is expected to accumulate at its targets, thus offering potentially favorable efficacy. This speculation has received initial validation through the Company's series of *in vitro* and *in vivo* experiments.

ROS1 G2032R has been identified in multiple cancer cases following Crizotinib treatment and is believed to contribute to the acquired resistance of Crizotinib. TYK Medicines evaluated TY-2136b's activity against the ROS1 mutation in a head-to-head study comparing it with Crizotinib and Repotrectinib (TPX-0005) in the Ba/F3 cell line. The results showed that TY-2136b inhibited cell proliferation in cell lines expressing wild-type and mutant ROS1, including the resistance-driving G2032R mutation. It also demonstrated more potent cell proliferation inhibition than Crizotinib and Repotrectinib.
Furthermore, NTRK mutations, such as NTRK1 G595R, confer resistance to Larotrectinib treatment. In a preclinical study, TYK Medicines evaluated TY-2136b's activity against the NTRK mutation in a head-to-head study comparing it with Larotrectinib (LOXO-101) in the Ba/F3 cell line. The result showed that TY-2136b had potent inhibitory activities of wild-type TRK and resistance driving TRK mutations, including TRKA G595R, TRKA G667C, and TRKA G595R/F589L,among others. Also, its cell proliferation inhibition activity was superior to that of Larotrectinib.
Therefore, as an innovative ROS1/NTRK inhibitor, TY-2136b is not only effective against the ROS1/NTRK oncogenic gene mutations, but it also exhibits high selectivity of ROS1 and NTRK mutations such as the ROS1 G2032R mutation and NTRK G595R, which commonly contribute to resistance against existing ROS1/NTRK drugs.

Other drug candidates

Clinical stage assets

TY-2699a – CDK7 Inhibitor

TY-2699a is a selective CDK7 inhibitor designed for the treatment of advanced/metastatic solid tumors. With its high oral bioavailability, excellent selectivity, enhanced safety profile and robust activity against various cancers such as triple-negative breast cancer and ovarian cancer, it is promising across a wide spectrum of indications, presenting significant market potential. TY-2699a received IND approvals from the FDA and the NMPA in February 2023 and in May 2023, respectively. TYK Medicines is currently conducting a Phase I clinical trial of TY-2699a monotherapy or combination therapy in locally advanced or metastatic solid tumors (especially in SCLC and TNBC) in China, and expects to commence the Phase Ib clinical trial in the first quarter of 2025.

Mechanism of action

CDK7, along with cyclin H and MAT1, forms the CDK-activating complex, which directs the progression through the cell cycle through T-loop phosphorylation of cell cycle CDKs. The CDK-activating complex also plays a role in the regulation of transcription, as a component of the general transcription factor, TFIIH. As an active gene promoter, CDK7 phosphorylates the C-terminal domain of RNA polymerase II at serine 5, to facilitate transcription initiation. CDK7 also phosphorylates CDK9, which in turn phosphorylates the C-terminal domain of RNA polymerase II at serine 2, to drive transcription elongation. The activities of a variety of transcription factors, including p53, retinoic acid receptor, oestrogen receptor and androgen receptor, are also regulated by CDK7-mediated phosphorylation.

Immunohistochemical analysis on a range of tumor types indicated that CDK7 expression is elevated in tumor cells compared to their normal counterparts, and subsequently numerous studies have provided support for this finding. In ER+ breast cancer, CDK7, cyclin H and MAT1 are overexpressed and are co-regulated at the mRNA level. Expression of the CDK-activating complex components positively correlates with ER expression and serine118 phosphorylation, as well as with improved patient outcomes. Conversely, in TNBC, CDK7 expression is correlated with poor prognosis. In addition, associations between CDK7 and reduced survival have been observed in gastric cancer, ovarian cancer, oral squamous cell carcinoma, hepatocellular carcinoma and glioblastoma. For oral squamous cell carcinoma, animal studies have also revealed a potential role for CDK7 in disease development.

These findings raise the possibility that tumors with increased expression of CDK7 may be more sensitive to CDK7 inhibition, particularly in the case of ER+ breast cancer, where the CDK7-activated nuclear receptor, ERα, drives tumor progression.

Common molecular features of cancer, such as mutation, copy number changes and genomic rearrangements, can either directly or indirectly impact gene expression profiles that drive cancer. Recently, clusters of enhancers, termed super-enhancers, that control the expression of genes integral for cell identity and function have been defined. Deregulation of the super-enhancer landscape is common in cancer and leads to dramatic changes in gene expression and high transcriptional outputs, which maintain the oncogenic cell state. As a result, cancer cells become transcriptionally addicted, requiring higher levels of transcription than normal cells to sustain growth. The phenomenon of transcriptional addiction suggests that cancer cells may be more responsive than normal cells to transcriptional inhibition and provides a strong basis for targeting transcriptional kinases, including CDK7, in cancer.

TY-0540 – CDK 2/4/6 Inhibitor

TY-0540 is a novel CDK 2/4/6 inhibitor intended for the treatment of advanced/ metastatic solid tumors. TYK Medicines received IND approvals from the FDA and the NMPA for conducting Phase I and Phase II clinical trials of TY-0540 for the treatment of advanced solid tumors in June 2023 and September 2023, respectively. TYK Medicines is currently conducting a Phase I clinical trial of TY-0540 monotherapy or combination therapy in solid tumors in China, and expects to commence the Phase Ib clinical trial in the first quarter of 2025.

Mechanism of action

The research has highlighted that inhibiting CDK4/6 activity triggers an increase in cyclin E amplification and the activation of the MYC gene. This upregulation activates CDK2, which forms a compensatory pathway by phosphorylating Rb, releasing E2F, and fueling tumor cell proliferation. This mechanism significantly contributes to acquired resistance to CDK4/6 inhibitors. The overexpression of Cyclin E drives tumor cells to resist the inhibitory effect of CDK4/6, preventing them from remaining in the G1 phase. Studies suggest that patients with elevated Cyclin E expression are insensitive to CDK4/6 inhibitors, experiencing significantly shorter progression-free survival. This mechanism has been confirmed in CDK4/6-resistant cell lines. Achieving prolonged efficacy requires the inhibition of both CDK4 and CDK2, leading to the emergence of CDK2/4/6 inhibitors as a novel therapeutic avenue to curb cancer cell proliferation.

Studies in breast cancer cells have revealed that CDK4/6 activity is modulated by the cell cycle protein D. The active CDK4/6-cell cycle protein D complex phosphorylates Rb proteins, releasing the transcription factor E2F. This cascade enables the transcription of numerous genes, facilitating the cell's entry into the S-phase, thereby propelling cell cycle progression. Clinical investigations have verified the benefits of CDK4/6 inhibitors in hormone receptor positive, HER2 receptor-negative breast cancer.

Despite the transformative impact of CDK4/6 inhibitors on HR+/HER2– breast cancer treatment, significant challenges persist, notably primary and acquired resistance. Approximately 20% of patients exhibit primary resistance to CDK4/6 inhibitors, rendering inginitial therapy ineffective, while others develop resistance within approximately 25 months. For instance, in the PALOMA-2 study, over 60% of patients experienced disease progression within 40 months when treated with Palbociclib in combination with Letrozole. Once resistance occurs, treatment options often entail higher toxicity and limited clinical benefit, such as the mammalian target of rapamycin inhibitors.

TY-1091 – RET Inhibitor

TY-1091 is a potent and selective RET inhibitor. It is intended for the treatment of advanced NSCLC with RET gene fusion, advanced MTC with RET gene mutation and other advanced solid tumors with RET gene alterations. It can inhibit more RET mutation/fusion sites compared to Pralsetinib and Selpercatinib, and has significant inhibitory effects on the G810S single point mutation and other mutations that display resistance to the first-generation RET inhibitors, which can potentially address the drug resistance of RET inhibitors.

In August 2022, TYK Medicines received the IND approval from the FDA to conduct Phase I and Phase II clinical trials of TY-1091 in solid tumors. In December 2022, TYK Medicines received the IND approval from the NMPA for conducting Phase I and Phase II clinical trials of TY-1091 as monotherapy in advanced solid tumors. TYK Medicines is currently conducting a Phase I clinical trial of TY-1091 in RET fusion-positive solid tumors in China.

Mechanism of action

RET is a proto-oncogene responsible for encoding RET transmembrane proteins and is a receptor tyrosine kinase. Transmembrane proteins are divided into three parts: one end of the protein is located outside the cell, one part is located in the cell membrane, and the other end is located inside the cell. When RET protein binds to GDNF, it causes the phosphorylation of RET protein receptors and activates RET. The activated RET will phosphorylate its substrate, causing activation of downstream signaling pathways.

If the RET gene undergoes oncogenic mutations, it activates downstream signaling pathways such as the PI3K-AKT-mTOR pathway, the JAK-STAT pathway and the RAS-RAF-MEKERK pathway, which would cause excessive cell growth and proliferation, thus driving tumor development. RET inhibitors can suppress the activation of the RET tyrosine kinase domain, thereby inhibiting downstream signaling pathways and playing antitumor effects.

If there are fusion, point mutations, and other cancer-promoting mutations, the RET protein will undergo abnormal over-activation independent of ligands. For example, the common RET missense mutations in MEN2A often occur in extracellular cysteine rich domains, causing RET proteins to form homologous dimers and activate without binding to ligands. Point mutations in the RET gene may also occur in the kinase domain within cells, such as the most common M918T mutation in the MEN2B type. Activating the RET protein does not require the formation of homologous dimers, but rather promotes cancer by enhancing the affinity between the RET protein and ATP, making the activated monomers of RET more stable, and activating downstream signaling pathways.

When RET fusion occurs, although the extracellular domain of the RET gene is lost, companion genes such as KIF5B and CCDC6 often carry a coiled helical domain, which induces homologous dimerization in new proteins, thereby enabling the RET kinase domain to continuously activate cancer promotion without relying on ligands. RET TKIs are effective treatments for cancers harbouring RET mutations.

TY-4028 – Exon 20 Insertion-TKI

TY-4028 is a potent, irreversible, oral exon 20 insertion-TKI, targeting locally advanced or metastatic NSCLC with EGFR exon 20 or HER2 exon 20 insertion mutations. It presents an innovative, targeted therapy for this specific subset of

NSCLC cases. In April 2023, TY-4028 received FDA approval for Phase I and Phase II clinical trials in locally advanced or metastatic NSCLC. Subsequently, it obtained NMPA approval in June 2023 for the same indication. TYK Medicines plans to initiate a Phase I trial of TY-4028 in NSCLC with the exon 20 insertion mutation in China in 2024.

Mechanism of action

According to Frost & Sullivan, the EGFR exon 20 insertion is the third most common mutation in NSCLC. Among NSCLC patients with EGFR mutations, approximately 7.7% of patients have the EGFR exon 20 insertion mutation in China. Patients with exon 20 insertion mutations are associated with primary resistance to targeted EGFR-TKIs and correlate with a poor patient prognosis.

Exon 20 insertion mutations are also found in HER2, which is another member of the EGFR family of receptor tyrosine kinases. HER2 mutations are present at a lower frequency (in approximately 2% of NSCLC patients) compared to EGFR mutations. Exon 20 insertion mutations are the most dominant type of HER2 aberration in NSCLC by far, representing greater than 90% of all observed HER2 mutations.

According to Frost & Sullivan, activated EGFR leads to downstream activation of proliferative pathways, including the MAPK and PI3K-AKT-mTOR signaling pathways. In cancers, predominantly NSCLC, the EGFR exon 19 deletion and exon 21 L858R mutations and EGFR exon 20 insertion result in constitutive activation of these pathways and thus drive tumor development and progression.

According to Frost & Sullivan, first-generation and second-generation EGFR-TKIs are effective treatments for NSCLC harbouring EGFR mutations of exon 19 deletion and exon 21L858R, and the third-generation EGFR-TKI is also active against the EGFR T790M resistance mutation that commonly arises in NSCLC with the classic activating mutations. However, these agents have limited activity against cancers harbouring the EGFR exon 20 insertion. EGFR exon 20 insertion-TKI with activity against EGFR with exon 20 insertions have therefore been developed. This agent might also promote antitumor immune responses against EGFR mutant cancers via the induction of Fc receptor signaling and antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.

Exon 20 insertion mutations are also found in HER2, which is another member of the ErbB receptor tyrosine kinase (RTK) family. HER2 plays a critical role in NSCLC development and progression by forming heterodimers with other HER family members (EGFR or HER1, HER2 and HER4) upon ligand binding, and activates the cytoplasmic kinase domain, which phosphorylates the receptor tail region of tyrosine. In addition, HER2 may form homodimers when it is highly expressed. Exon 20 insertions are the most dominant type of HER2 aberration in NSCLC by far, representing greater than 90% of all observed HER2 mutations. Disregulation of HER2 signaling is associated with HER2 amplification, overexpression, or mutation, and is a common oncogenic driver in a variety of tumors.

HER2 exon 20 insertion-TKIs can act in the tyrosine kinase domain of HER2, and inhibit the activation of downstream signaling pathways such as the RAS-RAF-MEK-ERK pathway and PI3K-AKT-mTOR pathway to exert antitumor effects.

Preclinical stage assets

TY-1054 is a small molecule, oral YAP-TEAD inhibitor developed for cancer treatment. The Hippo pathway plays an essential role in cell proliferation, tissue regeneration, and tumorigenesis, the hyper activation of which induces metastasis, chemoresistance, and the attribute of cancer stem cells. Its disregulation contributes to 10% of all cancers, including lung, gastric, colon, cervical, ovarian, breast, melanoma, hepatocellular and squamous cell carcinoma. The pathway is activated through the binding of the YAP/TAZ complex to palmitoylated TEAD. Despite the urgent need to develop a therapeutic strategy to curb the disregulated pathway, it is difficult to directly target YAP/TAZ with small molecule inhibitors because of the lack of a catalytic niche. Therefore, targeting small molecules that block the palmitoylation of TEAD is an effective strategy. It is currently in the IND-enabling stage.

TY-1210 is a small molecule, selective CDK2 inhibitor developed for cancer treatment. Although CDK4/6 inhibitors have significantly improved the PFS of HR+/HER2– breast cancer, many patients unfortunately eventually relapse to CDK4/6 therapy. Studies have shown that the activation of CDK2/cyclinE1 due to CCNE1 gene amplification can be the key contributor to resistance of CDK4/6 inhibitors. Thus, CDK2 inhibition represents a promising, novel therapeutic approach to treat or prevent CDK4/6 inhibitor resistance in HR+/HER2– breast cancer. It is currently in the preclinical development stage.

TY-0609 is a selective CDK4 inhibitor with significant sparing of CDK6 developed for cancer treatment. CDK4/6 inhibitors have achieved great commercial success in HR+/HER2– breast cancer. However, the CDK4/6 inhibitors currently approved by the FDA all have on-target toxicity and cause adverse effects such as neutropenia, which could potentially limit their clinical application. CDK6 activity was demonstrated to be the primary contributor to hematological toxicity, leading to the emergence of selective CDK4 inhibitors to address the safety concerns. The Company's preclinical data on TY-0609 demonstrated its improved efficacy and safety profile in combating HR+ breast cancer. Moreover, its potential extends beyond breast cancer, showing indications of antitumor activities in lung, colorectal, and prostate cancers. TY-0609 is currently in the preclinical development stage.

TY-3200 is a highly active, highly selective, orally available EGFR degrader. Although third-generation EGFR TKIs have achieved relatively good clinical efficacy, they are most effective against EGFR exon 19 deletion. Therefore, there is a great clinical unmet need in the areas of EGFR L858R, other EGFR mutations (such as exon 20 insertion, G719X and L747X), and third-generation EGFR TKI resistance. Data from preclinical studies of TY-3200 showed that it was highly effective in degrading proteins of EGFR L585R, and other EGFR mutations, including exon 20 insertion, G719X, L747X, exon 19 deletion/T790M/C797S, and L858R/T790M/C797S, but did not degrade wild type EGFR proteins. Currently, TY-3200 is in the preclinical development stage.

Medical chemistry-driven R&D capabilities

TYK Medicines consistently devotes resources to research and development to pave the way for long-term growth. The Company's research and development costs in 2022, 2023 and the three months ended March 31, 2024 amounted to RMB229.8 million, RMB249.3 million and RMB64.7 million, respectively. The Company's in-house R&D capabilities, built on the Company's proprietary technology platforms, are backed by the Company's R&D centers in Huzhou, Zhejiang and Zhengzhou, Henan. The Company's R&D centers are equipped with advanced laboratories and state-of-the-art equipment and instruments, such as liquid chromatography, a liquid chromatography mass spectrometer, and nuclear magnetic resonance. TYK Medicines believes that the Company's integrated capabilities give it the agility to formulate the Company's innovation, registration, commercialization and product optimization strategies that can navigate it through rapidly changing market needs, enabling it to improve its pipeline viability and expedite the product development cycle at a lower cost.

R&D platforms

The Company's fully-integrated platforms encompass all the key functionalities for developing small-molecule drugs, and enable TYK Medicines to identify and address potential clinical and manufacturing issues early in the development process so that it can direct the Company's efforts toward candidates with the best potential to become clinically active, cost-effective and commercially viable drugs. The Company's core platforms can be categorized as: the new drug design and screening platform, the druggability evaluation platform, the translational medicine platform, and the CADD/AIDD platform. The Company's platforms are integrated seamlessly to support key drug development functionalities, including new drug discovery and design, validation for preclinical candidates, and CMC. TYK Medicines has the expertise and capability to independently complete the entire drug development process from drug discovery to preclinical research, to clinical development and NDA/BLA application.

Drug design and screening platform

The Company's drug design and screening platform is a comprehensive small molecule drug discovery platform, currently focusing on kinase. This platform comprises two important functions: kinase biology and small molecule drug discovery. TYK Medicines operates a molecular physicochemical biology laboratory sprawling over 2,500 square meters in Huzhou, Zhejiang Province. Over 80% of the team members hold master's degrees or above. The lab curated a repository of approximately 250 cryopreserved human tumor cell lines sourced from ATCC and other institutions, spanning across 20 different cancer types. The laboratory enables comprehensive evaluations of kinase inhibitor physicochemical characteristics from diverse angles by conducting compound kinase activity tests, *in vitro* and *in vivo* cell activity tests, signaling pathway evaluations, gene expression assessments, cell cycle and apoptosis analyses, among others.

In addition, for the pharmaceutical synthesis of small molecules, TYK Medicines houses a pharmaceutical laboratory equipped with over 100 experimental fume hoods and an array of testing equipment. This setup provides robust support for synthesizing small molecules, facilitating efficient synthesis and the successful completion of the Company's medicinal chemistry projects. We note that all projects, aside from TY-9591 and TY-302, have been conceived and synthesized within this platform.

Druggability evaluation platform

Equipped with a druggability evaluation platform, TYK Medicines is capable of conducting a wide range of R&D activities in house, including DMPK studies, *in vitro* and *in vivo* bioactivity studies (including animal modeling), toxicity studies, physicochemical characterization, and CMC of drug candidates. TYK Medicines has built approximately 60 different mouse CDX tumor models, including breast cancer, liver cancer, pancreatic cancer, prostate cancer, lung cancer, head and neck squamous cancer, gastric cancer, ovarian cancer, colorectal cancer and hemangioma, which can be used to carry out the pharmacodynamic evaluation of kinase inhibitors in different mouse tumor models *in vivo*. Therefore, TYK Medicines is capable of comprehensively evaluating the efficacy of the company's drug candidates including kinase inhibitors in its in-house laboratory.

TYK Medicines has a drug metabolism analysis laboratory with an area of more than 1,000 square meters and an animal laboratory with an area of 350 square meters in Huzhou, Zhejiang Province. These laboratories are capable of performing cell culture, biochemical analysis, high-precision metabolite analysis, PPB analysis of kinase inhibitors in different species, CYP450 enzyme function analysis and liver microsomal stability analysis, DMPK analysis of kinase inhibitors in mice and rats, toxicological analysis of kinase inhibitors such as acute toxicity and long toxicity in mice and rats, and toxicity analysis of kinase inhibitors on bone marrow cells. The barrier area of the animal laboratory is 239 square meters, with a mouse operation room, a rat operation room and a nude mouse laboratory. The nude mice laboratory is equipped with SPF grade independent ventilated cage rearing equipment, with animal laboratory construction in strict accordance with the requirements of the "Technical Code for Laboratory Animal Buildings".

Translational medicine platform

Translational medicine advocates a two-way translational model from laboratory to clinical research (i.e., from bench to bedside, and from bedside to bench). It runs through multiple phases of new drug development, including the launch of drug discovery, drug efficacy mechanism research, biomarker development, indication expansion, combination therapy exploration, individualized medical guidance, drug resistance mechanism discovery, and the opening of next-generation drug design. Translational medicine research is basically characterized by multidisciplinary cross-cooperation, and its research results are the engine of new drug research and development, providing important support for new drug research and development.

TYK Medicines has assembled a translational medicine team with practical experience at home and abroad, and has established a platform for biomarker development. Using genomics, transcriptomics and proteomics methods, TYK Medicines can comprehensively and systematically assess the effects of drugs on the evolution of genetic variation, expression regulation, biochemical pathways and metabolic pathways during the development of tumors or neurological diseases, systematically search for and identify potential biomarkers and drug

targets, and evaluate the relationship between genetic variation, proteins, and metabolites as a function of disease prediction, diagnosis, therapeutic response and prognosis.

For example, for subjects participating in a clinical trial, human samples such as peripheral blood, puncture samples and urine are collected at different points in the treatment, and then, based on the biological mechanism of the target and the results of preclinical studies, a suitable multi-omics testing platform is selected, and at the same time, the subject's histological or biochemical indexes are collected, together with the detailed history, such as information on treatment efficacy, drug resistance, or progression in the course of the disease. All of this information is integrated and analyzed, and the results are validated for a range of clinical applications, such as biomarker development, to find the population for whom treatment is effective and thus guide individualized medicine.

CADD/AIDD platform

The CADD/AIDD platform is dedicated to aiding the Company's internal drug discovery team. Internally, TYK Medicines employs both receptor-based and ligand-based approaches in their structure-based drug discovery, utilizing traditional computational tools and diverse modeling techniques. These methods are crucial in lead optimization, preclinical selection, and have integrated CADD/AIDD to streamline processes and reduce computational needs. In receptor-based drug discovery, TYK Medicines uses a variety of modelling techniques including similarity search based on 2-D fingerprints, shape-based, pharmacophore and/or substructure. In receptor-based drug discovery, TYK Medicines use a variety of modelling techniques including molecular docking, virtual screening and molecular dynamics simulations. When TYK Medicines adopts the platform in drug design, in many cases, both approaches can be attempted in practice.

As a drug candidate enters the later stages before preclinical studies, TYK Medicines uses methods such as quantitative SAR studies and ADME/Tox prediction in ligand triage, so as to help select the proper candidate. The rather new CADD/AIDD are incorporated in the software and therefore can serve as an alternative to the traditional applications. For instance, active CADD/AIDD has been applied in quantitative SAR as well as docking-based virtual screening, to reduce the need for extensive computation.

The platform has yielded several promising pipeline products. TY-2136b, designed to target tyrosine kinases ROS1/NTRK, emerged during lead optimization in CADD, exhibiting strong activity and is currently in a Phase I clinical trial in China. Similarly, TY-1091, targeting RET kinase, evolved through CADD focusing on selectivity and is now in a Phase I clinical trial in China. TY-2699a, a CDK7 inhibitor, employed CADD/AIDD in compound design, highlighting the value of AIDD in identifying overlooked aspects to improve the therapeutic window. TY-2699a is currently in the Phase I clinical trial stage.

R&D Team

As of the Latest Practicable Date, TYK Medicines had 100 members in the company's R&D team, around 60.0% of whom held master's or doctoral degrees in relevant fields. The expertise of the company's team members spans the entire spectrum of drug development, encompassing drug discovery, medicinal chemistry design and virtual screening, preclinical pharmaceutical research, drug testing and purification, formulation development, clinical research, regulatory submissions and platform construction. All the key R&D personnel that have been involved in the development of the company's Core Product have remained with the group as of the Latest Practicable Date.

The Company's R&D team is led by Dr. WU Yusheng, the chairperson of the company's Board, the Company's executive director and chief executive officer, who has 24 years of experience in biomedical research and management. Prior to co-founding the company, Dr. Wu held prominent positions at pharmaceutical companies, such as Schering-Plough Corporation. Dr. Wu has also been a "State Specially Recruited Expert" as conferred by the Ministry of Human Resources and Social Security of the PRC since 2013. Dr. Wu obtained his doctorate degree in organic chemistry from Iowa State University of Science and Technology. Dr. Wu has also authored more than 120 scientific publications in leading chemistry and medicinal chemistry journals and has been granted more than 40 patents.

In addition to Dr. Wu, core members of the Company's R&D team also include Dr. CHEN Shaoqing and Mr. CHEN Xiugui. Dr. CHEN Shaoqing, the Company's senior vice president of the medicinal chemistry department, has more than 23 years of experience in medicinal chemistry. Dr. Chen worked as a senior principal scientist at Hoffman-La Roche Inc. for more than 13 years and has served in executive roles in a number of prominent listed companies such as Pharmaron, Inc. Dr. Chen obtained a master's degree and doctorate degree in chemistry from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. Dr. Chen has been accredited as a "National Level Talent" by the Ministry of Industry and Information Technology of the PRC since October 2023.

Mr. CHEN Xiugui, the Company's senior vice president of the clinical and registration department, has more than 16 years of experience in the clinical development and registration of pharmaceutical products. Mr. Chen has worked in prominent pharmaceutical companies such as Ascletis Pharmaceutical (Hangzhou) Co., Ltd., Betta Pharmaceuticals Co., Ltd. and Yangtze River Pharmaceutical (Group) Co., Ltd.
TYK Medicines has also established a Scientific Committee, consisting of Dr. Wu, Dr. LI Jun and Dr. XU Wenqing. The primary duties of the scientific committee include, but are not limited to: (i) reviewing, evaluating and providing recommendations to the company's Board on the quality, direction and competitiveness of the company's R&D projects, (ii) providing recommendations to the company's Board on the company's internal and external technology projects and investments, and (iii) reviewing the company's R&D capabilities and organizational capabilities, including product development processes. Dr. Li, the Company's non-executive director, worked for over 20 years as a principal scientist and program leader at Bristol-Myers Squibb Co., USA, where he was primarily responsible for new drug discovery.

Collaboration with third parties

In addition to conducting the company's core R&D activities in house, TYK Medicines also engages reputable CROs to manage, conduct, and support the company's preclinical research and clinical trials. The services they provide under the company's supervision primarily include performing data management and statistical analyses, conducting site management, patient recruitment and pharmacovigilance services in the company's clinical trials, and carrying out laboratory tests and other tasks based on the company's needs. TYK Medicines selects CROs based on various factors, such as professional qualifications, research experience in the related fields, service quality and efficiency, industry reputation, and pricing. Depending on the type of services needed, TYK Medicines enters into service agreements with the company's CROs on a project-by-project basis, which set out detailed work scopes, procedures, timelines, payment schedules and so forth. TYK Medicines closely supervises the company's CROs to ensure their performance in a manner that complies with the Company's protocols and applicable laws, which in turn protects the integrity and authenticity of the data from the company's trials and studies.

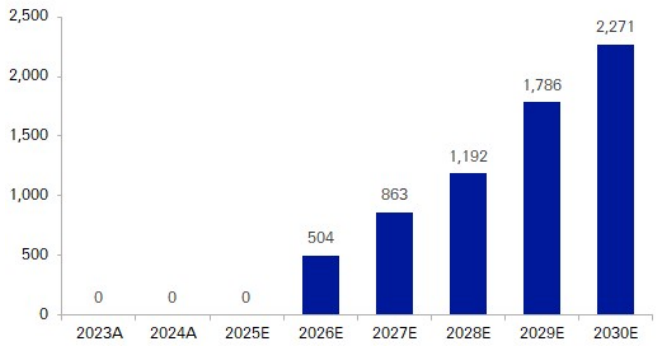
Financial analysis

TYK is still an R&D stage biopharmaceutical company and we do not expect the Company to record any revenue from product sales before the expected launch of its core product TY-9591 in 2026. The Company still needs to invest in major clinical trials in the next three years for the development of the products. As such, we believe the Company would continue to be loss making in 2025E and 26E, and to be profitable starting 2027E.

Start recording revenue in 2026 with the launch of potential blockbuster. We expect the Company to submit NDA to NMPA for TY-9591 for 1L treatment of brain metastases from NSCLC in 1H25. We expect the Company to receive approval and to launch its first product in 2026. As such, TYK is expected to start recording product sales revenue in 2026.

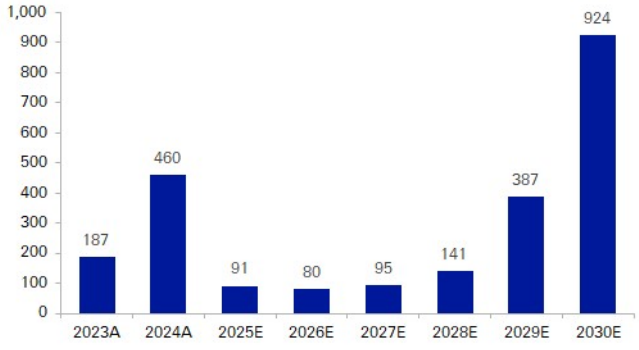
Cash to support development in the next two years. The Company has cash and cash equivalents of Rmb460mn as of the end of 2024. We believe the cash resources should be enough to support the Company in 2025, before the launch of revenue generation of the new product in 2026.

Figure 29: Revenue of TYK Medicines (Rmb mn)



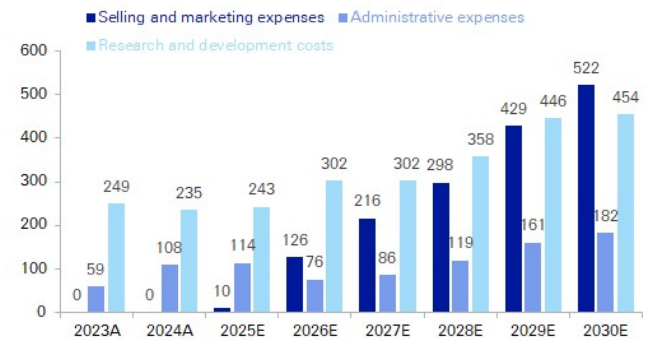
Source : Company data, Deutsche Bank estimates

Figure 30: Cash and cash equivalents (Rmb mn)



Source : Company data, Deutsche Bank estimates

Figure 31: Operating expenses of TYK Medicines (Rmb mn)



Source : Company data, Deutsche Bank estimates

Figure 32: Net loss/profit of TYK Medicines (Rmb mn)

Source : Company data, Deutsche Bank estimates

Figure 33: P&L

	2023A Rmb mn	2024A Rmb mn	2025E Rmb mn	2026E Rmb mn	2027E Rmb mn	2028E Rmb mn	2029E Rmb mn	2030E Rmb mn
TY-9591	*0*	*0*	*0*	*504*	*863*	*1,192*	*1,739*	*2,180*
Other product revenue	*0*	*0*	*0*	*0*	*0*	*0*	*47*	*91*
Revenue	**0**	**0**	**0**	**504**	**863**	**1,192**	**1,786**	**2,271**
Cost of sales	0	0	0	-151	-173	-179	-276	-349
Gross profit	0	0	0	353	690	1,013	1,509	1,923
Other income and gains	22	27	12	15	15	18	22	23
Selling and marketing expenses	0	0	-10	-126	-216	-298	-429	-522
Administrative expenses	-59	-108	-114	-76	-86	-119	-161	-182
Research and development costs	-249	-235	-243	-302	-302	-358	-446	-454
Operating profit	-286	-317	-354	-136	101	256	496	787
Non-operating item	-75	-60	0	0	0	0	0	0
Net finance cost	-22	-11	-14	-24	-25	-20	-14	-8
PBT	-383	-388	-368	-160	76	236	483	779
Income tax expense	0	0	0	0	-11	-35	-72	-117
Profit for the year	-383	-388	-368	-160	65	201	410	662
Attributable to non-controlling interests	-1	-1	-1	0	0	0	1	1
Attributable loss	**-382**	**-387**	**-367**	**-160**	**65**	**200**	**409**	**661**

Source : Deutsche Bank estimates

Figure 34: Balance sheet

	2023A Rmb mn	2024A Rmb mn	2025E Rmb mn	2026E Rmb mn	2027E Rmb mn	2028E Rmb mn	2029E Rmb mn	2030E Rmb mn
Restricted bank deposit	5	0	0	0	0	0	0	0
PP&E	158	160	170	180	188	196	201	206
Right-of-use assets	92	50	38	28	21	16	12	9
Intangible assets	68	62	57	51	45	40	34	28
Prepayments and other receivables	17	74	74	74	74	74	74	74
Total non-current assets	**339**	**347**	**339**	**333**	**329**	**326**	**321**	**318**
Prepayments and other receivables	40	76	32	39	38	43	51	50
Inventories	0	0	10	38	40	38	52	63
Trade receivables	0	0	0	76	129	179	268	341
Financial assets at fair value through profit or los	6	0	0	0	0	0	0	0
Restricted bank deposit	0	0	0	0	0	0	0	0
Others	0	32	32	32	32	32	32	32
Cash and cash equivalents	187	460	91	80	95	141	387	924
Total current assets	**234**	**569**	**165**	**265**	**334**	**433**	**791**	**1,409**
Trade payables	133	119	69	173	174	168	212	215
Redemption liabilities on equity shares	1,145	0	0	0	0	0	0	0
Lease liabilities	22	26	26	26	26	26	26	26
Others	0	0	0	0	0	0	0	0
Interest bearing debts	0	144	150	300	300	200	100	50
Total current liabilities	**1,301**	**289**	**245**	**499**	**500**	**395**	**338**	**291**
Deferred income	48	44	44	44	44	44	44	44
Other long-term payables	84	103	103	103	103	103	103	103
Lease liabilities	20	6	6	6	6	6	6	6
Total non-current liabilities	**152**	**154**	**154**	**154**	**154**	**154**	**154**	**154**
Share capital	307	371	371	371	371	371	371	371
Reserves	-1,192	98	-270	-430	-365	-164	246	908
Non-controlling interests	4	3	3	3	3	3	3	3
Shareholders equity	**-880**	**473**	**105**	**-56**	**9**	**210**	**620**	**1,282**

Source : Deutsche Bank estimates

Figure 35: Cash flow statement

	2023A Rmb mn	2024A Rmb mn	2025E Rmb mn	2026E Rmb mn	2027E Rmb mn	2028E Rmb mn	2029E Rmb mn	2030E Rmb mn
Loss before tax	-383	-388	-368	-160	76	236	483	779
Depreciation and amortisation	28	29	45	39	37	35	37	38
Change in working capital	51	-54	-15	-7	-54	-58	-69	-79
Income tax paid	0	0	0	0	-11	-35	-72	-117
Others	104	104	0	0	0	0	0	0
Net cash from operating activities	**-201**	**-308**	**-338**	**-128**	**48**	**178**	**378**	**622**
CAPEX	-76	-74	-37	-33	-33	-32	-32	-35
Others	149	23	0	0	0	0	0	0
Net cash from investing activities	**73**	**-51**	**-37**	**-33**	**-33**	**-32**	**-32**	**-35**
Net cash from financing activities	**224**	**635**	**6**	**150**	**0**	**0**	**0**	**0**
Net change in cash	**96**	**277**	**-369**	**-11**	**15**	**147**	**346**	**586**
Beginning cash level	91	187	460	91	80	95	141	387
Exchange difference	0	0	0	0	0	0	0	0
Cash at the end of the year	**187**	**464**	**91**	**80**	**95**	**241**	**487**	**974**

Source : Deutsche Bank estimates

Figure 36: Cash flow statement

	2023A	2024A	2025E	2026E	2027E	2028E	2029E	2030E
Sales mix								
Drug sales	N/A	N/A	N/A	100.0%	100.0%	100.0%	100.0%	100.0%
Upfront, milesontes and royalties	N/A	N/A	N/A	0.0%	0.0%	0.0%	0.0%	0.0%
P&L ratios								
EBIT margin	N/A	N/A	N/A	N/A	N/A	21.5%	27.8%	34.7%
EBITDA margin	N/A	N/A	N/A	N/A	N/A	24.5%	29.8%	36.3%
Net margin	N/A	N/A	N/A	N/A	N/A	16.8%	22.9%	29.1%
Effective tax rate	N/A	N/A	N/A	N/A	N/A	15.0%	15.0%	15.0%
Growth ratios								
Revenue	NM	NM	NM	NM	71.3%	38.1%	49.8%	27.2%
EBIT	NM	NM	NM	NM	NM	NM	93.6%	58.7%
EBITDA	NM	NM	NM	NM	NM	NM	82.7%	54.9%
Net profit	NM	NM	NM	NM	NM	NM	104.3%	61.4%
Balance sheet								
Current ratio	0.2	2.0	0.7	0.5	0.7	1.1	2.3	4.8
Trade receivables turnover days	N/A	N/A	N/A	28.5	16.0	13.1	10.5	8.0
Trade payables turnover days	N/A	N/A	N/A	418.5	367.3	343.8	280.5	225.4
Net debt to equity ratio	N/A	Net cash	56%	N/A	2201%	28%	Net cash	Net cash
Returns								
ROE	NM	NM	NM	NM	NM	95.4%	66.0%	51.5%
ROA	NM	NM	NM	NM	NM	26.4%	36.8%	38.2%

Source : Deutsche Bank estimates

Valuation

TYK is a R&D stage biopharmaceutical company. The Company's core product, TY-9591, is a potential EGFR TKI for the treatment of lung cancer. We expect the Company to launch and start recording revenue from the product in 2026E. As it takes several more years for the product to reach its peak sales, we believe employing a valuation matrix that capture the true long term potential of the Company is essential. As such, we employed a 10-year DCF model as our primary valuation method.

DCF valuation

As mentioned, the true value of the TYK's products is still years away and only looking at present operating numbers would significantly underestimate the Company. We therefore employ a 10-year DCF model to include the growth of the products. We created potential DCF values based on our previous described financial forecasts, WACC of 12.2% and terminal growth rate of 1.5%.

For the HK/China biopharmaceutical companies under our current coverage, we have applied 9.0%-12.0% WACC in the DCF valuation. As TYK is of a smaller size and with a smaller product pipeline compared to other established biopharmaceutical companies, we are applying a higher WACC of 12.2% in our 10-year DCF model. For our covered HK/China healthcare companies, we have adopted terminal growth rate of 0 - 2.5% in DCF valuation model. We adopted terminal growth rate of 1.5% for TYK, which is in-line with our covered companies.

Figure 37: DCF model of TYK

	2024A Rmb mn	2025E Rmb mn	2026E Rmb mn	2027E Rmb mn	2028E Rmb mn	2029E Rmb mn	2030E Rmb mn	2031E Rmb mn	2032E Rmb mn	2033E Rmb mn	2034E Rmb mn	2035E Rmb mn
Net profit	(387)	(367)	(160)	65	200	409	661	1,026	1,478	1,890	2,181	2,239
Net interest after tax	9	12	21	21	17	12	7	0	(6)	(15)	(26)	(25)
Depreciation & amortisation	29	45	39	37	35	37	38	40	43	46	50	54
CAPEX	(74)	(37)	(33)	(33)	(32)	(32)	(35)	(39)	(43)	(47)	(52)	(57)
Change in working capital	(54)	(15)	(7)	(54)	(58)	(69)	(79)	(124)	(95)	(64)	(26)	(15)
FCF	(476)	(363)	(141)	36	163	357	592	904	1,378	1,810	2,128	2,196
Terminal value												20,894
	(476)	(363)	(141)	36	163	357	592	904	1,378	1,810	2,128	23,090
Corporate value (Rmb mn)	10,450											
Debt (Rmb mn)	144											
Cash and cash equivalent (Rmb mn)	460											
Equity value (Rmb mn)	10,767											
Equity value (HK$ mn)	**11,703**											
TP (HK$ per share)	**31.60**											
Risk free rate	3.2%											
Beta	1.5											
Risk premium	6.0%											
Cost of equity	12.2%											
Cost of debt	4.0%											
WACC	12.2%											
Terminal growth rate	1.5%											

Source : Deutsche Bank estimates

Figure 38: Sensitivity analysis of DCF model

		WACC				
	HK$/share	11.2%	11.7%	12.2%	12.7%	13.2%
Terminal growth	0.5%	33.8	31.6	29.6	27.8	26.1
	1.0%	35.0	32.6	30.5	28.6	26.8
	1.5%	36.2	33.7	31.6	29.4	27.5
	2.0%	37.6	34.9	32.5	30.3	28.3
	2.5%	39.1	36.2	33.6	31.3	29.2

Source : Deutsche Bank estimates

Figure 39: WACC and terminal growth rate assumptions of biotechs under our coverage

Company	Price (LC)	Ticker	WACC	Terminal growth
HK/China Biotech				
Beigene	134.00	6160.HK	9.5%	2.5%
Innovent	50.40	1801.HK	10.0%	2.5%
Akeso	81.90	9926.HK	10.0%	2.5%
Remegen	41.35	9995.HK	10.6%	2.0%
Hutchmed	13.30	HCM.OQ	9.0%	2.0%
Cutia	6.21	2487.HK	12.0%	0.0%

Source : Deutsche Bank estimates

Risks

Risks related to delay or failure in developing pipeline candidates

TYK Medicines may not be able to identify, discover or develop new drug candidates, or to identify or develop new indications for the company's drug candidates, to expand or maintain the company's product pipeline. TYK Medicines invests substantial resources in research and development in order to develop, enhance or adapt to new technologies and methodologies, which may not be successful attempts. Clinical drug development involves a lengthy and expensive process with uncertain outcomes, and TYK Medicines may encounter unexpected difficulties executing the company's clinical trials and commercializing the company's drug candidates on a timely basis.

TYK Medicines may be unable to successfully develop or market the company's drug candidates or may experience significant regulatory delays, if safety, efficacy or other issues arise from any pharmaceutical product or medical treatment used, or intended to be used, in combination with the company's drug candidates.

Market acceptance of products

TYK Medicines' drug candidates, once approved, may fail to achieve the degree of market acceptance by physicians, patients, third-party payers and others in the medical community that would be necessary for the company's drug candidates' commercial success.

Meanwhile, TYK's products may also receive better-than-expected acceptance because of their efficacy and indications, which may drive faster revenue and net profit growth for the Company.

Intensifying market competition

TYK Medicines faces intense competition and the company's competitors may discover, develop or commercialize competing drugs faster or more successfully than TYK Medicines does, which may adversely affect the company's ability to successfully commercialize the company's drug candidates.

Pricing pressure from government guidance

The company's drug candidates may not be covered by insurance or reimbursement programmes or may become subject to unfavorable insurance policies or reimbursement practices, either of which could harm the company's business, and TYK Medicines may be subject to unfavorable pricing regulations, which could make it difficult for the company to sell its drugs profitably.

Potential risks related to commercialization

TYK Medicines has no experience in the commercialization of drugs. If TYK Medicines is unable to build, manage, expand and optimize an effective sales and distribution network for the company's drug candidates, either by the company itself or through third parties, TYK Medicines may not be able to successfully create or increase market awareness of the company's products or sell the company's products, which will materially affect the company's ability to generate product sales revenue.

Potential risks related to intellectual property rights

If TYK Medicines is sued for infringing, misappropriating or otherwise violating intellectual property rights of third parties, or engaging in unfair competition, such litigation could be costly and time-consuming and could prevent or delay it from developing or commercializing its drug candidates.

Potential government supportive policies

Development of innovative drugs and biopharmaceutical companies are supported by the government. The launch of any supportive policies may speed up the development of drugs, or shorten the ramp up period of a launched drugs. These may all bring faster growth to the Company's business.

Expanding into new markets

TYK Medicines currently mainly operates in China. If the Company expands its coverage in other regions, where purchasing power and pricing mechanism would be different from China, it may positively affect the Company's development and growth.

Expanding pipeline by collaborations with partners

Revenue may be elevated if TYK Medicines adds new products of high market potential into its portfolio via new collaborations.

Appendix A: Company background

Overview

TYK Medicines is a clinical-stage biopharmaceutical company committed to the discovery, development and commercialization of differentiated targeted therapies to address unmet medical needs in cancer treatment. Leveraging the company's capabilities in medicinal chemistry, deep understanding of cancer (particularly in lung cancer), and efficient clinical development strategy, TYK Medicines is proceeding with its Core Product TY-9591 for advanced NSCLC in two pivotal clinical trials in China. Since the company's inception in 2017, TYK Medicines has built a robust pipeline with 11 drug candidates, including Core Product TY-9591 and Key Product TY-302, our internally developed Key Product TY-2136b, four other innovative clinical products and four products in preclinical stage. As a China-based company with a global vision, TYK Medicines' mission is to tackle the challenges of drug accessibility, ensuring affordability and availability for diverse patient groups.

Figure 40: Business development milestones

Year	Milestone
2017	TYK Medicines was incorporated as a joint stock company with limited liability in the PRC on November 2, 2017
2018	TYK Medicines completed the Angel Investment and raised RMB20.0 million in June
2019	TYK Medicines completed the Series A Financing and raised RMB30.0 million in April TYK Medicines obtained NMPA approval for the Phase I clinical trial of TY-9591 monotherapy in advanced NSCLC in October
2021	TYK Medicines completed the Series B Financing and raised RMB230.0 million in April TYK Medicines completed the Series B+ Financing and raised RMB158.7 million in August TYK Medicines obtained IND approvals for the Phase I and Phase II clinical trial of TY-302 in combination with toremifene citrate in advanced solid tumors, especially in relapsed or metastatic ER+/HER2− breast cancer in November TYK Medicines obtained the IND approval for conducting Phase I and II clinical trials of TY-2136b in the U.S. for the treatment of solid tumors from the FDA in November
2022	TYK Medicines obtained NMPA approval for the registrational Phase III trial of TY-9591 monotherapy as first-line treatment in locally advanced or metastatic NSCLC with EGFR exon 21 L858R mutation in March TYK Medicines completed the Phase I clinical trial of TY-9591 monotherapy in healthy adult subjects in May TYK Medicines completed the Series C Financing and raised RMB325.0 million in March
2023	TYK Medicines initiated the Phase I clinical trial of TY-2136b monotherapy in advanced or metastatic solid tumors in the U.S. in April TYK Medicines completed the Phase I clinical trial of TY-9591 monotherapy in advanced NSCLC in May TYK Medicines obtained NMPA approval for the pivotal Phase II clinical trial of TY-9591 monotherapy as first-line treatment in EGFR mutated NSCLC with brain metastases in April TYK Medicines received the Orphan Drug Designation of TY-2136b from the FDA in September TYK Medicines completed the Series D Financing and raised RMB185.0 million in December
2024	TYK Medicines received IND approval from the NMPA for conducting Phase II and Phase III clinical trials of TY-9591 in combination with pemetrexed and cisplatin or carboplatin as first-line treatment in EGFR mutated advanced or metastatic NSCLC in March

Company data

Model updated: 16 May 2025

Running the numbers

Asia

China

Pharmaceuticals / Biotechnology

TYK Medicines

Reuters: 2410.HK Bloomberg: 2410 HK

Buy

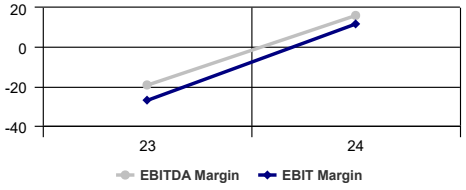
Price (15 May 25)	HKD 25.40
Target Price	HKD 31.60
52 Week range	HKD 13.70 - 55.50
Market cap (m)	HKDm 9,419.2 USDm 1,206.6

Company Profile

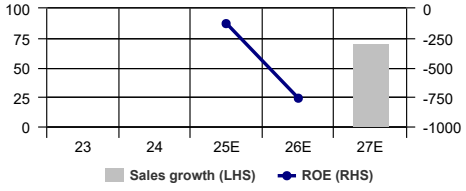
TYK Medicines is a clinical-stage biopharmaceutical company committed to the discovery, acquisition, development and commercialization of differentiated targeted therapies to address unmet medical needs in cancer treatment.

Price Performance

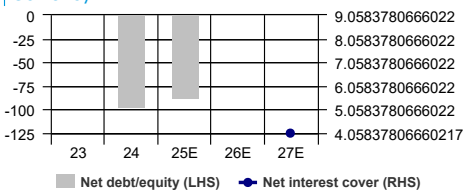
Margin Trends



Growth & Profitibility



Solvency



Cyrus Ng, CFA
+852 2203 6208 cyrus-a.ng@db.com

Fiscal year end 31-Dec	2023	2024	2025E	2026E	2027E
Financial Summary					
DB EPS (CNY)	-1.32	-1.15	-0.99	-0.43	0.17
Reported EPS (CNY)	-1.32	-1.15	-0.99	-0.43	0.17
DPS (CNY)	0.00	0.00	0.00	0.00	0.00
BVPS (CNY)	-3.1	1.4	0.3	-0.2	0.0
Weighted average shares (m)	289	338	371	371	371
Average market cap (CNYm)	na	10,039	8,701	8,701	8,701
Enterprise value (CNYm)	na	9,582	8,614	8,625	8,610
Valuation Metrics					
P/E (DB) (x)	nm	nm	nm	nm	134.2
P/E (Reported) (x)	nm	nm	nm	nm	134.2
P/BV (x)	0.00	31.30	86.04	-147.25	1,486.27
FCF Yield (%)	na	nm	nm	nm	0.2
Dividend Yield (%)	na	0.0	0.0	0.0	0.0
EV/Sales (x)	nm	nm	nm	17.1	10.0
EV/EBITDA (x)	nm	nm	nm	nm	62.1
EV/EBIT (x)	nm	nm	nm	nm	84.9
Income Statement (CNYm)					
Sales revenue	0	0	0	504	863
Gross profit	0	0	0	353	690
EBITDA	-259	-287	-309	-97	139
Depreciation	22	24	39	33	32
Amortisation	6	6	6	6	6
EBIT	-286	-317	-354	-136	101
Net interest income(expense)	-22	-11	-14	-24	-25
Associates/affiliates	0	0	0	0	0
Exceptionals/extraordinaries	0	0	0	0	0
Other pre-tax income/(expense)	-75	-60	0	0	0
Profit before tax	-383	-388	-368	-160	76
Income tax expense	0	0	0	0	11
Minorities	-1	-1	-1	0	0
Other post-tax income/(expense)	0	0	0	0	0
Net profit	-382	-387	-367	-160	65
DB adjustments (including dilution)	0	0	0	0	0
DB Net profit	-382	-387	-367	-160	65
Cash Flow (CNYm)					
Cash flow from operations	-201	-308	-338	-128	48
Net Capex	-76	-69	-37	-33	-33
Free cash flow	-277	-377	-375	-161	15
Equity raised/(bought back)	185	581	0	0	0
Dividends paid	0	0	0	0	0
Net inc/(dec) in borrowings	65	147	6	150	0
Other investing/financing cash flows	123	-163	0	0	0
Net cash flow	96	188	-369	-11	15
Change in working capital	51	-54	-15	-7	-54
Balance Sheet (CNYm)					
Cash and other liquid assets	187	460	91	80	95
Tangible fixed assets	158	160	170	180	188
Goodwill/intangible assets	68	62	57	51	45
Associates/investments	6	0	0	0	0
Other assets	155	233	186	288	335
Total assets	573	916	504	598	663
Interest bearing debt	0	0	0	0	0
Other liabilities	1,453	443	399	654	654
Total liabilities	1,453	443	399	654	654
Shareholders' equity	-884	469	101	-59	6
Minorities	4	3	3	3	3
Total shareholders' equity	-880	473	105	-56	9
Net debt	-187	-460	-91	-80	-95
Key Company Metrics					
Sales growth (%)	nm	nm	nm	nm	71.3
DB EPS growth (%)	na	13.5	13.6	56.5	na
EBITDA Margin (%)	nm	nm	nm	-19.3	16.1
EBIT Margin (%)	nm	nm	nm	-27.0	11.7
Payout ratio (%)	nm	nm	nm	nm	0.0
ROE (%)	nm	nm	-128.8	-760.8	nm
Capex/sales (%)	nm	nm	nm	6.6	3.8
Capex/depreciation (x)	2.8	2.5	0.8	0.9	0.9
Net debt/equity (%)	nm	-97.4	-87.0	nm	nm
Net interest cover (x)	nm	nm	nm	nm	4.1

Source: Company data, Deutsche Bank estimates

Appendix 1

Important Disclosures

*Other information available upon request

Disclosure checklist

Company	Ticker	Recent price*	Disclosure
TYK Medicines	2410.HK	25.4 (HKD) 15 May 2025	1, 7, 24, 26

*Prices are current as of the end of the previous trading session unless otherwise indicated and are sourced from local exchanges via Reuters, Bloomberg and other vendors . Other information is sourced from Deutsche Bank, subject companies, and other sources. For disclosures pertaining to recommendations or estimates made on securities other than the primary subject of this research, please see the most recently published company report or visit our global disclosure look-up page on our website at https://research.db.com/Research/Disclosures/EquityResearchDisclosures. Aside from within this report, important risk and conflict disclosures can also be found at https://research.db.com/Research/Disclosures/Disclaimer. Investors are strongly encouraged to review this information before investing.

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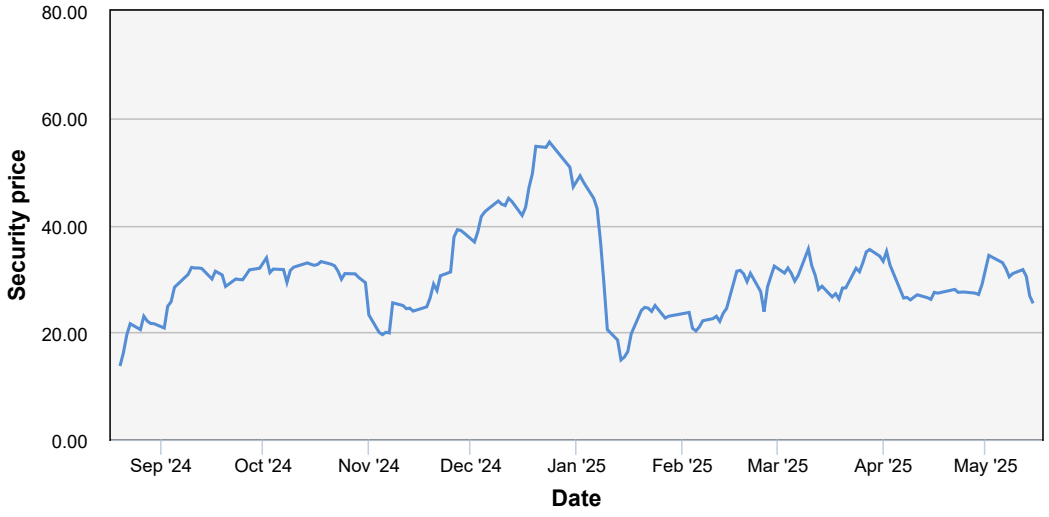
Historical recommendations and target price: TYK Medicines (2410.HK)

(as of 05/15/2025)

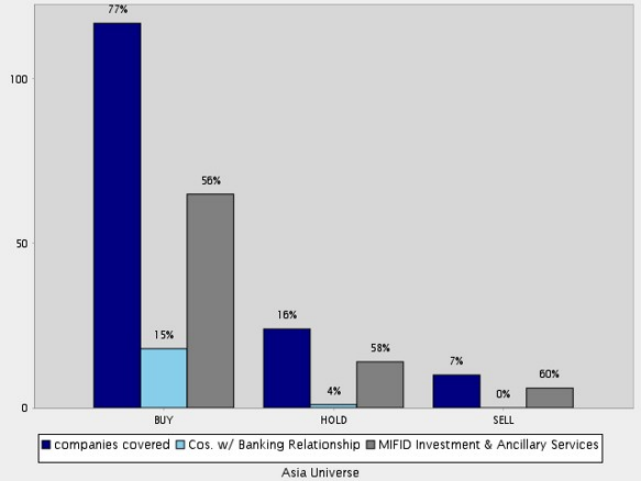


Current Recommendations

Buy
Hold
Sell
Not Rated
Suspended Rating

** Analyst is no longer at Deutsche Bank

Equity rating dispersion and banking relationships



Equity Rating and Dispersion Key

The Equity Rating Dispersion Chart depicts the following:

The proportion of recommendations that are rated "buy", "sell" and "hold" over the previous 12 months. This is shown for securities issued in the stated region e.g. "Europe Universe". See rating definitions below. This is represented by the "Companies Covered" bars in the chart. The percentage value displayed above the bar is the proportion as a percentage. E.g. 50% above the “buy” / “Companies Covered” bar means that 50% of DB’s equity research covered companies over the past 12 months have a “buy” rating.

Next to each of the three respective bars showing the proportion of "buy", "sell" and "hold" recommendations we provide two additional bars to show:

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- The proportion of "buy" (or "sell" or "hold) recommendations where Deutsche Bank and or/Affiliates has provided Investment Banking services in the past 12 months for which it has received compensation. The percentage value displayed above the bar shows the proportion of Companies Covered with the stated rating where DB has also provided Investment Banking services in the past 12 months. E.g. 50% above the “Cos. w/ Investment Banking relationship” bar means 50% of the Companies Covered with the rating stated also have an Investment Banking Relationship with DB.

Buy: Based on a current 12- month view of TSR, we recommend that investors buy the stock.

Sell: Based on a current 12-month view of TSR, we recommend that investors sell the stock.

Hold: We take a neutral view on the stock 12-months out and, based on this time horizon, do not recommend either a Buy or Sell.

TSR = Total Shareholder Return. Percentage change in share price from current price to projected target price plus projected dividend yield

Newly issued research recommendations and target prices supersede previously published research.

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