Innovative Small Molecule Anti-tumor Drugs Market

Independent Market Study

FROST & SULLIVAN (BEIJING) INC., SHANGHAI BRANCH CO.
弗若斯特沙利文(北京)咨询有限公司上海分公司

Frost & Sullivan

2024.8.12

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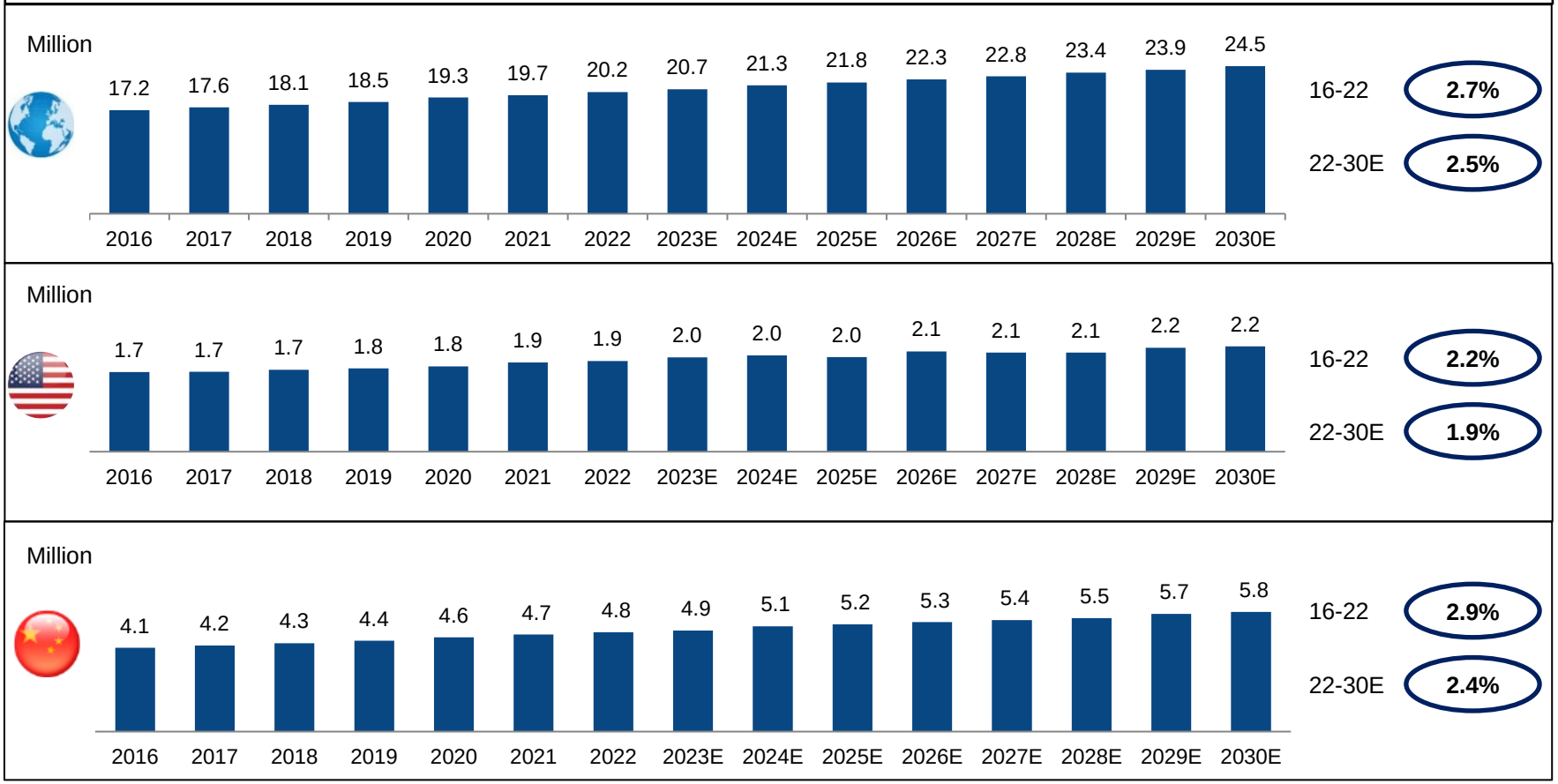
Overview of Global Cancer Incidence

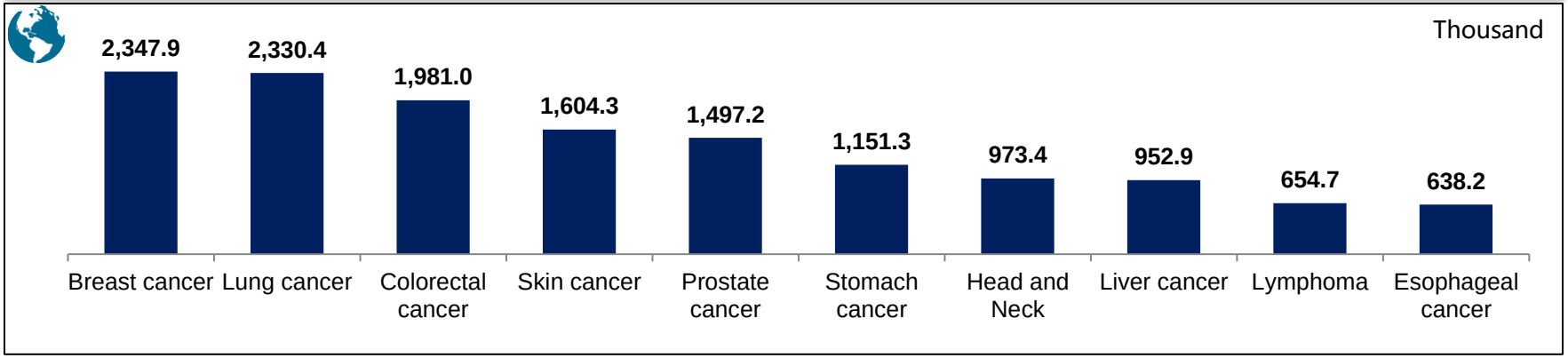
- Cancer is the leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. The overall risk accumulation of cancer is combined with the tendency for cellular repair mechanisms to be less effective as a person grows older. The incidence of cancer rises dramatically with age, most likely due to risks for specific cancers that increase with age. The global incidence of cancer increased from 17.2 million in 2016 to 20.2 million in 2022, representing a CAGR of 2.7%. In China, the number of new cancer cases increased from 4.1 million in 2016 to 4.8 million in 2021, representing a CAGR of 2.9%, which is higher than the global average level. It is estimated that the global cancer incidence will reach 24.5 million in 2030 and the number in China will reach 5.8 million in the same year.

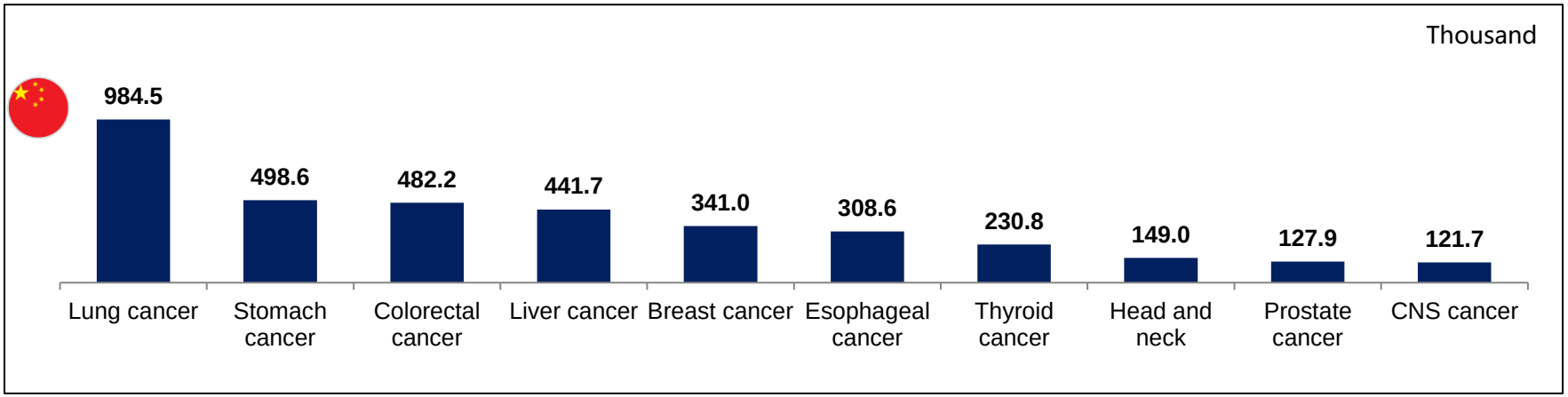


Source: IARC，ACS，NCRA，Frost & Sullivan analysis

Overview of Top 10 Cancer Cases in 2022

- The burden of cancer incidence and mortality is rapidly growing worldwide.
- In 2022, breast cancer was the most commonly diagnosed cancer with 2,347.9 thousand new cases globally, followed by lung cancer and colorectal cancer which amounted to 2,330.4 thousand and 1,981.0 thousand new cases respectively. In 2022, the most commonly diagnosed cancer in China are lung cancer, gastric cancer and colorectal cancer, with 984.5 thousand, 498.6 thousand and 482.2 thousand new cases identified respectively.



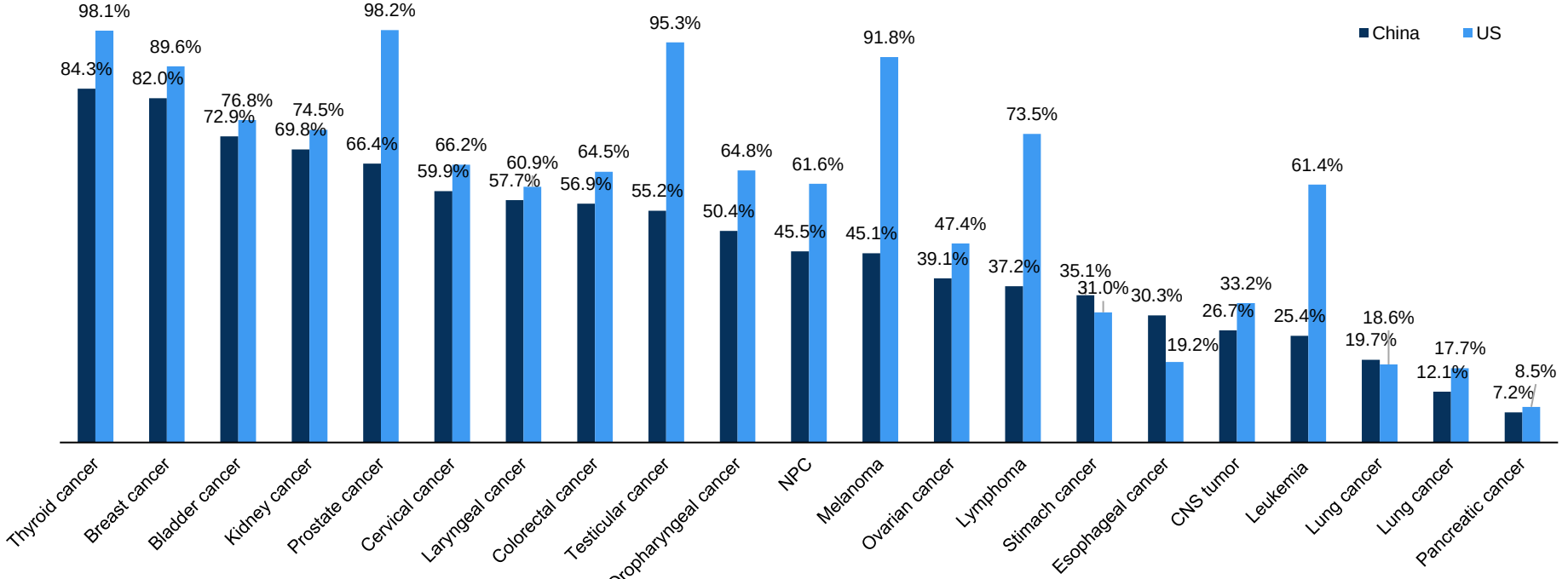


Source: GLOBOCAN，ACS，NCCR， Frost & Sullivan analysis

5-year Survival Rate of various cancers in China and the U.S.

- Due to the lack of awareness for cancer screening, the availability of innovative oncology drugs and therapies, the 5-year survival rates of various cancers in China are generally lower than those in the U.S. The 5-year survival rates for prostate cancer, testicular cancer, melanoma, lymphoma and leukemia in China are significantly lower than the rates of the U.S.
- The 5-year survival rate of stomach cancer, esophageal cancer and lung cancer in China are higher than the rates in the US. The main reason is that China has a large number of patients with stomach cancer, esophageal cancer and lung cancer; therefore, Chinese doctors have relatively more experience in clinical diagnosis and treatment of these cancers.

5-year Survival Rate of Various Cancers in China and the U.S.



Note: The 5-year survival rate data of various cancers in China were derived from the analysis of population cancer data from 17 cancer registries in China released in 2018 by researchers from NCRA, the Chinese Academy of Medical Sciences, and Peking Union Medical College Hospital. The 5-year survival rates of various cancers in the US were derived from cancer statistics published by the American Cancer Society.

Source: ACS，NCRA，Frost & Sullivan analysis

The role of surgery and cell therapy for the management of different types of cancers

- The field of cancer treatment has developed significantly in the past century. Conventionally, treatment methods such as surgery, radiotherapy and chemotherapy, has been widely utilized to fight against tumor cells, but was proved deficit due to side effects and limited efficacy.
- Development of targeted therapies, which target specific molecules, generally proteins, enzymes or a signaling pathway, or genetic changes that play a role in the spread of cancer, has embarked a new era of cancer treatment with enhanced specificity and efficacy. With a better understanding of cancer biology and advancement of modern technology, it is expected in the future, more edge-cutting technologies will be leveraged, bringing new treatment options to cancer patients.

	Conventional Cancer Treatments			New Era of Cancer Treatments		
	Surgery	Radiotherapy	Chemo-therapy	Targeted Therapy	Immuno-therapy	Emerging Technology
Description	A procedure in which a surgeon removes cancer from a patient's body	High doses of radiation to kill cancer cells and shrink tumors	Use single or combinations of anti-tumor drugs to stop or slow tumor growth	Act on specific targets that are associated with cancer development	Harness the patient's own immune system to fight cancer	Leverage novel platform or technology to fight against tumor
Features	Effective for early stage tumors that are locoregional but limited for cancers that have metastasized	Affects neighboring healthy cells, causing side effects such as fatigue, hair loss	Targets all fast growing cells, causing side effects such as hair loss, easy bruising/bleeding	Includes both small molecule drugs and mAbs, less harmful to healthy cells	Include cytokines, mAbs, checkpoint inhibitors, adoptive T-cell therapy and cancer vaccine	Provide wider solution to patients of cancer subtypes that suffer from unmet clinical needs

Source: Frost & Sullivan Analysis

Overview of Small Molecule Anti-tumor Drugs

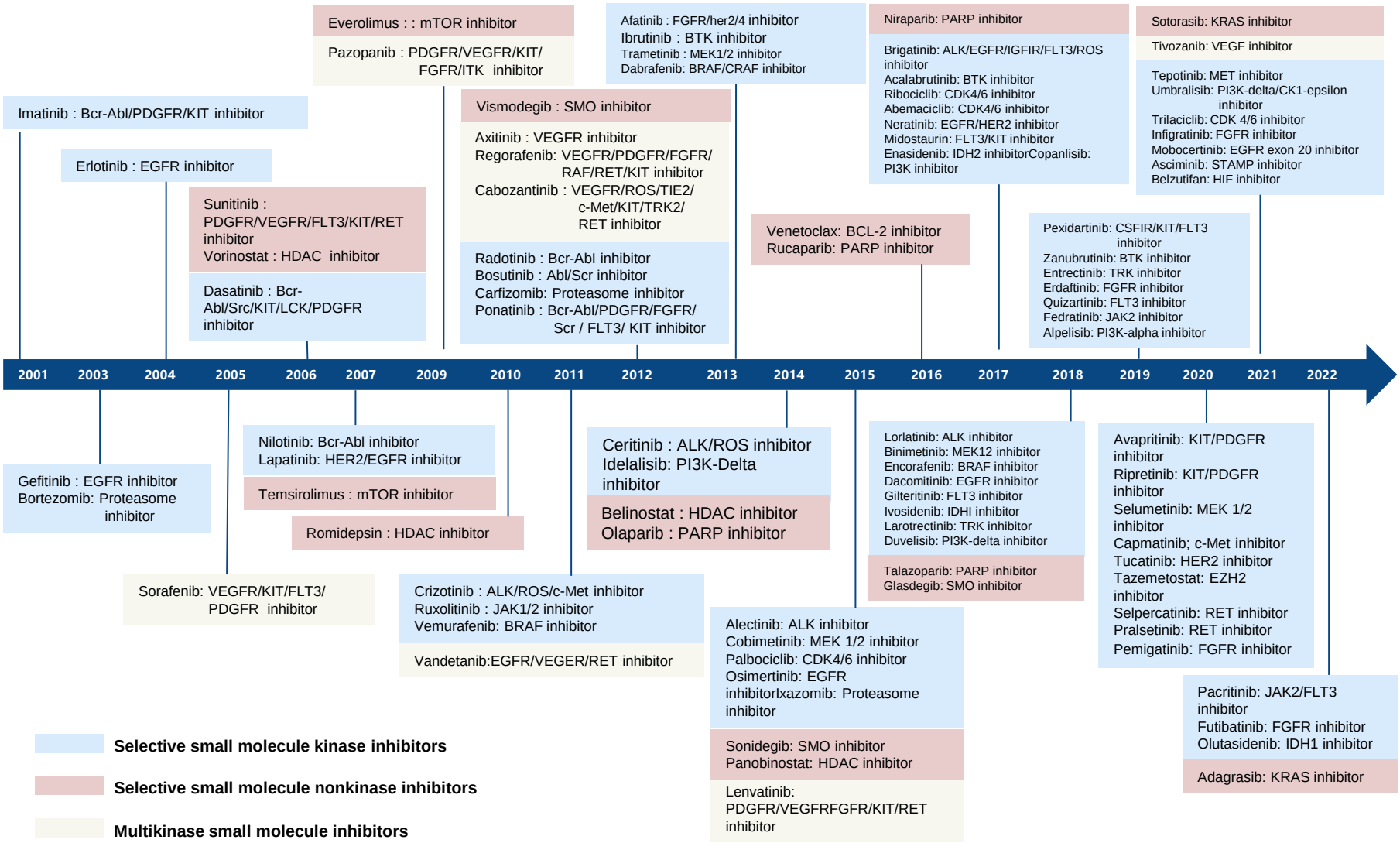
- Small molecule drugs usually refer to organic compound molecules with a molecular weight of less than 900 Daltons, and the active ingredients are organic compounds derived from chemical synthesis or natural extracts. Drugs with molecular weight greater than 1,000 Daltons are usually classified as macromolecular therapeutics. Comparing with macromolecular biologics, small-molecule targeted drugs have advantages in some aspects such as the pharmacokinetic (PK) properties, costs, patient compliance, and drug storage and transportation.
- Drug treatment together with surgical operation, radiotherapy and biotherapy constitute the main approaches to cancer treatment. For a long time, chemotherapy, which is a method of killing tumor cells and/or inhibiting the growth and proliferation of tumor cells by chemical drugs, was the only approach to cancer drug treatment. Over the past two decades, there has been a tremendous shift in cancer treatment, from broad-spectrum cytotoxic drugs to targeted drugs. Compared with traditional chemotherapy drugs, targeted drugs can specifically target cancer cells but spare normal cells, hence having high potency and low toxicity.
- Encouraged by the approval of the first small-molecule tyrosine kinase inhibitor (TKI) imatinib for clinical use by the US FDA in 2001, targeted drugs have rapidly developed and entered a golden period of development. In the past 20 years, there has been a significant increase in FDA-approved targeted drugs for cancer treatment.
- Currently, the global anti-tumor drugs market is dominated by targeted drugs, accounting for approximately 60% of the global anti-tumor drug market share in 2022. According to target selectivity, small molecule inhibitors can be divided into selective small molecule inhibitors and multikinase small molecule inhibitors. According to whether the substrate is a protein kinase, selective small molecule inhibitors are further divided into selective small molecule kinase inhibitors and selective small molecule nonkinase inhibitors.

Classification of small molecule inhibitors

<table>
<tr><td rowspan="2">Selective small molecule inhibitors</td><td>Selective small molecule kinase inhibitors</td><td>Accounting for most selective small molecule inhibitors:
• Receptor-related kinase inhibitors;
➢ ABL, HER, RGFR, FGFR, …
• Selective intracellular kinasesmall molecule inhibitors ;
➢ CDK, MEK, RAF, JAK, …
• Inhibitors targeting other cytoplasmic kinases.</td></tr>
<tr><td>Selective small molecule nonkinase inhibitors</td><td>• HIF-1 alpha inhibitors;
• PARP inhibitors;
• Epigenetic inhibitors
• mTOR inhibitors;
• …</td></tr>
<tr><td colspan="2">Multikinase small molecule inhibitors</td><td>Most approved drugs are multikinase inhibitors of the VEGFR.</td></tr>
</table>

Source: Frost & Sullivan Analysis

Timeline for the approval of small-molecule anti-tumor drugs



Source: FDA, Literature Review, Frost & Sullivan Analysis

Value chain analysis of small molecule anti-tumor drugs market

- In the value chain of small molecule anti-tumor drug market, the upstream market participants are mainly raw material suppliers and equipment suppliers, mainly providing APIs, intermediates, pharmaceutical equipment and instruments; the midstream participants include various innovative small molecule anti-tumor drug manufacturers , including multinational pharmaceutical companies and domestic innovative pharmaceutical companies; downstream participants are health care institutions and retail pharmacies at all levels across the country.

Value Chain of Small Molecule Anti-tumor Drugs Market

Upstream	Midstream	Downstream
Raw materials/equipment	**Innovative drug development & manufacturing companies**	**Medical institutions and pharmacies**
• The upstream of value chain are raw material and equipment providers, providing raw materials, intermediates, pharmaceutical equipment and instruments.	• The midstream of the value chain are innovative drug development and manufacturing companies, including multinational pharmaceutical companies and domestic companies that specialize in R&D of innovative drugs.	• Downstream of the value chain are medical institutions and retail pharmacies at all levels across the country, including general hospitals and specialized hospitals, physical pharmacies and online pharmacies.

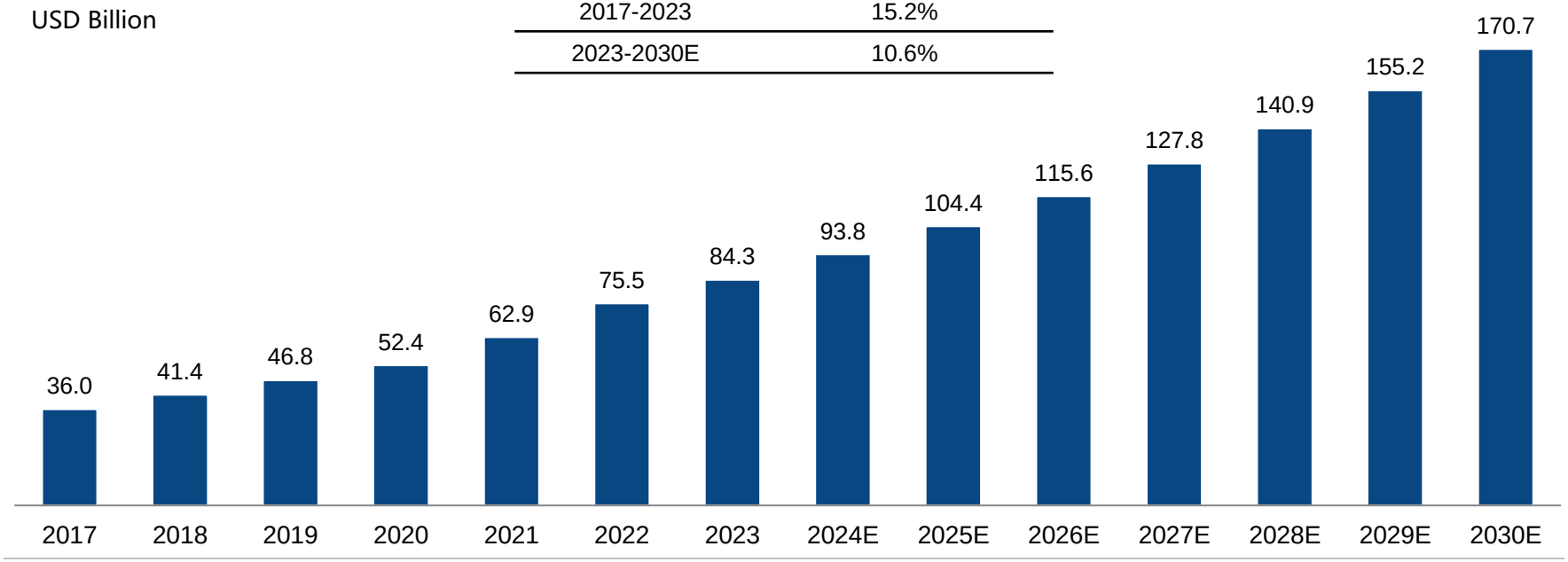
Source: Frost & Sullivan Analysis

Market Size of Global Small Molecule Anti-tumor Drugs Market, 2017-2030E

- The global small molecule anti-tumor drugs market has experienced a rapid growth, increasing from USD$36.0 billion in 2017 to USD$84.3 billion in 2023, representing a CAGR of 15.2%. It is expected that by 2030, the market size of global small molecule anti-tumor drugs market will reach $170.7 billion, representing a CAGR of 10.6%.
- Small molecule drug have many advantages including cost-effectiveness, simplified production processes, and enhanced patient compliance compared to biologics. Small molecules' ability to precisely target intracellular functions, improve blood-brain barrier permeability. Despite FDA approvals for novel drugs, small molecule drugs still occupy over 60% of FDA novel drug approvals in 2023.

Global Small Molecule Anti-tumor Drugs Market, 2017-2030E

Period	CAGR
2017-2023	15.2%
2023-2030E	10.6%



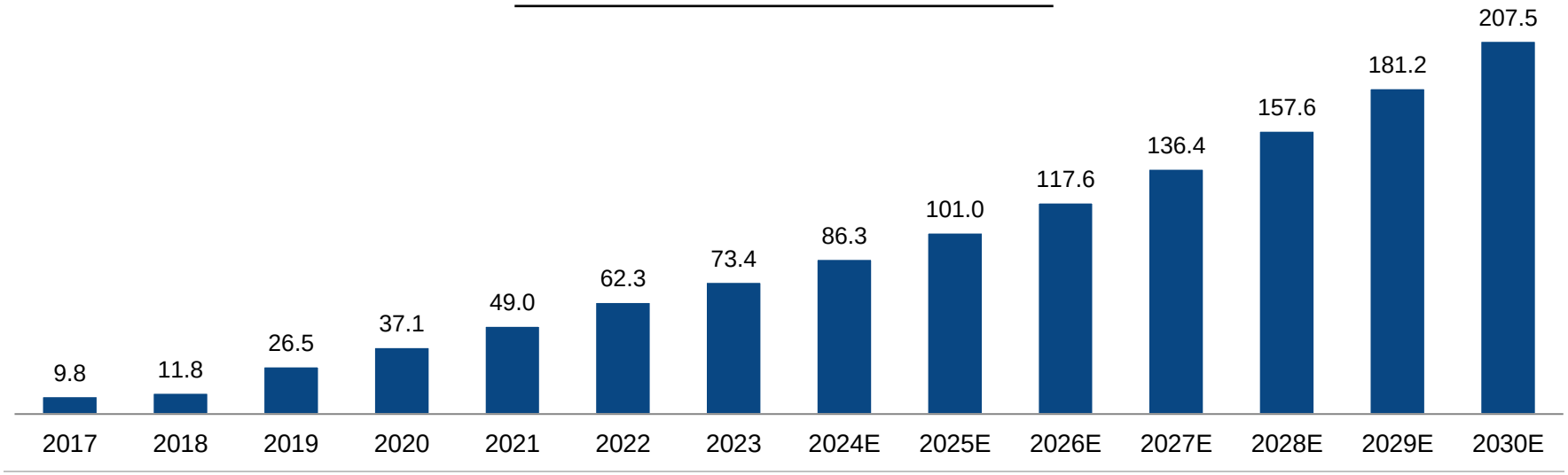
Source: Frost & Sullivan Analysis

Market Size of Small Molecule Anti-tumor Drugs Market in China, 2017-2030E

- The small molecule anti-tumor drugs market in China has developed at a faster pace than the global market, increasing from RMB 9.8 billion in 2017 to RMB73.4 billion in 2023, representing a CAGR of 39.9%. It is expected that by 2030, the market size of small molecule anti-tumor drugs market in China will grow at a CAGR of 16.0%, reaching RMB207.5 billion.

Small Molecule Anti-tumor Drugs Market in China, 2017-2030E

Period	CAGR
2017-2023	39.9%
2023-2030E	16.0%



Source: Frost & Sullivan Analysis

Factors that Drive the small molecule anti-tumor drugs market in China

Policies encourage industry innovation and development	• Since 2015, the Chinese government has launched a series of policies to encourage the creation of innovative drugs, improve drug quality, and promote industrial upgrading. Policies such as the 2015 "Opinions of the State Council on Reforming the Review and Approval System for Drugs and Medical Devices" and the 2017 "Opinions on Encouraging Drug Innovation to Implement Prioritized Review and Approval" have raised the threshold for approval of innovative drugs while accelerating the development of new drugs with clinical value, and the launch of clinically urgently needed generic drugs. The "Measures for the Administration of Drug Registration" and "Procedures for Review of Breakthrough Therapeutic Drugs (Trial)" promulgated in 2020 have further accelerated the review and approval of innovative drugs.
Increasing R&D investment from PRC pharmaceutical companies	• The R&D investment of pharmaceutical market in China has great growth potential. In 2021, the total investment in pharmaceutical R&D in China reached USD 31.9 billion. “Guiding principles for clinical value-oriented clinical research and development of anti-tumor drugs” in 2021 put forward higher requirements for the effectiveness and innovation for pharmaceutical companies in China. Since the ‘ 14th Five-Year Plan ’, the R&D investment of pharmaceutical companies in China has increased by more than 20% annually. In 2022, the cumulative R&D investment of China‘s top 10 pharmaceutical companies exceeded RMB 40 billion.
Increased accessibility of anti-tumor innovative small molecule drugs	• On January 18, 2023, NHSA officially announced the results of the adjustment to the Medicines List. At present, the total number of drugs in the national health insurance Medicines List reaches 2,967, and the new Medicines List will be officially implemented from March 1, 2023 onwards. Notably, the latest health insurance Medicines List includes 23 types of anti-tumor drugs, of which 14 drugs are included in the health insurance for the first time which include small molecule drugs such as Brigatinib and Lorlatinib. The expansion of medical insurance payment scope and preferential pricing policies have improved the accessibility of innovative cancer target therapies which will promote the development of small molecule anti-tumor drug market.
Innovative approaches to overcoming drug resistance	• Drug resistance has been a major obstacle which largely limit the clinical efficacy of small molecule drugs in cancer treatment. Gene mutations and amplification of other genes are major causes of resistance to anti-tumor targeted drugs. Overcoming these resistance mutations requires the development of next-generation inhibitors which facilitates the development of second-, third-, and newer-generation inhibitors on same targets and disease. Various innovative methods include combination therapy, proteolysis-targeted chimera (PROTAC), the drug discovery against new type cancer targets are also used to overcome the resistance of targeted anti-tumor drugs. Drug resistance remains a big challenge of anti-tumor targeted drugs, promoting the replacement and direction of the R&D of targeted drugs.

Source: Frost & Sullivan Analysis

Trends of small molecule anti-tumor drugs market in China

Innovative approaches addressing brain metastases	• The blood-brain barrier is a tightly packed layer of endothelial cells that protects the brain from harmful substances in the bloodstream and allows essential nutrients to pass through. It is a highly selective barrier that presents challenges in delivering therapeutic drugs to the brain. Innovative drugs with better blood-brain barrier permeability can improve efficacy while ensuring safety, and can further prolong the survival of patients with brain metastases, bringing more benefits to patients. Therefore, innovative drugs with good blood-brain barrier permeability will be more competitive in the small molecule antitumor drug market in China.
Combination therapies help to overcome targeted drugs resistance	• Overcoming drug resistance in antitumor small molecule targeted drugs is a critical challenge. Combining multiple small molecule inhibitors has been utilized to combat this resistance. For instance, in response to third-generation EGFR-TKIs resistance due to abnormal cell cycle regulation, combining osimertinib with CDK4/6 inhibitors like palbociclib can sensitize osimertinib-resistant cells, showing promise in addressing this issue. Combining small molecule targeted drugs with immunotherapies, such as anti-PD-1 antibody, also enhances efficacy for patients with drug resistance. Lenvatinib, a multi-receptor tyrosine kinase inhibitor, when combined with pembrolizumab, earned FDA breakthrough therapy designation in 2018 for advanced or metastatic renal cell carcinoma. With the gradual clarification of the drug resistance mechanism, more signal bypasses are being discovered and researched.
AI empowering R&D in the pharmaceutical industry	• AI including CADD/AIDD can be applied to all stages of pharmaceutical R&D. In the traditional pharmaceutical model, drug structure design relies on expert experience and the failure rate of new drug screening is high. New drug R&D usually requires more than US$1 billion and a cycle of more than 10 years. AI technologies have supported a new wave of drug development platforms by utilizing massive data sets to quickly identify patient response markers and develop viable drug targets in a more cost-effective and efficient manner.
Innovative modalities incorporating small molecule drugs	• Proteolysis-Targeting Chimeras (PROTACs) are a promising class of innovative drug modalities that exploit the body's own protein degradation mechanisms to selectively eliminate disease-causing proteins, opening up a new avenue for disease treatment. Oral PROTACs offer possibilities for the treatment of various diseases, including cancer, neurodegenerative diseases, and autoimmune diseases. This innovative therapy directly degrades disease-causing proteins and is expected to overcome the limitations of traditional small molecule inhibitors and monoclonal antibody therapies. Small molecular-drug conjugates (SMDCs) are another promising approach to targeted therapies which allow small molecules to act as targeted ligands to selectively release potent cytotoxic agents in the tumor microenvironment, thereby enhancing the therapeutic potential of anticancer drugs. SMDCs have the advantages of controllable cost, faster research and development, and good industrial foundation, etc. SMDCs are composed of small molecules, which are easy to control the synthesis process and cost, and compared with antibody drugs, the industrial operation is simple, and lower-cost mass production can be achieved in the future. In addition, SMDCs are not immunogenic in theory with easier safety control.

Source: Literature Review, Frost & Sullivan Analysis

Policies related to Small Molecule Anti-tumor Drugs Market in China

Policies	Issued Date	Institution	Content
Guiding principles for clinical application of new anti-tumor drugs (2022 Edition)	2022-12	NHC	The Guiding provides basic principles of clinical application of new anti-tumor drugs (small molecule inhibitors and monoclonal antibodies) and the clinical application of drugs in anti-tumors.
The 14th Five-Year Plan for the development of Pharmaceutical industry	2022-1	Ministry of Industry and Information Technology and other departments	The plan promotes the research and development of innovative products and the industrial application of innovative drugs, encourages global innovative drugs to be the first to be registered in China, and supports companies to implement simultaneous registration of innovative drugs at home and abroad.
Guiding principles for clinical value-oriented clinical research and development of anti-tumor drugs	2021-11	NMPA	The principles include that the research and development of anti-tumor drugs should be based on the needs of patients from the beginning. The research and development of new drugs should be the highest goal of providing patients with better treatment options.
Working Procedures for Review of Breakthrough Therapy Drugs (Interim)	2020-7	NMPA	The Procedures stipulate that during the clinical trials of breakthrough therapy drugs, applicants can apply for breakthrough therapy drug procedures during the Phase I and II clinical trials, usually no later than before the start of Phase III clinical trials.
Good Manufacturing Practice for Drugs (2020 Revision)	2020-7	NMPA	The new revision refers to common international practices, highlights the problem-oriented approach, refines and clarifies the responsibilities and requirements of all parties involved in drug clinical trials, and is consistent with the basic requirements of the ICH Technical Guidelines.
Provisions for Drug Registration	2020-1	SAMR	In order to support clinical value-oriented drug innovation, NMPA promotes the reform of the review and approval system and establishes a new registration system to speed up the drug registration.

Source: Government website, Frost & Sullivan analysis

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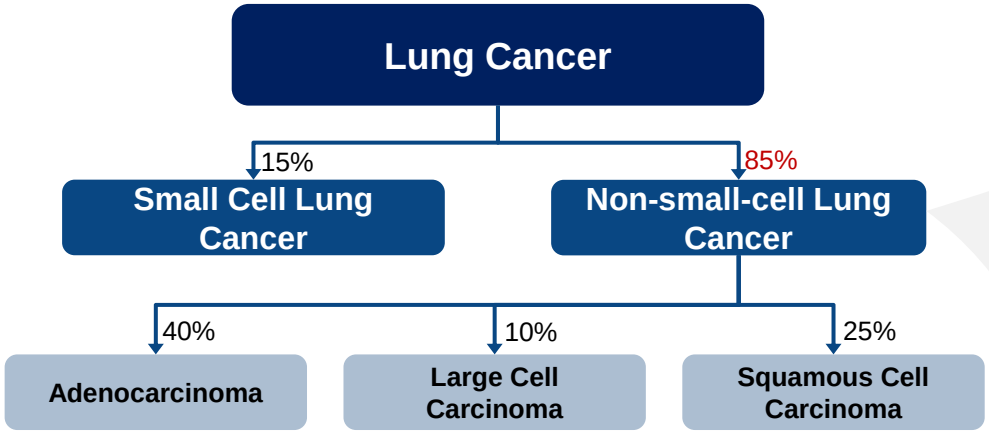
Overview of Non-small-cell Lung Cancer (NSCLC)

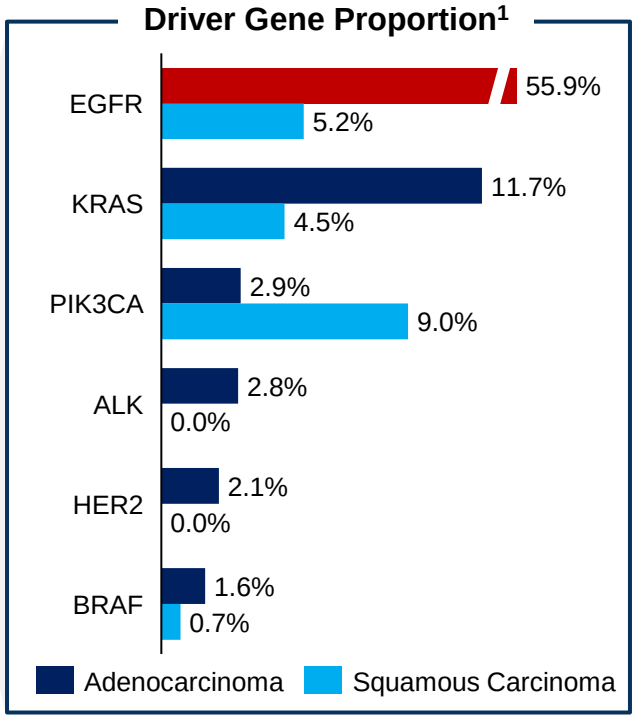
- Lung cancer is the most common malignant tumor in the world in terms of incidence and death rate. Most of the patients are diagnosed at advanced stages and the prognosis is often poor. Based on pathologic and histomorphologic features, lung cancer can be classified as non-small-cell lung cancer and small cell lung cancer. Non-small-cell lung cancer (NSCLC) is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. All types can occur in unusual histologic variants and developed as mixed cell-type combinations. Symptoms of more advanced NSCLC cases include bone pain, headache, weakness and vomiting.



- Most common subtype.
- Adenocarcinoma is usually found in outer parts of the lung, it tends to grow slower than other types of lung cancer.

- It can appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat.

- These cancers start in early versions of squamous cells, which are flat cells that line the inside of the airways in the lungs.



Notes : (1) The driver gene proportion only represents the situation in China.

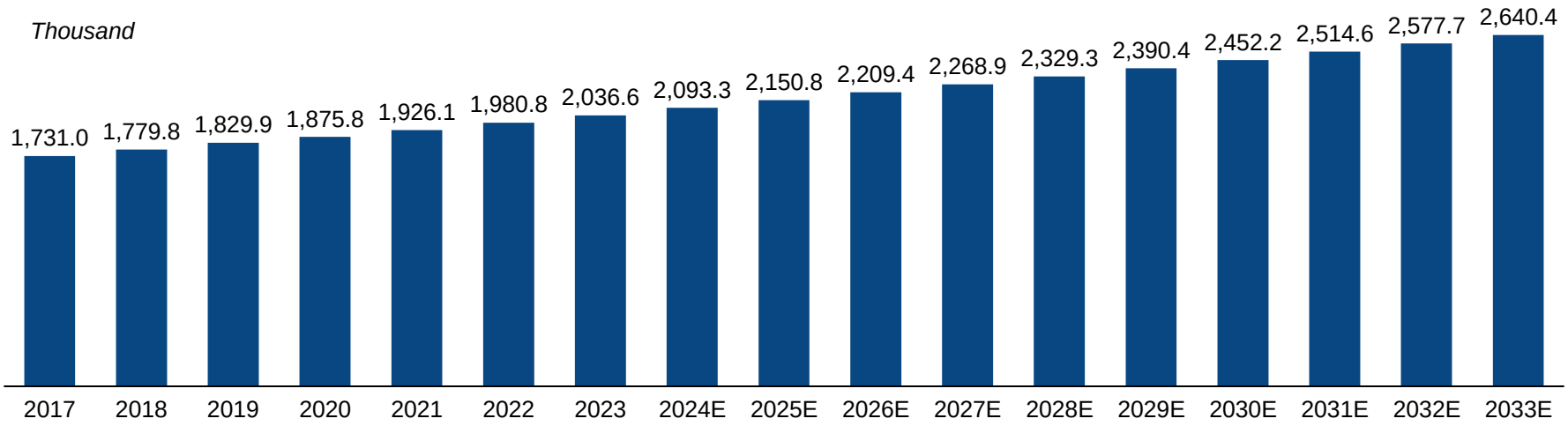
Source: Literature Review, Frost & Sullivan Analysis

Global Incidence of NSCLC, 2017-2033E

- The most common types of lung cancer are non-small cell carcinoma (NSCLC). From 2017 to 2023, the number of new NSCLC cases worldwide increased from 1,731.0 thousand to 2,036.6 thousand, representing a compound annual growth rate of 2.7 percent. It is estimated that by 2027 and 2033, the number of new NSCLC patients worldwide will reach 2,268.9 thousand and 2,640.4 thousand respectively.

Global Incidence of NSCLC, 2017-2033E

Period	CAGR
2017-2023	2.7%
2023-2027E	2.7%
2027E-2033E	2.6%



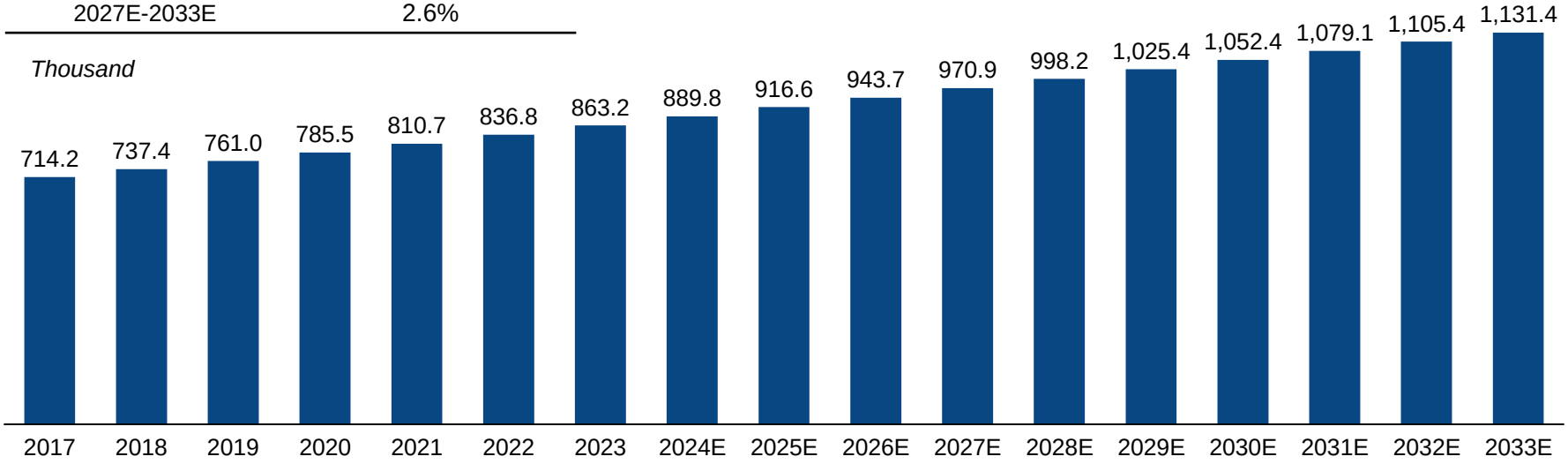
Source: NCCR, Frost & Sullivan analysis

Incidence of NSCLC in China, 2017-2033E

- Lung cancer is the first malignant tumor with the highest incidence and mortality rate in China.
- In China, NSCLC has a large patient pool, reaching 714.2 thousand in 2017. In the next 5 years, it increased to 863.2 thousand in 2023, representing a CAGR of 3.2% from 2017. Since a large amount of people are following an unhealthy lifestyle including smoking, it is estimated that the NSCLC patients would be 970.9 thousand and 1,131.4 thousand by 2027 and 2033.

Incidence of NSCLC in China, 2017-2033E

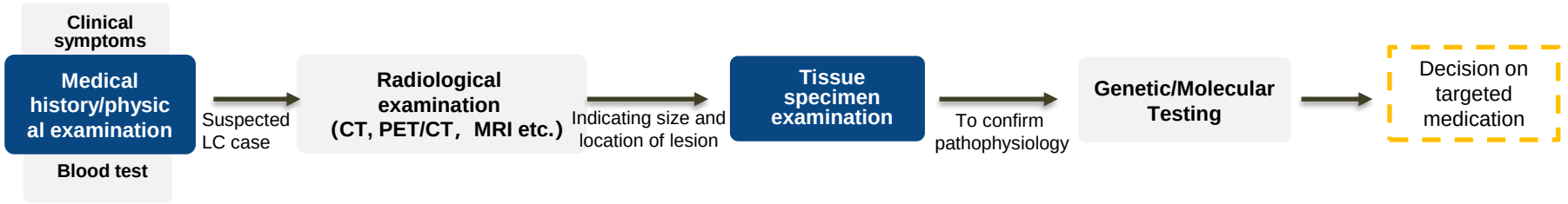
Period	CAGR
2017-2023	3.2%
2023-2027E	3.0%
2027E-2033E	2.6%



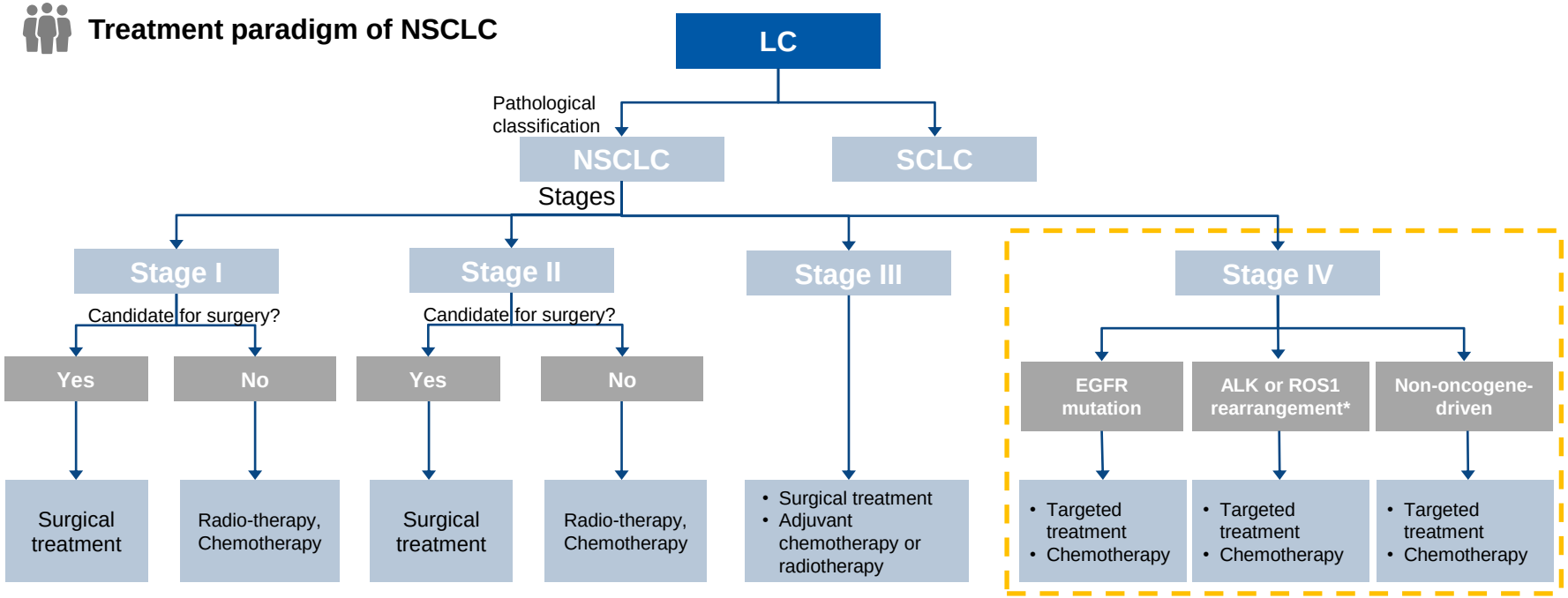
Source: NCCR, Frost & Sullivan analysis

Diagnosis and treatment flow of NSCLC

Diagnosis flow of NSCLC



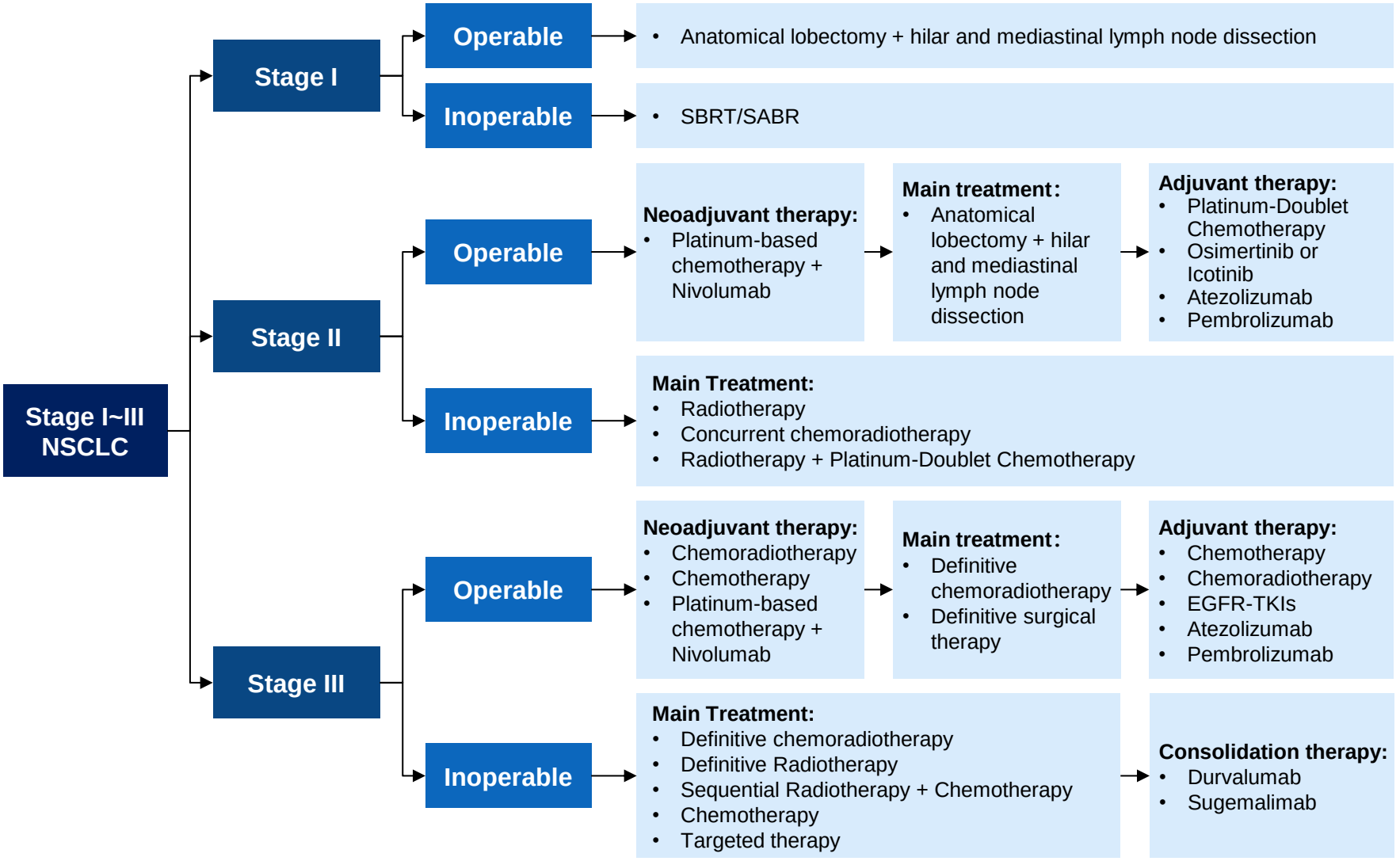
Treatment paradigm of NSCLC



Notes : (1) In China, the treatment paradigm for patients with BRAF V600E mutation and NTRK rearrangement can refer to the non-oncogene-driven part.

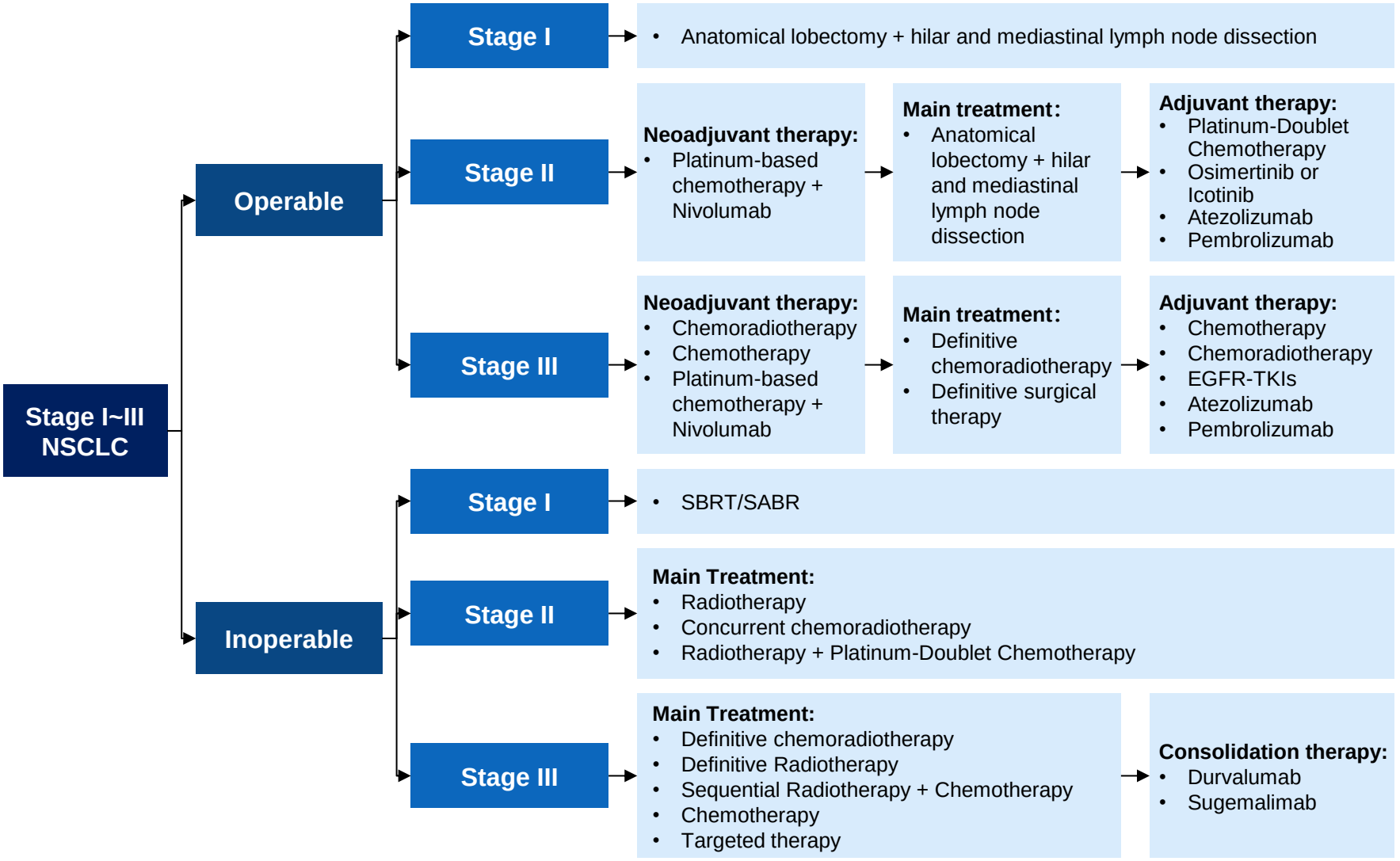
Source: Literature Review, Frost & Sullivan Analysis

Treatment pathway of stage I~III NSCLC patients



Source: CSCO, Frost & Sullivan Analysis

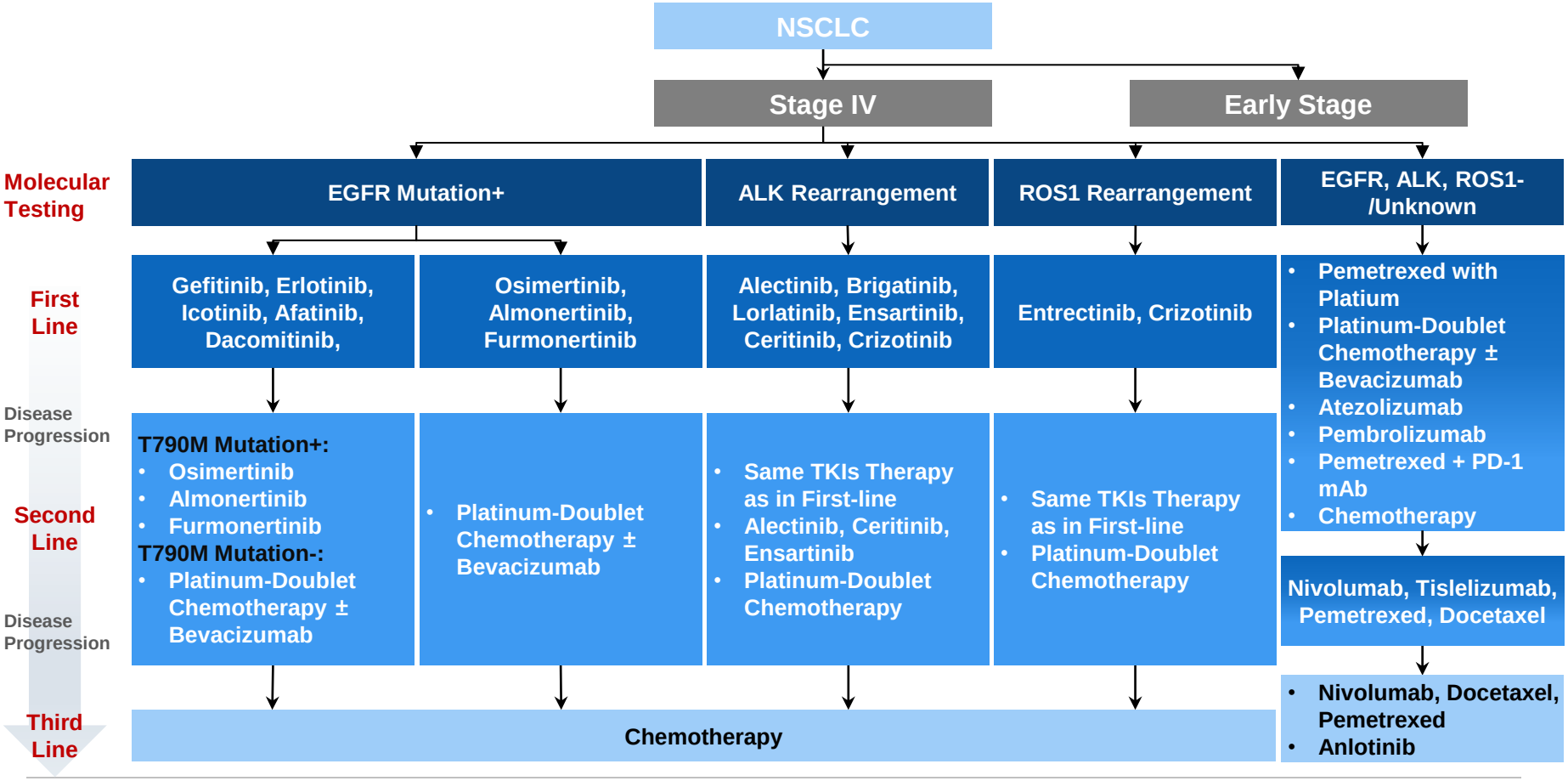
Treatment pathway of stage I~III NSCLC patients



Source: CSCO, Frost & Sullivan Analysis

Treatment Paradigm for Stage IV NSCLC in China

- For the treatment of patients with early stage NSCLC, surgical treatments, chemotherapy and radiotherapy are dominant treatment methods in China. Targeted therapies focusing on cancer driver genes get involved in treatments of patients with stage IV NSCLC.



Source: CSCO NSCLC Treatment Guideline 2023, Frost & Sullivan Analysis

Pain points and unmet needs of NSCLC treatment

- Despite the achievement in NSCLC treatment, there are still some pain points and unmet needs to be addressed.

Pain Point: Prognosis of patients with brain metastasis is poor.

- Brain is the most common site of lung cancer metastases, and the incidence rate are higher if patients have driver gene mutation.
- Patients with brain metastasis have a poor prognosis; furthermore, different treatment methods affect the disease status and prognosis.

Unmet need: Targeted drugs with better blood-brain barrier permeability

- The blood-brain barrier (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 the 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 metastasis.

Pain Point: Targeted therapies faced the acquired resistance problems.

- 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.

Unmet need: New generation target drugs or better treatment solutions

- To overcome the on-target resistance, researchers are developing the new generation target drugs against the tumor cells with drug-resistant mutation.
- 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.

Pain Point: OS & PFS of EGFR L858R patients remain to be improved.

- 19del and 21L858R are the two most common EGFR mutation subtypes, yet OS and PFS of L858R patients treated with EGFR-TKI were significantly lower than those of 19del patients due to different molecular mutation mechanisms, different rates of combined coexisting mutations, different mechanisms of resistance to mutation subtypes, and different tumor mutational loads.

Unmet need: More effective targeted drugs for EGFR L858R patients

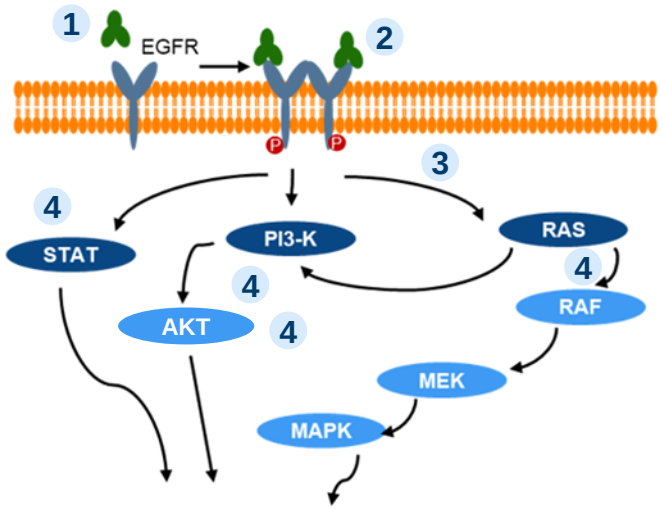
- In terms of molecular structure, the molecular characteristics of L858R allow it to bind TKI drugs with a lower affinity than 19del. Increased drug dosage has the potential to elevate the affinity for the drug, thereby improving the drug's inhibition of the enzyme. Therefore, EGFR-TKI with lower toxicity may become a more effective targeted drug for EGFR L858R patients as it's safer to increase drug dosage.

Source: Literature Review, Frost & Sullivan Analysis

Overview and Mechanism of EGFR

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

Mechanism of EGFR



Promote cancer cell proliferation
Promote neovascularization within the tumor
Promote cancer cell migration
Prevent cancer cell apoptosis

RAS–RAF–MEK–ERK Pathway

- The RAS–RAF–MEK–ERK pathway is a conserved signaling pathway that plays vital roles in cell proliferation, survival, and differentiation.
- The aberrant activation of the RAS–RAF–MEK–ERK signaling pathway induces tumors. About 33% of tumors harbor RAS mutations, while 8% of tumors are driven by RAF mutations.

PI3K/Akt Pathway

- The phosphoinositide 3-kinase (PI3K)/Akt signaling pathway is a major signaling pathway in various types of cancer. It controls hallmarks of cancer, including cell survival, metastasis and metabolism.
- The PI3K/Akt pathway also plays essential roles in the tumor environment, functioning in angiogenesis and inflammatory factor recruitment.

STAT3 Pathway

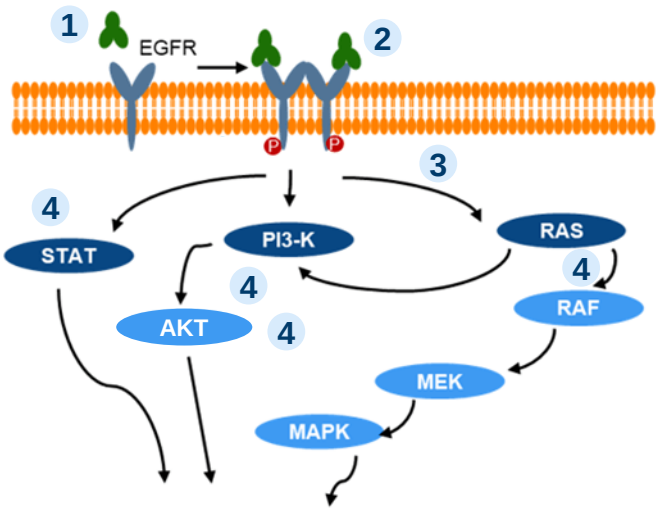
- Signal transducer and activator of transcription 3 (STAT3), a member of the STAT family plays a significant role in biological functions.
- In cancer tissues, STAT3 is activated in an aberrant manner and is induced by certain cytokines. Aberrantly, phosphorylated STAT3 is also involved in tumor formation, development, and metastasis.

Source: Literature review, Frost & Sullivan Analysis

Overview and Mechanism of EGFR-TKI

- 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, thereby blocking the downstream cascade by inhibiting the upstream signaling pathway.
- The activating EGFR gene mutants mainly occur in the 18-21 exon which encodes the intracellular tyrosine kinase domain. The frequent mutations refer to EGFR exon 19 deletion and exon 21 point mutations (including exon 21 L858R) which in the aggregate account for approximately 85% of all EGFR mutations. EGFR exon 19 deletion is the most prevalent, representing approximately 45% of all EGFR mutations and complex for many different mutant positions and patterns.

Mechanism of EGFR-TKI



Promote cancer cell proliferation
Promote neovascularization within the tumor
Promote cancer cell migration
Prevent cancer cell apoptosis

Mechanism of EGFR pathway

1. Bind ligands such as EGF to the EGFR receptor
2. Form the EGFR dimers
3. Activate the EGFR intercellular tyrosine trans-phosphorylation
4. Trigger the downstream cascade and promote the proliferation and growth of tumors and cancer cells through the RAS, PI3K, STAT signaling pathways

Core Mechanism of EGFR-TKI:
EGFR-TKI inhibits the activation of the EGFR intracellular tyrosine kinase domain by competing with ligands such as EGF for binding to the EGFR receptor, thereby blocking the downstream cascade by inhibiting the upstream signaling pathway

Source: Literature review, Frost & Sullivan Analysis

Development path of EGFR-TKI

- There are three generations of EGFR-TKIs that have been approved for marketing. The first-generation EGFR-TKI includes 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 have been more and more drug researches around EGFR and its resistance targets. The following table lists the key features of the three generations of EGFR-TKIs.

Development path of EGFR-TKI

	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, L858R	Exon19 del, L858R	Exon19 del, L858R, T790M
BBB[1] permeability	Weak	Weak	Ordinary

Notes : (1) BBB = Blood-Brain Barrier.

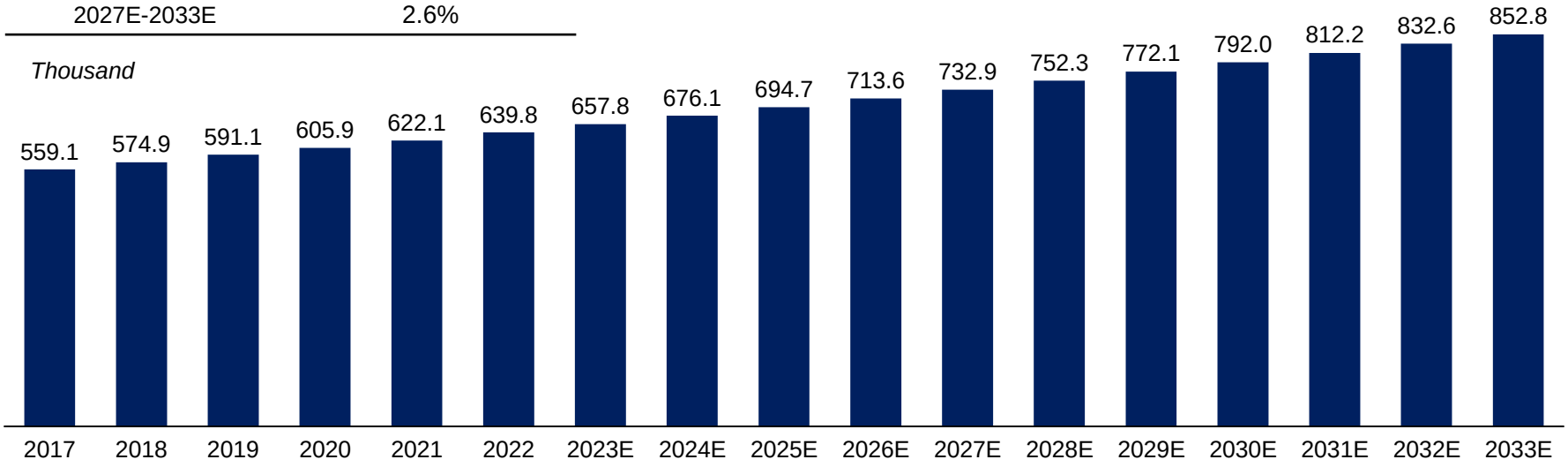
Source: Literature review, Frost & Sullivan Analysis

Global Incidence of NSCLC patients with EGFR mutation, 2017-2033E

- From 2017 to 2022, the number of new NSCLC cases with EGFR mutation worldwide increased from 559.1 thousand to 639.8 thousand, representing a compound annual growth rate of 2.7 percent. It is estimated that by 2027 and 2033, the number of new NSCLC patients with EGFR mutation worldwide will reach 732.9 thousand and 852.8 thousand respectively.

Global Incidence of NSCLC patients with EGFR mutation, 2017-2033E

Period	CAGR
2017-2022	2.7%
2022-2027E	2.8%
2027E-2033E	2.6%



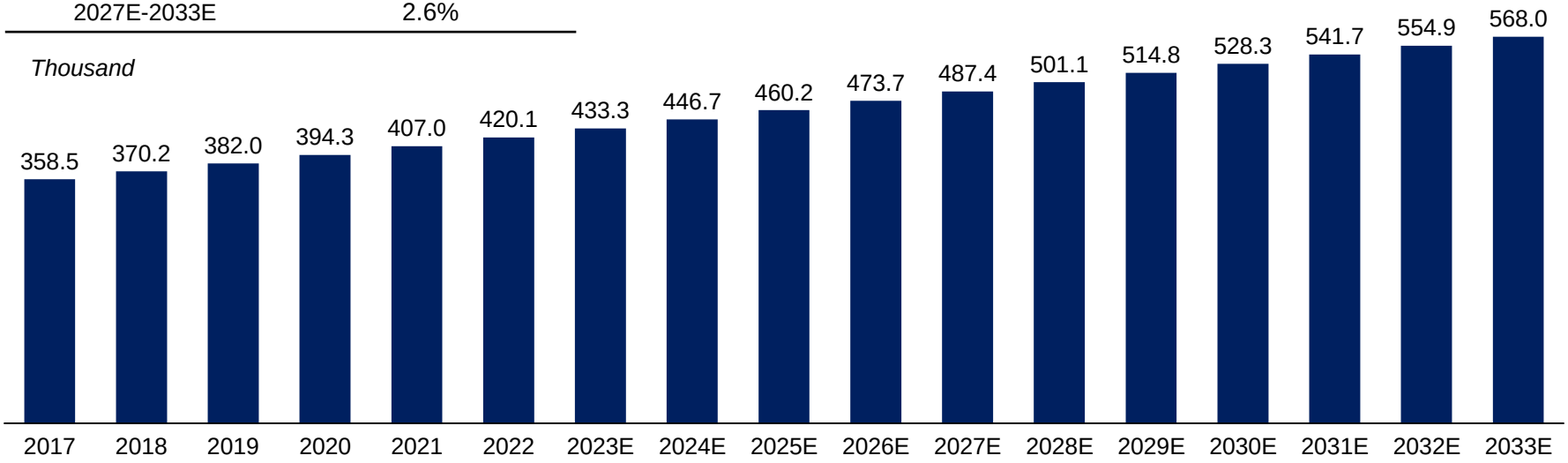
Source: NCCR, Frost & Sullivan analysis

Incidence of NSCLC patients with EGFR mutation in China, 2017-2033E

- From 2017 to 2022, the number of new NSCLC cases with EGFR mutation in China increased from 358.5 thousand to 420.1 thousand, representing a compound annual growth rate of 3.2 percent. It is estimated that by 2027 and 2033, the number of new NSCLC patients with EGFR mutation in China will reach 487.4 thousand and 568.0 thousand respectively.

Incidence of NSCLC patients with EGFR mutation in China, 2017-2033E

Period	CAGR
2017-2022	3.2%
2022-2027E	3.0%
2027E-2033E	2.6%



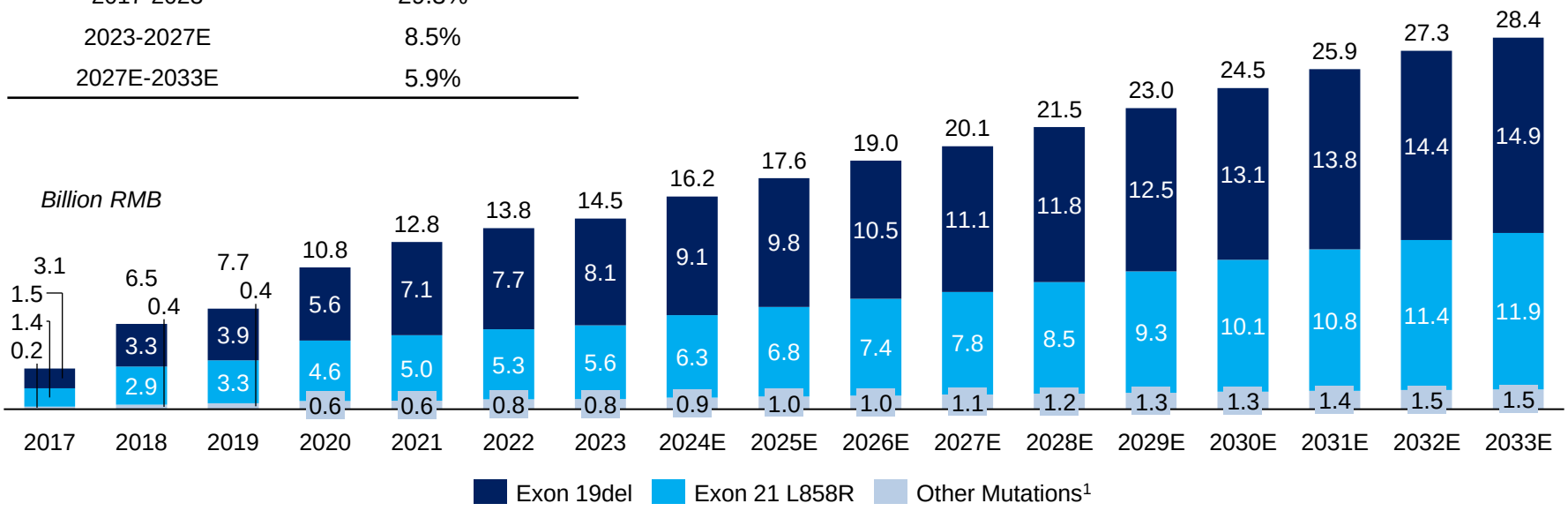
Source: NCCR, Frost & Sullivan analysis

Market size of EGFR-TKI in China, 2017-2033E

- In China, the EGFR-TKI market increased from RMB3.1 billion in 2017 to RMB14.5 billion in 2023, representing a CAGR of 29.3% during the historical periods. Driven by increasing demand for targeted therapies and new approaches to solve the drug resistance, the EGFR-TKI market in China is expected to reach RMB20.1 billion and RMB28.4 billion by 2027 and by 2033 respectively, growing at a CAGR of 8.5% from 2022 to 2027 and a CAGR of 5.9% from 2027 to 2033.

Historical and Forecasted Market Size of EGFR-TKI in China, 2017-2033E

Period	CAGR
2017-2023	29.3%
2023-2027E	8.5%
2027E-2033E	5.9%

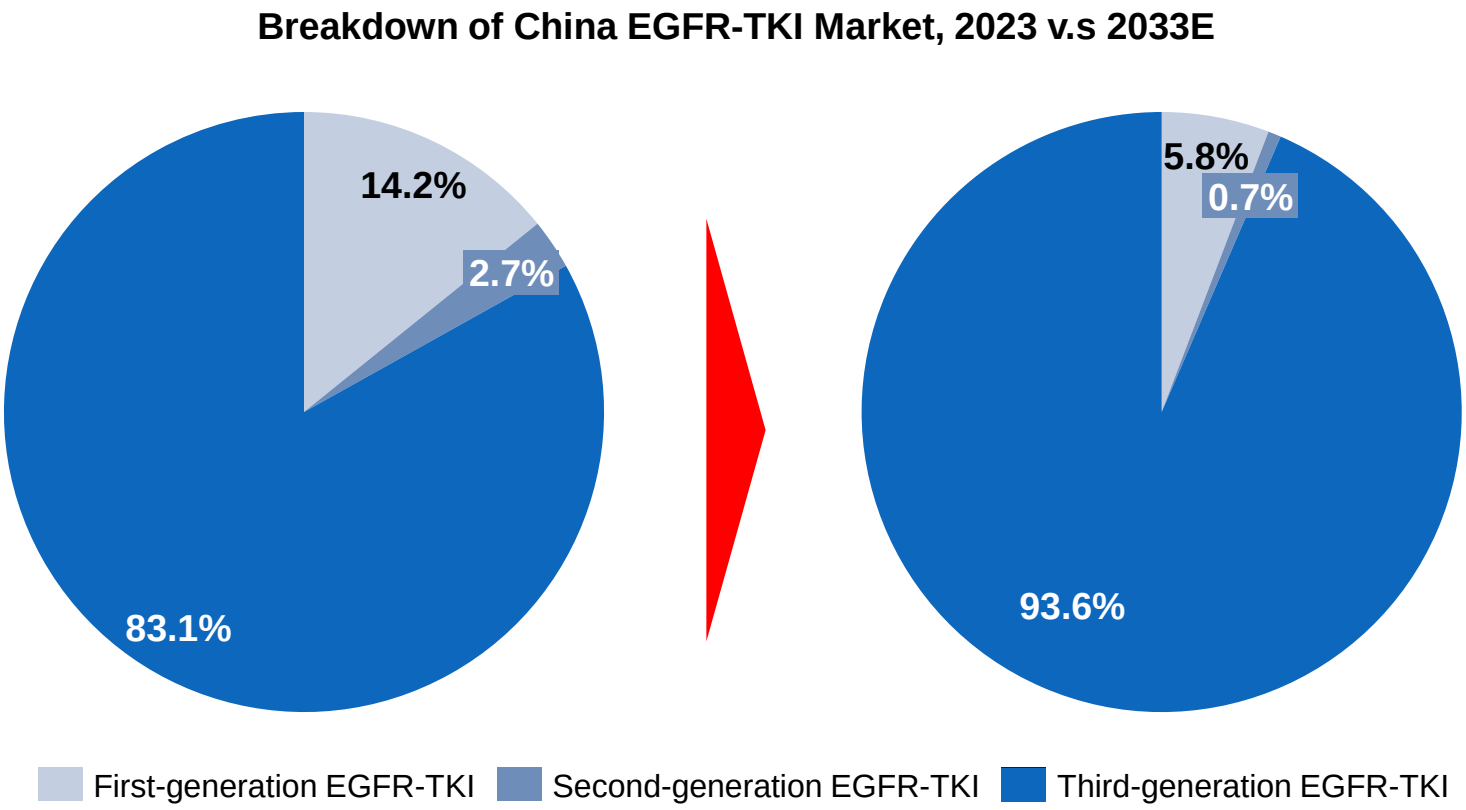


Notes : (1) The EGFR-TKI for EGFR exon 20 insertion can not be defined as first to third generation EGFR-TKI, so the market size of EGFR-TKI excludes the market size of EGFR-TKI for EGFR exon 20 insertion. The Other mutations refer to all EGFR mutation subtypes excluding exon 19 deletion, exon 21 L858R substitution and exon 20 insertion mutations.

Source: Frost & Sullivan analysis

Breakdown of China EGFR-TKI Market, 2023 vs 2033E

- In 2023, the third-generation EGFR-TKI dominated the EGFR-TKI drug market, accounting for approximately 83.1% of total market share in China. In the future, the market share of the third-generation EGFR-TKI will keep increased, as it will account for 93.6% of the China EGFR-TKI market in 2033.



Source: Frost & Sullivan analysis

Growth Drivers of EGFR-TKI Market in China

Large number of patients with EGFR mutation-positive	• Among all malignant tumors in China, lung cancer ranks No.1 in terms of annual incidence rate. Early lung cancer typing is based on pathophysiology and is divided into two main categories: NSCLC and SCLC. NSCLC is the main type, accounting for about 85% of all lung cancers. EGFR is a transmembrane receptor that is associated with a variety of signaling pathways including cell proliferation, metastasis and apoptosis. In Asian populations, EGFR mutation is the main type of lung cancer gene mutation. The positive rate of EGFR mutations in lung adenocarcinoma patients in China is around 50%. The increasing demand for drugs from the large number of patients with EGFR mutation positive will promote the rapid development of the EGFR-TKI market in China.
Increased recognition of EGFR-TKIs from clinicians	• The earliest approved indications for first-generation EGFR-TKIs were for locally advanced or metastatic NSCLC after failure of chemotherapy, and did not focus on the EGFR-mutant patient population. Gefitinib was delisted due to inappropriate targeting of indications that led to the failure of its phase III clinical trial. However, as researchers discovered the significant efficacy of EGFR-TKI for EGFR mutation positive patients in clinical trials, EGFR-TKI has become an important option for the treatment of EGFR mutation positive patients. As clinicians continue to accumulate clinical practice experience in the use of EGFR-TKI for the treatment of NSCLC patients, the recognition of efficacy in EGFR-TKI by clinicians continues to increase, and the market penetration of EGFR-TKI continues to rise.
New approaches to solve the drug resistance	• Drug resistance is an unavoidable problem for EGFR-TKIs and continues to drive the continuous development and evolution of EGFR-TKIs. Both first-generation and second-generation EGFR-TKIs have a high probability of finding T790M mutations after treating patients for a certain period of time and generating EGFR on-target resistance, which has led to the birth of the third-generation EGFR-TKIs capable of targeting the T790M mutation, and the third-generation TKIs are currently encountering the problem of on-target resistance generated by the C797X mutation. In addition to the problem of on-target resistance, there is also the problem of off-target resistance that has yet to be solved. The acquired resistance problem has also driven the development of new generation EGFR-TKIs and the exploration of related combination therapies.
Implementation of favorable policies	• In order to encourage the R&D of new drugs, and to meet the clinical demand for drugs, and to speed up the review of innovative drugs, the Center for Drug Evaluation of the NMPA has issued the "Procedures for Accelerating the Review of Innovative Drugs for Marketing Application (Trial)". Innovative medicines included in the breakthrough therapeutic drug program that are eligible for "accelerated review", which significantly shorten the time of drug approval to market. On July 7, 2020, NMPA issued the Guidelines for Updating the Specification of Tumor-Concomitant Diagnostic Reagents Based on Similar Therapeutic Drugs and Technical Review. With the continuous development of companion diagnostic technology in China and the continuous improvement of companion diagnostic system, the proportion of targeted therapy will further increase, and the market of a series of targeted drugs, such as EGFR-TKI, will also continue to grow rapidly.

Source: Frost & Sullivan Analysis

Future Trends of EGFR-TKI Market in China

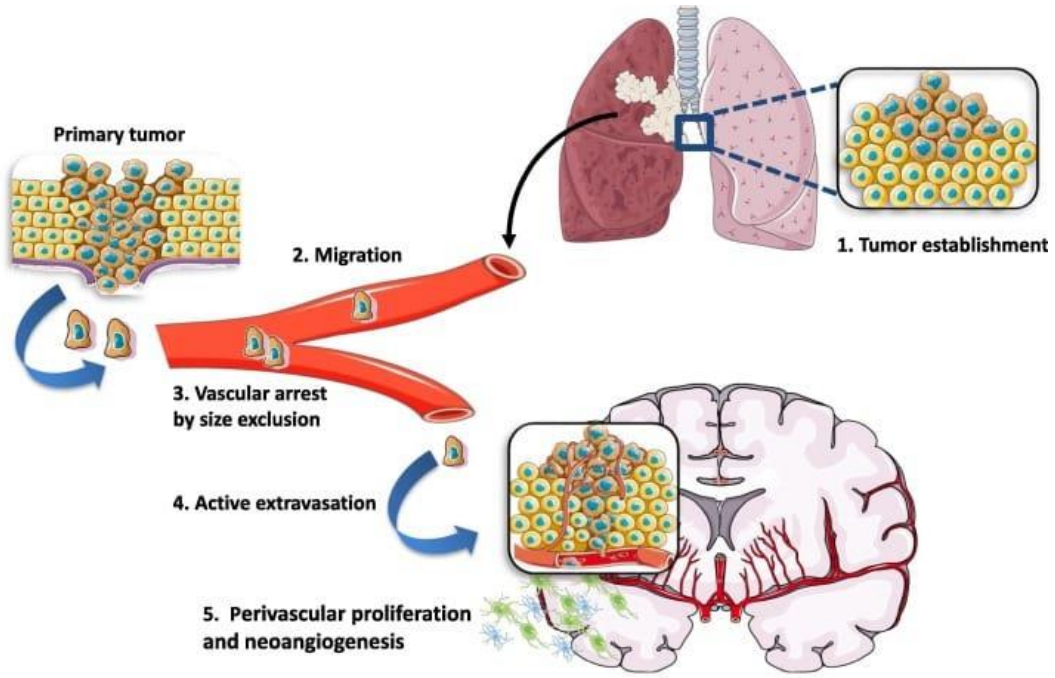
Fill in treatment vacuum	• Although targeted therapies including EGFR-TKI have significantly improved the treatment of NSCLC patients, due to the influence of the blood-brain barrier, the concentration of targeted drugs and chemotherapeutic agents in the cerebrospinal fluid is often lower than that in peripheral blood, making it relatively difficult to treat NSCLC patients with brain metastases, and the survival period is shorter. In the future, EFGR-TKI with better blood-brain barrier permeability will be developed to broaden the therapeutic window of EGFR-TKI, thus 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. Continuous 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 will enable doctors to select distinct drugs tailored for various EGFR mutation subtypes, paving the way for a more precise and effective EGFR-targeted therapy.
Increasing market share of 3rd-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, and the utilization rate and penetration rate of EGFR-TKI continue to rise. Since the price of Osimertinib has been reduced and entered the NRDL, the accessibility of 3rd-generation EGFR-TKI to patients has been greatly improved. With the successful exploration of combination therapy between 3rd-generation EGFR-TKI and other drugs in the future, the scope of application of 3rd-generation EGFR-TKI will continue to expand. and the market share of third-generation EGFR-TKI will continue to increase.
Continue addressing drug resistance	• The next generation of EGFR-TKIs-based regimen is currently in development to combat on-target resistance. New EGFR-TKIs are poised to directly address emerging mutations like 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 like osimertinib. Moreover, in cases where resistance mechanisms remain unknown, researchers are exploring the amalgamation of targeted agents with chemotherapy or immune checkpoint inhibitors. . Combination therapy can bring synergistic antitumor effect and thus significantly improve the clinical outcome. The FLAURA2 study in Asia showed that the combined therapy of osimertinib and chemotherapy greatly improved the efficacy than osimertinib monotherapy.These tailored development efforts will effectively tackle new challenges in cancer treatment in the future.

Source: Frost & Sullivan Analysis

Overview of brain metastasis from lung cancer

- 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 lung, breast, colon, kidney and melanoma.
- Brain metastases may form one tumor or many tumors in the brain. As the metastatic brain tumors grow, they create pressure on and change the function of surrounding brain tissue. This causes signs and symptoms, such as headache, personality changes, memory loss and seizures.

Mechanism of brain metastasis from lung cancer



Symptoms

- Headache
- Vomiting
- Visual impairment
- Mental abnormality
- Weakness or numbness on one side of the body
- Hallucinatory smell
- Hemiplegic or staggering gait
- Tinnitus, deafness

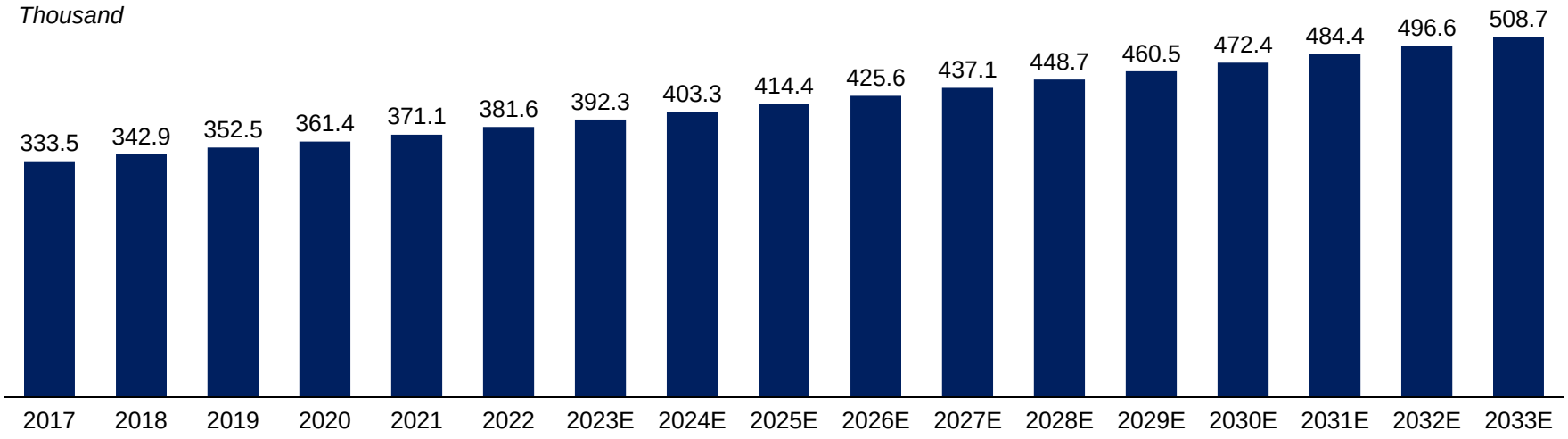
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of patients with brain metastases from lung cancer, 2017-2033E

- From 2017 to 2022, the number of new cases with brain metastases from lung cancer worldwide increased from 333.5 thousand to 381.6 thousand, representing a compound annual growth rate of 2.7 percent. It is estimated that by 2027 and 2033, the number of new patients with brain metastases from lung cancer worldwide will reach 437.1 thousand and 508.7 thousand respectively.

Global incidence of patients with brain metastases from lung cancer, 2017-2033E

Period	CAGR
2017-2022	2.7%
2022-2027E	2.8%
2027E-2033E	2.6%



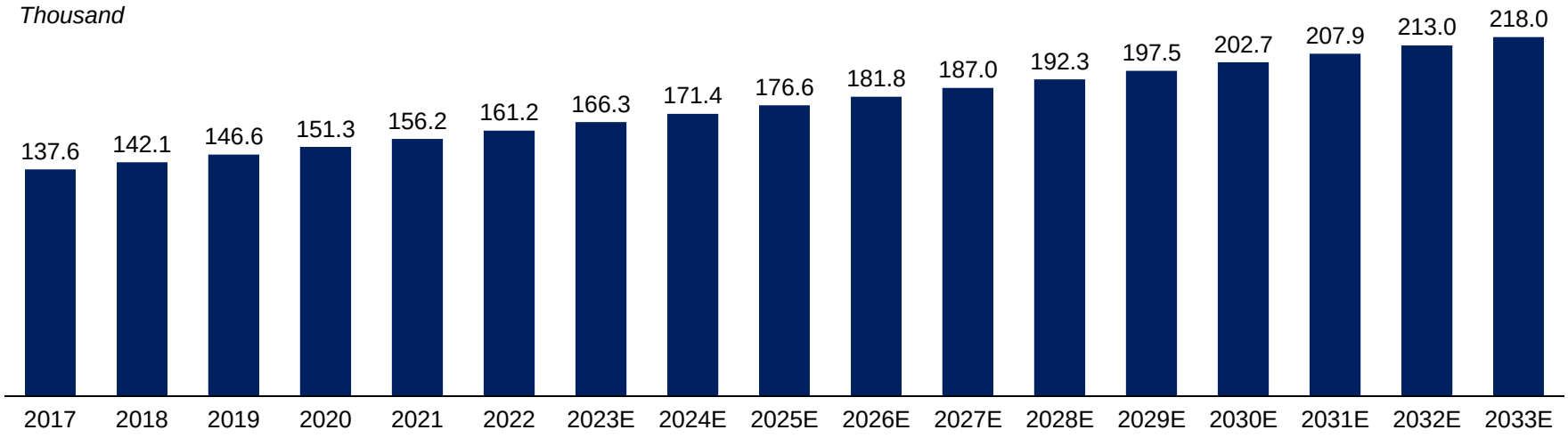
Source: NCCR, Frost & Sullivan analysis

Incidence of patients with brain metastases from lung cancer in China, 2017-2033E

- From 2017 to 2022, the number of new cases with brain metastases from lung cancer in China increased from 137.6 thousand to 161.2 thousand, representing a compound annual growth rate of 3.2 percent. It is estimated that by 2027 and 2033, the number of new patients with brain metastases from lung cancer will reach 187.0 thousand and 218.0 thousand respectively.

Incidence of patients with brain metastases from lung cancer in China, 2017-2033E

Period	CAGR
2017-2022	3.2%
2022-2027E	3.1%
2027E-2033E	2.7%



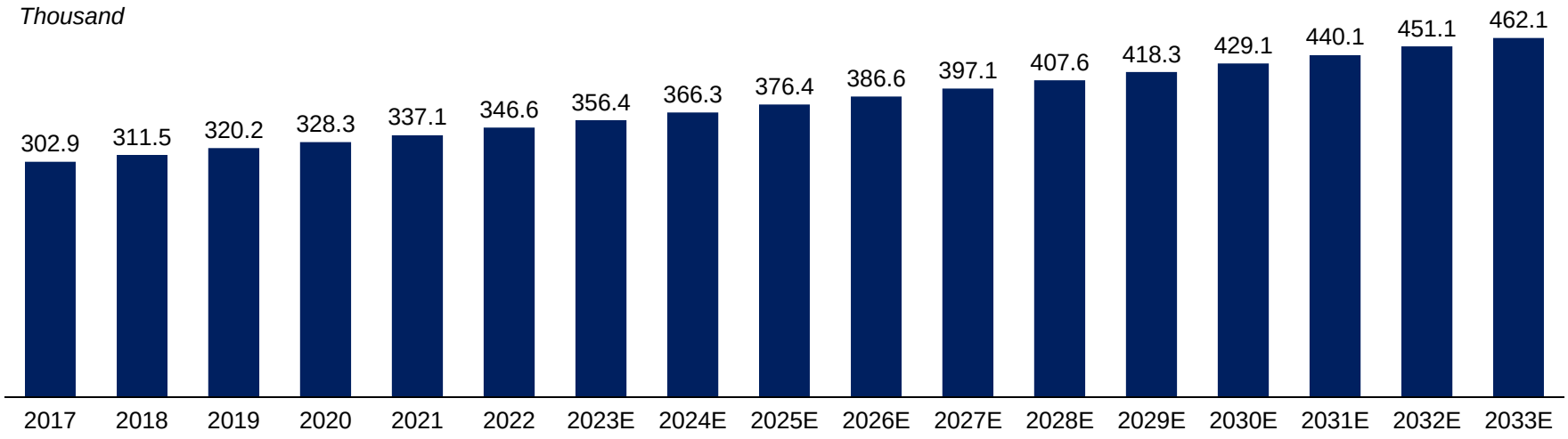
Source: NCCR, Frost & Sullivan analysis

Global incidence of patients with brain metastases from NSCLC, 2017-2033E

- From 2017 to 2022, the number of new cases with brain metastases from NSCLC worldwide increased from 302.9 thousand to 346.6 thousand, representing a compound annual growth rate of 2.7 percent. It is estimated that by 2027 and 2033, the number of new patients with brain metastases from lung cancer worldwide will reach 397.1 thousand and 462.1 thousand respectively.

Global incidence of patients with brain metastases from NSCLC, 2017-2033E

Period	CAGR
2017-2022	2.7%
2022-2027E	2.8%
2027E-2033E	2.6%



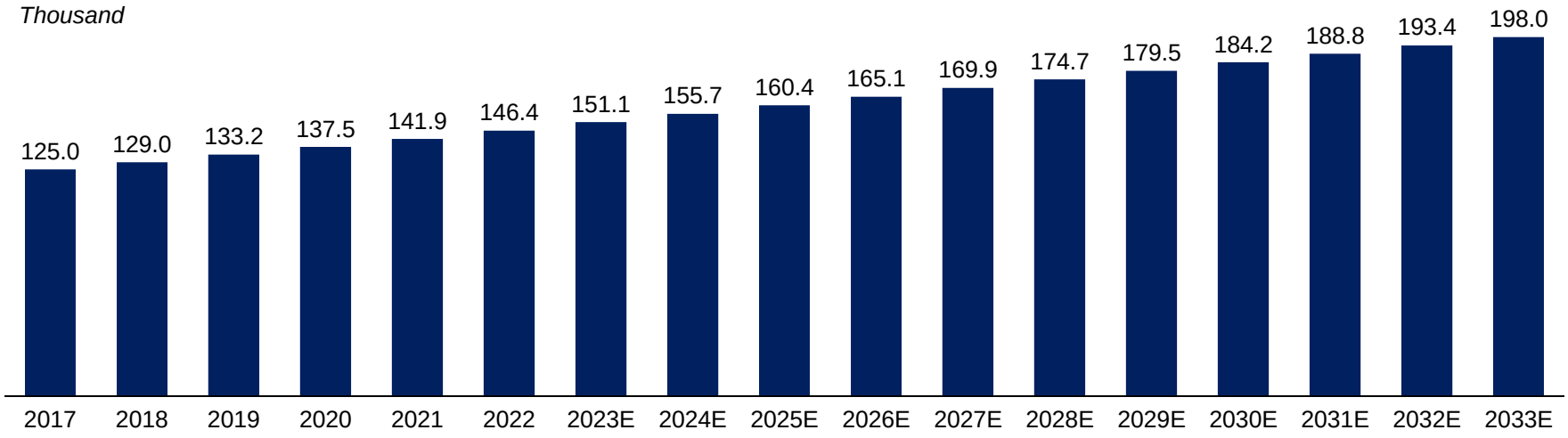
Source: NCCR, Frost & Sullivan analysis

Incidence of patients with brain metastases from NSCLC in China, 2017-2033E

- From 2017 to 2022, the number of new cases with brain metastases from NSCLC in China increased from 125.0 thousand to 146.4 thousand, representing a compound annual growth rate of 3.2 percent. It is estimated that by 2027 and 2033, the number of new patients with brain metastases from lung cancer will reach 169.9 thousand and 198.0 thousand respectively.

Incidence of patients with brain metastases from NSCLC in China, 2017-2033E

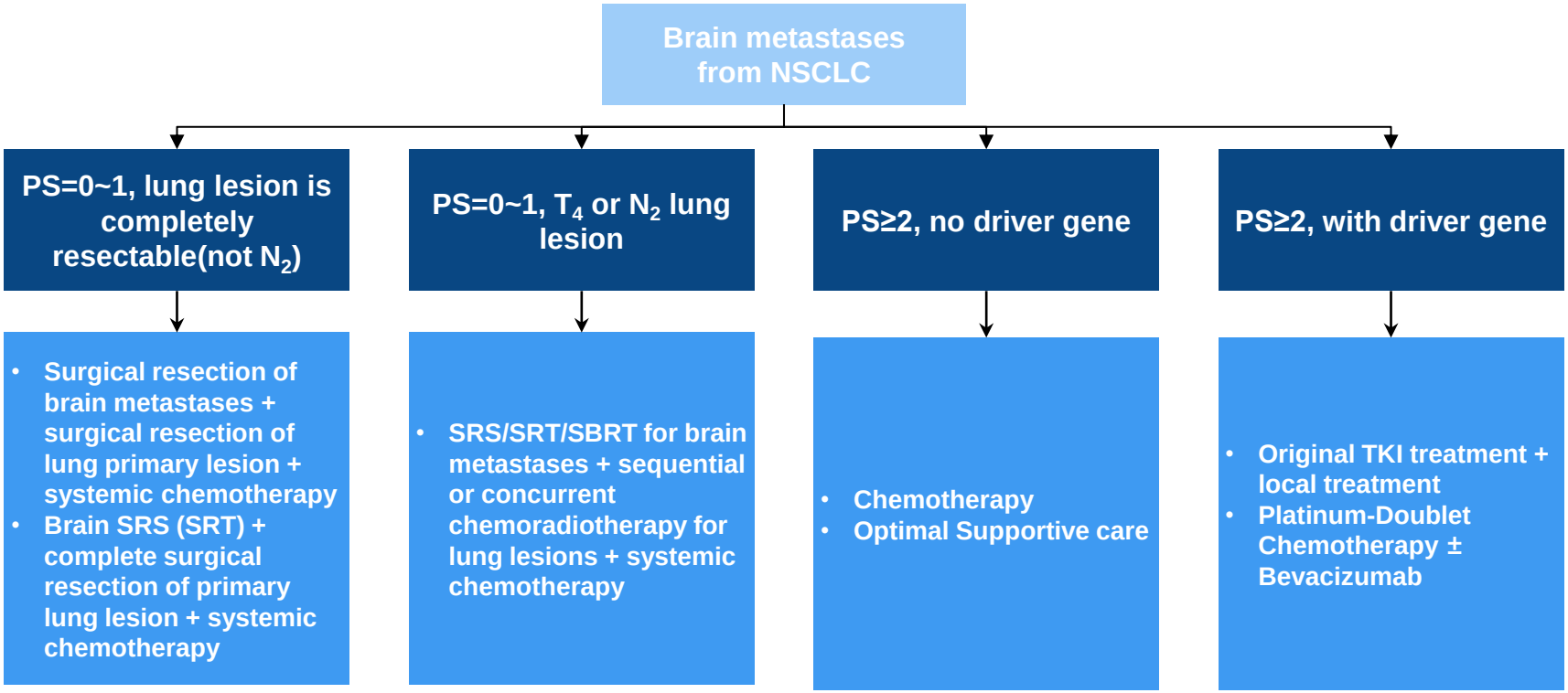
Period	CAGR
2017-2022	3.2%
2022-2027E	3.1%
2027E-2033E	2.7%



Source: NCCR, Frost & Sullivan analysis

Treatment Paradigm for Brain metastases from NSCLC in China

- For the treatment of patients with Brain metastases from NSCLC, surgical treatments, chemotherapy and radiotherapy are dominant treatment methods in China. For patients with brain metastases from NSCLC with driver genes, current targeted therapy regimens are only effective for a small percentage of patients with slow progression, and most patients can only be treated by chemotherapy.



Abbreviation: SRS = Stereotactic Radiosurgery; SRT = Stereotactic Radiation Therapy; SBRT = Stereotactic Body Radiotherapy

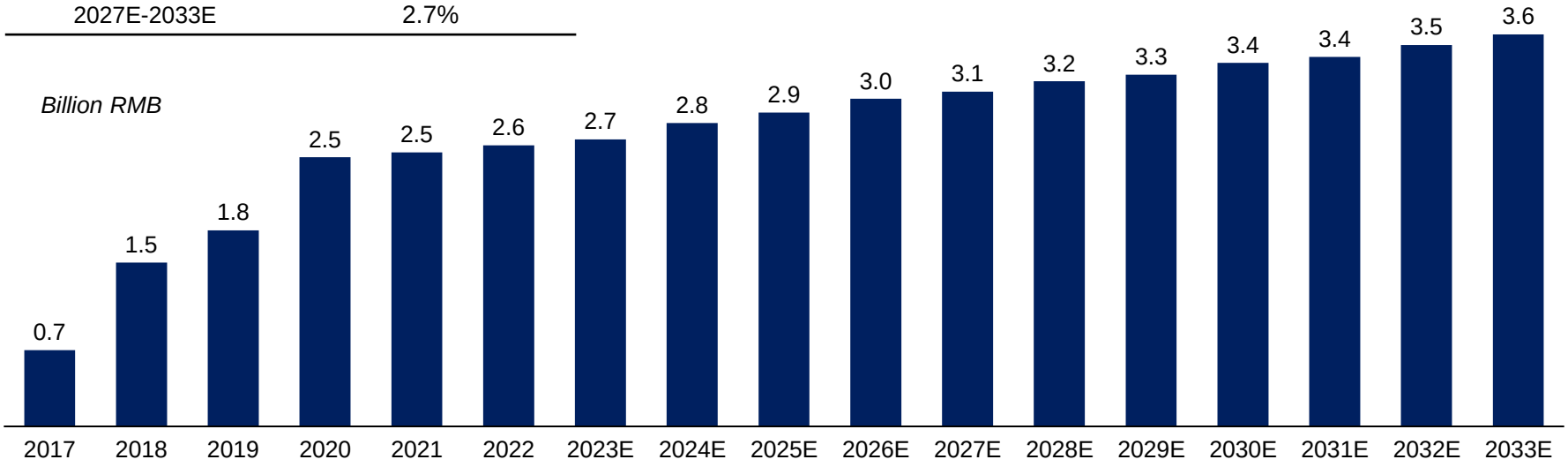
Source: CSCO NSCLC Treatment Guideline 2023, Frost & Sullivan Analysis

Market size of EGFR-TKI for brain metastases from lung cancer in China, 2017-2033E

- In China, the EGFR-TKI market for brain metastases from lung cancer increased from RMB0.7 billion in 2017 to RMB2.6 billion in 2022. It is expected to reach RMB3.1 billion in 2027 with a CAGR of 3.6% and RMB3.6 billion in 2033 with a CAGR of 2.7%.

Historical and Forecasted Brain Metastases of Lung Cancer EGFR-TKI Market in China, 2017-2033E

Period	CAGR
2017-2022	29.8%
2022-2027E	3.6%
2027E-2033E	2.7%



Source: Frost & Sullivan analysis

Growth Drivers of Innovative Small Molecule Drug Market targeting brain metastases of lung cancer in China

High incidence of brain metastases from lung cancer	• Primary lung cancer is one of the most common malignant tumors in China, and one of the most common distant metastatic sites of lung cancer is the brain. The incidence of brain metastasis from lung cancer is significantly higher than that from melanoma, breast cancer, kidney cancer and colorectal cancer. 20% to 65% of lung cancer patients will develop brain metastasis during the course of the disease, and it is the most common type of metastatic brain tumor. As the incidence of lung cancer rises and the survival time of patients is prolonged, the incidence of brain metastasis from lung cancer also rises gradually, which also leads to the increasing market demand.
Poor prognosis of brain metastases from lung cancer	• The prognosis of patients with brain metastasis from lung cancer is poor. Although chemotherapy, targeted therapy, immune checkpoint inhibitors and other drugs can be used for systematic treatment, the concentration of drugs in cerebrospinal fluid is lower than that in blood due to the existence of blood-brain barrier, which makes the therapeutic effect limited. Even if regular drug therapy can prolong the survival of patients to a certain extent, the prognosis of patients with brain metastases from lung cancer is still poor. The unmet need for clinical treatment will drive the development of innovative drugs for brain metastases from lung cancer.
Advances in molecular diagnostic technology	• For specific gene mutation typing, corresponding targeted drugs can be selected for treatment, while gene mutation typing needs to rely on molecular diagnostic techniques. Liquid biopsy is a new diagnostic technique based on the analysis of circulating tumor cells and/or molecules released by tumor cells. Liquid biopsy is a minimally invasive alternative to tissue biopsy, especially for hard-to-access tissues, such as the brain. The development of liquid biopsy technology helps clinicians to select more appropriate targeted drugs for treatment in response to the patient's genetic mutation typing, and enhances the penetration rate of targeted drugs on clinical applications.
Drug discovery and innovation	• The blood-brain barrier is a protective barrier that provides the brain with a defense mechanism against foreign pathogens and toxins in the bloodstream. Drug development for the treatment of lung cancer brain metastasis is complicated by the presence of the blood-brain barrier. Although the approved EGFR-TKIs have achieved good results in the treatment of NSCLC, their efficacy in treating patients with brain metastases from lung cancer needs to be improved due to the insufficient permeability of the blood-brain barrier. In the future, innovative small molecule drugs with better blood-brain barrier permeability will be approved and promote the market development of lung cancer brain metastasis.

Source: Frost & Sullivan Analysis

Future Trends of Innovative Small Molecule Drug Market targeting brain metastases of lung cancer in China

Increased utilization of targeted drugs	• Liquid biopsy has the advantages of being minimally invasive, fast and easy to monitor dynamically; it reflects the overall mutation status of the tumor to a certain extent and is not affected by the heterogeneity of the tumor; and it is applicable to a wide range of people. For patients with brain metastasis from lung cancer who have difficulty in obtaining biopsied tumor tissue, liquid biopsy provides an effective way to understand the state of genetic variation of the tumor. With the gradual maturation of liquid biopsy technology, driver gene testing for lung cancer brain metastasis patients will become an essential part of the diagnosis and treatment process, and more patients with driver gene mutations will be discovered, and the utilization rate of targeted drugs will be gradually increased.
Innovative drugs with better blood-brain barrier permeability dominate the market	• The blood-brain barrier is a tightly packed layer of endothelial cells that protects the brain from harmful substances in the bloodstream and allows essential nutrients to pass through. It is a highly selective barrier that presents challenges in delivering therapeutic drugs to the brain. Innovative drugs with better blood-brain barrier permeability can improve efficacy while ensuring safety, and can further prolong the survival of patients with brain metastases from lung cancer , bringing more benefits to patients. Therefore, innovative drugs with better blood-brain barrier permeability will dominate the lung cancer brain metastasis drug market.
Improved prognosis for patients with brain metastases from lung cancer	• The prognosis of patients with lung cancer brain metastasis is poor, and the natural average survival time, i.e. the average survival period for NSCLC patients with brain metastases without any treatment, is only 1 to 2 months. However, the rapid development of surgery, radiotherapy techniques and internal medicine treatment has provided more and more treatment options for patients with brain metastases from lung cancer, and the treatment level of stage IV primary lung cancer in China has been improving, improving the quality of life and prolonging the survival time of patients with brain metastases from lung cancer. Benefiting from the overall progress in diagnosis and treatment and the accumulation of experience in treating patients with lung cancer brain metastases, the prognosis of patients with brain metastases from lung cancer has been improved.
Increased utilization of combination therapies	• Due to the special location of brain metastases from lung cancer, the blood-brain barrier limits the efficacy of drug therapy; relatively few patients with brain metastases from lung cancer are able to undergo surgery; and there is a risk of irreversible damage to brain tissue from radiation therapy. Whether it is drug therapy, surgical therapy or radiation therapy, it is difficult to bring high clinical benefits to patients with only one treatment. As clinicians continue to explore combination therapies, it is expected that the combination of different therapies will bring more clinical benefits to patients.

Source: Frost & Sullivan Analysis

Competitive Landscape：EGFR-TKI Approved by FDA

- To date, there are 5 EGFR-TKI gained approval from FDA, which can be used in the treatment of NSCLC. Only 1 3rd-generation EGFR-TKI is approved.

Drug Name	Brand Name	Target	Generation	Company	Indications	Approval Date
Dacomitinib	Vizimpro	HER2, EGFR, HER4	2nd-generation	Pfizer	NSCLC	2018-09-27
Osimertinib	Tagrisso	EGFR	3rd-generation	Astrazeneca	NSCLC	2015-11-13
Afatinib	Gilotrif	HER2, EGFR, HER4	2nd-generation	Boehringer Ingelheim	NSCLC, Squamous NSCLC	2013-07-12
Erlotinib	Tarceva	EGFR	1st-generation	Astellas/Roche	NSCLC, Pancreatic cancer	2004-11-18
Gefitinib	Iressa	EGFR	1st-generation	Astrazeneca	NSCLC	2003-05-05

*Note: Approval date refers to the first approval date; Astrazeneca delisted Iressa in 2011 and relisted it in 2015.

Source: FDA, Frost & Sullivan Analysis

Competitive Landscape：EGFR-TKI Approved by NMPA

- To date, there are 11 EGFR-TKI gained approval from NMPA, which can be used in the treatment of NSCLC, and 6 of them are 3rd-generation EGFR-TKI.

Drug Name	Brand Name	Target	Generation	Company	Indications	Approval Date
Rilertinib	Sanrisso	EGFR	3rd-generation	Sanhome Pharmaceutical	NSCLC	2024-06-17
Rezivertinib	Undisclosed	EGFR	3rd-generation	Beta Pharma	NSCLC	2024-05-20
Befotertinib	Surmana	EGFR	3rd-generation	Betta Pharma	NSCLC	2023-05-31
Furmonertinib	Ivesa	EGFR	3rd-generation	Allist Pharmaceutical	NSCLC	2021-03-03
Icotinib	Conmana	EGFR	1st-generation	Betta Pharma	NSCLC	2021-02-01
Almonertinib	Ameile	EGFR	3rd-generation	Hansoh Pharma	NSCLC	2020-03-17
Dacomitinib	Vizimpro	EGFR	2nd-generation	Pfizer	NSCLC	2019-12-10
Osimertinib	Tagrisso	EGFR	3rd-generation	Astrazeneca	NSCLC	2017-03-22
Afatinib	Gilotrif	HER2, EGFR, HER4	2nd-generation	Boehringer Ingelheim	NSCLC, Squamous NSCLC	2017-02-21
Erlotinib	Tarceva	EGFR	1st-generation	Astellas/Roche	NSCLC	2006-04-06
Gefitinib	Iressa	EGFR	1st-generation	Astrazeneca	NSCLC	2004-12-06

*Note: Approval date refers to the first approval date; Astrazeneca delisted Iressa in 2011 and relisted it in 2015.

Source: FDA, Frost & Sullivan Analysis

Competitive Landscape：3rd-generation EGFR-TKI Approved by NMPA(1/2)

- To date, there are 6 3rd-generation EGFR-TKI gained approval from NMPA, which can be used in the treatment of NSCLC, including rilertinib approved for EGFR exon 20 T790M, rezivertinib approved for EGFR exon 20 T790M, befotertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M, furmonertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M, almonertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M, and osimertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M.

Drug Name	Brand Name	Target	Generation	Company	Indications	mPFS(month)			Line	Approval Date	2023 Global sales (million USD)
						Ex19del	L858R	Overall			
Rilertinib	Sanrisso	EGFR	3rd-generation	Sanhome Pharmaceutical	NSCLC	13.8	9.7	12.6	2rd line	2024-06-17	NA
Rezivertinib	Undisclosed	EGFR	3rd-generation	Beta Pharma	NSCLC	12.4	10.3	12.2	2rd line	2024-05-20	NA
Befotertinib	Surmana	EGFR	3rd-generation	Betta Pharma	NSCLC	NE	17.9	22.1	1st line	2023-10-12	Undisclosed
Furmonertinib	Ivesa	EGFR	3rd-generation	Allist Pharmaceutical	NSCLC	20.8	13.4	19.3	1st line	2022-06-28	274.0
Almonertinib	Ameile	EGFR	3rd-generation	Hansoh Pharma	NSCLC	Undisclosed		20.8	1st line	2021-12-16	Undisclosed
Osimertinib	Tagrisso	EGFR	3rd-generation	Astrazeneca	NSCLC	21.6	14.2	18.9	1st line	2019-08-30	5,799

*Abbreviations: NE = Not evaluated

Source: NMPA, Frost & Sullivan Analysis

Competitive Landscape：3rd-generation EGFR-TKI Approved by NMPA(2/2)

- To date, there are 6 3rd-generation EGFR-TKI gained approval from NMPA, which can be used in the treatment of NSCLC, including rilertinib approved for EGFR exon 20 T790M, rezivertinib approved for EGFR exon 20 T790M, befotertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M, furmonertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M, almonertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M, and osimertinib approved for EGFR exon 19 deletion, exon 21 L858R and exon 20 T790M.

Drug Name	Brand Name	Target	Mutation Subtype	Monotherapy or combined therapy	Whether is covered by the NRDL	End user price (RMB/box)	Treatment cost (RMB/month)
Rilertinib	Sanrisso	EGFR	T790M	Monotherapy	No	NA	NA
Rezivertinib	Undisclosed	EGFR	T790M	Monotherapy	No	NA	NA
Befotertinib	Surmana	EGFR	Ex19del, L858R, T790M	Monotherapy	Yes	2,862.4	8,587.2
Furmonertinib	Ivesa	EGFR	Ex19del, L858R, T790M	Monotherapy	Yes	2,494.5	4,989.0
Almonertinib	Ameile	EGFR	Ex19del, L858R, T790M	Monotherapy	Yes	2,016.0	5345.4
Osimertinib	Tagrisso	EGFR	Ex19del, L858R, T790M	Monotherapy	Yes	4,966.2	4,966.2

Source: NMPA, Frost & Sullivan Analysis

Competitive Landscape of Global 3rd-generation EGFR-TKI Pipeline(1/2)

- To date, there are 16 3rd-generation EGFR-TKI under development globally.

Drug Name/Code	Target	Mutation subtype	Company	Clinical Stage	Indications	First Posted Date
Furmonertinib	EGFR	Ex19del, L858R, T790M	Allist Pharmaceuticals	III	NSCLC	2021-04-12
Lazertinib	EGFR	Ex19del, L858R, T790M	Yuhan Corporation	III	NSCLC	2020-01-14
AZD3759	EGFR	Ex19del, L858R	Alpha Biopharma/Astrazeneca	II/III	NSCLC with Brain metastases	2018-08-22
Olmutinib	EGFR	Ex19del, L858R, T790M, G719X, L861Q	Hanmi Pharmaceutical	II	NSCLC	2017-07-17
BBT-207	EGFR	C797S	Bridge Biotherapeutics	I/II	NSCLC	2023-05-26
BBT-176	EGFR	Ex19del, L858R, L861Q		I/II	NSCLC	2021-03-23
JIN-A02	EGFR	C797S, T790M	J Ints Bio	I/II	NSCLC	2022-05-24
KP-673	EGFR	Ex19del, L858R, T790M, G719X, L861Q	Zentalis Pharmaceuticals	I/II	NSCLC	2018-02-16

*Note: First posted date: 首次公示日期;
NSCLC= Non Small Cell Lung Cancer; GC= Gastric Cancer; BC= Breast Cancer

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global 3rd-generation EGFR-TKI Pipeline(2/2)

- To date, there are 16 3rd-generation EGFR-TKI under development globally.

Drug Name/Code	Target	Mutation subtype	Company	Clinical Stage	Indications	First Posted Date
Almonertinib	EGFR	Ex19del, L858R, T790M, G719X, L861Q	Hansoh Pharmaceutical	I/II	NSCLC	2016-11-28
BLU-945	EGFR	C797S, T790M	Blueprint Medicines	I/II	NSCLC	2021-04-21
H002	EGFR	C797S	RedCloud Bio	I/II	NSCLC	2022-08-03
TAS3351	EGFR	C797S	Taiho Oncology	I/II	NSCLC	2023-02-08
BDTX-1535	EGFR	G719X, C797S	Black Diamond Therapeutics	I	Glioblastoma, NSCLC	2022-02-15
WSD0922	EGFR	Ex19del, L858R, T790M, G719A, L861Q, C797S	Wayshine Biopharm	I	Glioblastoma, Anaplastic Astrocytoma, NSCLC with Brain metastases	2019-11-25
EGF816	EGFR	Ex19del, L858R, T790M	Novartis	I	NSCLC	2017-10-31
Olafertinib	EGFR	Ex19del, L858R, T790M, G719X, L861Q	Checkpoint Therapeutics	I	NSCLC	2016-09-29

*Note: First posted date: 首次公示日期;
NSCLC= Non Small Cell Lung Cancer; GC= Gastric Cancer; BC= Breast Cancer

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of China 3rd-generation EGFR-TKI Pipeline

- According to CDE, there are 9 3rd-generation EGFR-TKI in China pipeline, used to treat NSCLC, including 4 agents in Phase III and two of them were indicated for NSCLC with brain metastases, among which TY-9591 was the most clinically advanced EGFR-TKI candidate. As of the Latest Practicable Date, Kentinib was still at Phase II clinical trials and is expected to have clinical trials for two more years before it obtains approval for marketing. In the meantime, TY-9591 is the only EGFR-TKI currently undergoing a head-to-head registrational trial directly comparing its efficacy with Osimertinib, which is by far the most effective third-generation EGFR-TKI.

Drug Name/Code	Target	Mutation subtype	Company	Control	Clinical Stage	Indications	First Posted Date
TY-9591	**EGFR**	**L858R**	**TYK Medicines,Inc**	**Osimertinib**	**III**	**NSCLC**	**2022-05-19**
		Ex19del, L858R, T790M			**II (Pivotal)**	**NSCLC with Brain metastases**	**2021-11-16**
Abivertinib	BTK, EGFR	Ex19del, L858R, T790M	Sorrento/Essen Pharmaceutical	Gefitinib	III	NSCLC	2019-04-09
FHND9041	EGFR	Ex19del, L858R, T790M	Chia Tai Fenghai Pharmaceutical	Afatinib	III	NSCLC	2021-08-31
Limertinib	EGFR	Ex19del, L858R, T790M	Aosaikang Pharmaceutical	Gefitinib	III	NSCLC	2019-08-29
Kenatinib	EGFR	Ex19del, L858R	Suzhou Teligene	NA	II	NSCLC with Brain metastases	2020-05-12
TQB3456	EGFR	Ex19del, L858R, T790M	Chia Tai-tianqing Pharmaceutical	NA	I	NSCLC	2018-08-31
QLH11811	EGFR	Ex19del, L858R, T790M	Qilu Pharmaceuticals	NA	I	NSCLC	2022-09-22
YZJ-0318	EGFR	Ex19del, L858R, T790M	Yangtze River Pharmaceutical	NA	I	NSCLC	2018-01-28
DZD6008	EGFR	Ex19del, L858R, T790M	Dizal Pharma	NA	I	NSCLC	2024-05-24

*Note: First posted date: 首次公示日期;
NSCLC= Non Small Cell Lung Cancer; GC= Gastric Cancer; BC= Breast Cance

Source: CDE, Frost & Sullivan Analysis

Competitive Landscape of China 4th-generation EGFR-TKI Pipeline

Drug Name/Code	Target	Mutation subtype	Company	Clinical Stage	Indications	First Posted Date
WJ13404	EGFR	C797S	Junjing Biopharmaceutical	I/II	NSCLC	2022-09-14
BPI-361175	EGFR	C797S	Betta Pharmaceuticals	I/II	NSCLC	2021-05-13
DAJH-1050766	EGFR	C797S	Chengdu Di'ao Jiuhong Pharmaceutical	I/II	NSCLC	2022-05-07
HS-10375	EGFR	C797S	Hansoh Pharmaceutical	I/II	NSCLC	2022-01-10
H-002	EGFR	C797S	RedCloud Bio	I/II	NSCLC	2022-06-21

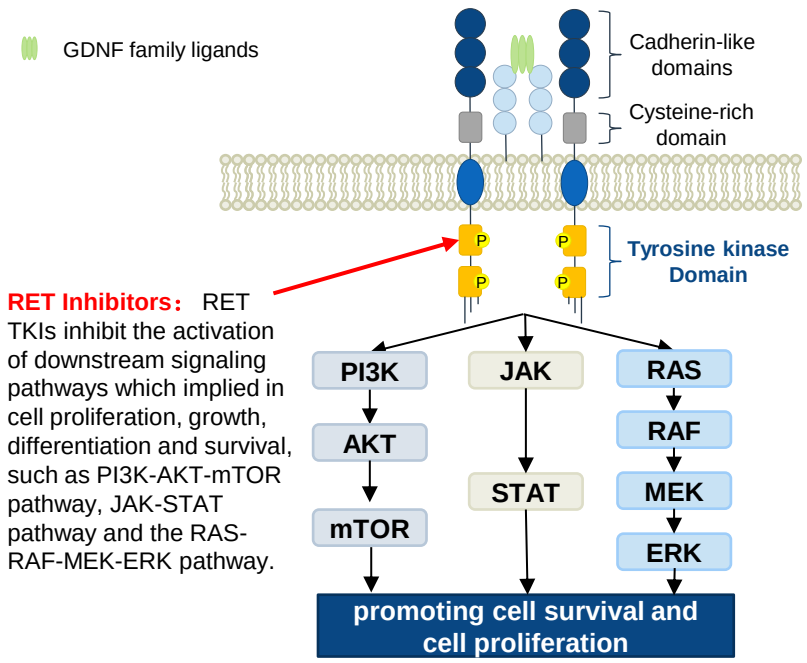
*Note: First posted date: 首次公示日期;
NSCLC= Non Small Cell Lung Cancer; GC= Gastric Cancer; BC= Breast Cancer

Source: CDE, Frost & Sullivan Analysis

Overview and Mechanism of RET-TKI

- 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 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 PI3K-AKT-mTOR pathway, JAK-STAT pathway and the RAS-RAF-MEK-ERK pathway, which would cause excessive cell growth and proliferation, thus drive tumor development. RET inhibitors can suppress the activation of the RET tyrosine kinase domain, thereby inhibiting downstream signaling pathways and playing anti-tumor effects.

Mechanism of RET-TKI



RET Inhibitors： RET TKIs inhibit the activation of downstream signaling pathways which implied in cell proliferation, growth, differentiation and survival, such as PI3K-AKT-mTOR pathway, JAK-STAT pathway and the RAS-RAF-MEK-ERK pathway.

- 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 harboring RET mutations.

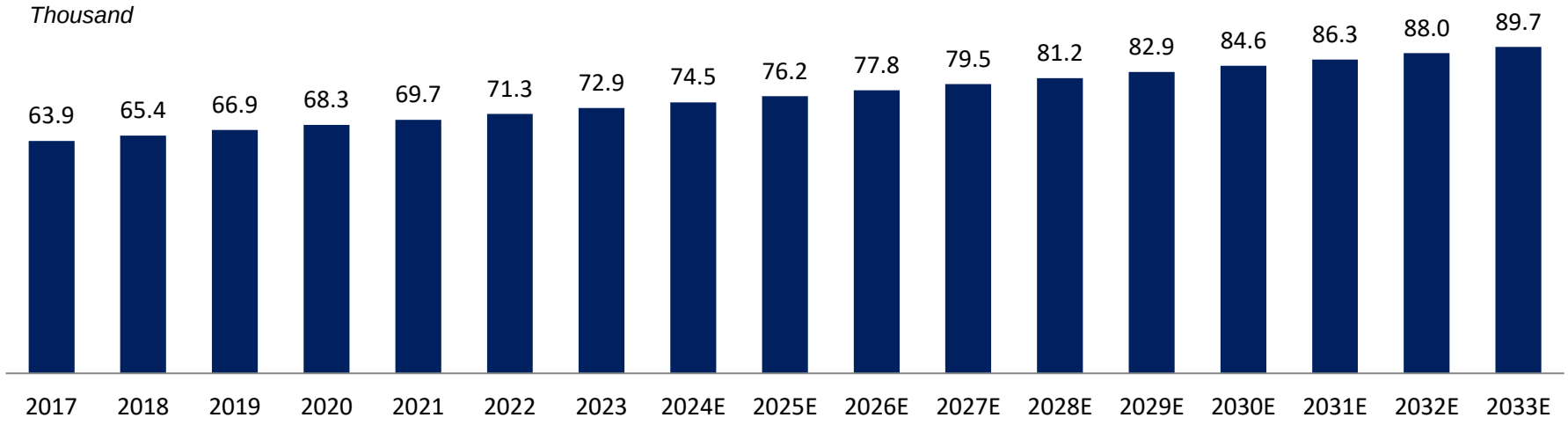
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of NSCLC and thyroid cancer patients with RET mutations, 2017-2033E

- RET fusions can occur in common tumors such as NSCLC and thyroid cancer. From 2017 to 2023, the number of new cases of NSCLC and thyroid cancer with RET mutations worldwide increased from 63.9 thousand to 72.9 thousand, representing a compound annual growth rate of 2.2%. It is estimated that by 2027 and 2033, the number of new patients of NSCLC and thyroid cancer with RET mutation worldwide will reach 79.5 thousand and 89.7 thousand respectively.

Global incidence of NSCLC and Thyroid cancer patient with RET mutations, 2017-2033E

Period	CAGR
2017-2023	2.2%
2023-2027E	2.2%
2027E-2033E	2.0%



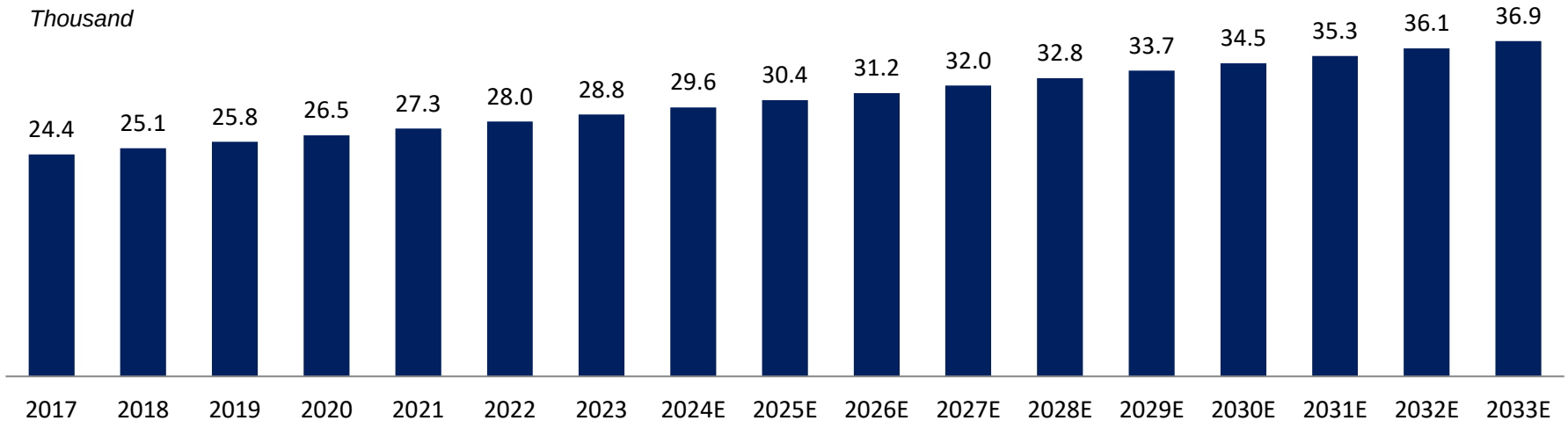
Source: NCCR, Frost & Sullivan analysis

Incidence of NSCLC and thyroid cancer patients with RET mutations in China, 2017-2033E

- From 2017 to 2023, the number of new cases of NSCLC and thyroid cancer with RET mutations in China increased from 24.4 thousand to 28.8 thousand, representing a compound annual growth rate of 2.8%. It is estimated that by 2027 and 2033, the number of new patients of NSCLC and thyroid cancer with RET mutation in China will reach 32.0 thousand and 36.9 thousand respectively. In China, the prevalence of RET fusion in NSCLC is approximately 2%, while in MTC, RET fusion is significantly more prevalent, accounting for 70% of cases. MTC itself represents 5% to 12% of all thyroid cancer cases.

Incidence of NSCLC and Thyroid cancer patient with RET mutation in China, 2017-2033E

Period	CAGR
2017-2023	2.8%
2023-2027E	2.7%
2027E-2033E	2.4%



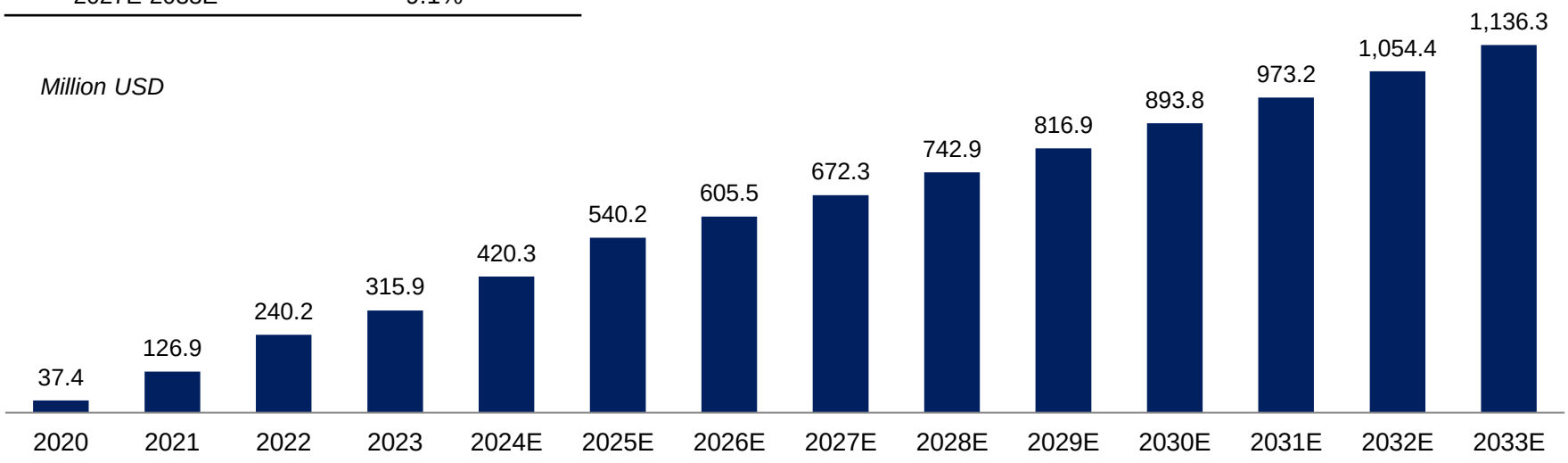
Source: NCCR, Frost & Sullivan analysis

Global Market Size of RET-TKI, 2020-2033E

- The global RET-TKI market has experienced a robust growth, increasing from USD37.4 million in 2020 to USD315.9 million in 2023, representing a CAGR of 103.7%. It is expected to reach USD672.3 million with a CAGR of 20.8% by 2027 and reach USD1,136.3 million with a CAGR of 9.1% by 2033.

Historical and Forecasted Global Market size of RET-TKI, 2020-2033E

Period	CAGR
2020-2023	103.7%
2023-2027E	20.8%
2027E-2033E	9.1%



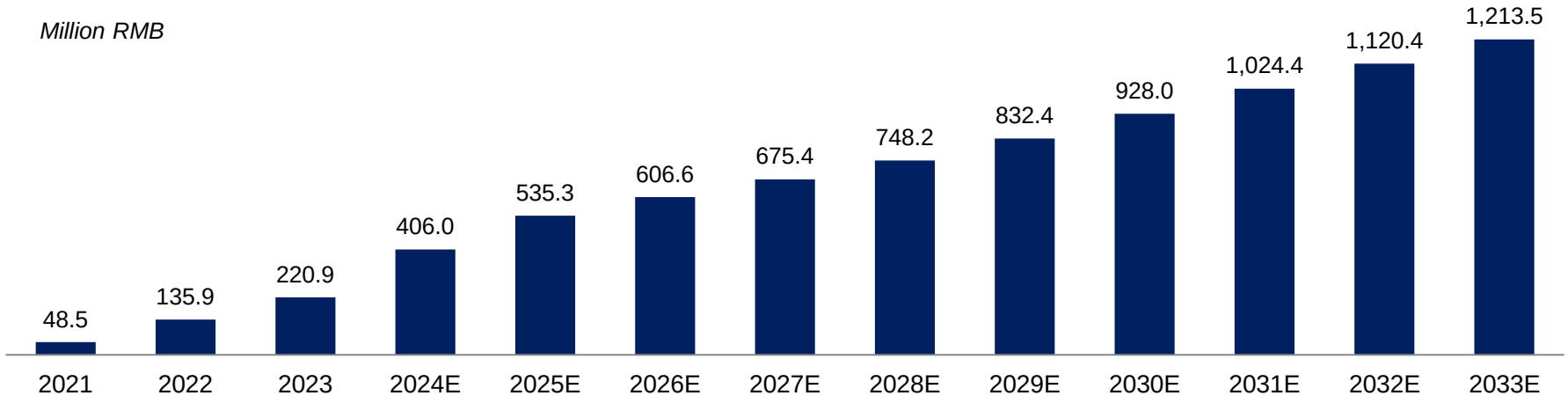
Source: Frost & Sullivan analysis

Market size of RET-TKI in China, 2021-2033E

- RET-TKI market in China has increased significantly from RMB48.5 million in 2021 to RMB220.9 million in 2023, representing a CAGR of 113.4%. It is expected to reach RMB675.4 million by 2027 and RMB1,213.5 million by 2033.

Market size and forecast of RET-TKI in China, 2021-2033E

Period	CAGR
2021-2023	113.4%
2023-2027E	32.2%
2027E-2033E	10.3%



Source: Frost & Sullivan analysis

Analysis of market drives of RET-TKI Market

Increasing incidence of cancer patients with RET mutations	• Changes in the RET gene are often found in lung and thyroid cancers but are also found in other cancer types. From 2017 to 2022, the number of new cases of NSCLC and thyroid cancer with RET mutations worldwide increased from 358.3 thousand to 410.0 thousand, representing a CAGR of 2.7%. As the number of cancer patients with RET mutation increases, the demand for efficient clinical treatment also rises, which drives the development of RET TKI.
Advantages of targeted therapy	• RET TKIs can specifically inhibit RET mutations, thereby inhibiting or blocking tumor progression. RET TKI drugs can specifically target cancer cells, thus reducing the impact on other healthy cells, and are safer and have fewer side effects than traditional chemotherapy drugs. Driven by factors such as more small molecule targeted anti-tumor drugs being approved in China and increased awareness of targeted oncology drugs among the population, the concept of oncology treatment for patients and doctors has evolved from the traditional chemotherapy and radiotherapy treatments to small molecule targeted drug treatments, which has contributed to the development of RET TKI markets .
Advances in molecular diagnostic technology	• With the help of molecular diagnostic technology, specific gene mutation of cancer can be detected, and then the corresponding TKIs can be used for efficient treatment. The development of molecular diagnostic technology helps clinicians to select more appropriate targeted drugs for treatment according to patients' gene mutation typing, and improve the penetration rate of targeted drugs such as RET TKIs in clinical application. Advances in molecular diagnostic technology can help to individualize oncology treatments, which can also improve the development of RET TKI markets.
Supportive policies for innovative medicines	• In order to accelerate the review and approval process and meet the needs of clinical medication, a priority review and approval system has been gradually established on the basis of the existing special approval channels for drug registration, reducing the number of clinical trials of drugs under research in China to II for market application. Innovative drugs and new drugs that have not been listed domestically or internationally will be included in the priority review channel to accelerate clinical application

Source: Public data, Frost & Sullivan analysis

Future trends of RET-TKI market

Rising Market Size of RET-TKI Market	• RET activating mutations are therapeutically actionable oncogenic drivers which can be effectively targeted by novel and potent inhibitors selectively targeting the RET kinase. RET gene mutations are often found in lung and thyroid cancers. As the incidence of NSCLC and thyroid cancer increase constantly, the patient number of NSCLC and thyroid cancers with RET mutations rise accordingly. Growing number of patients is one of the prime reasons driving the RET-TKI market rise during the next few years. • Also, an expansion of research areas in RET-TKI will lead to sizable demand in the market continually. There are several kinds of RET-TKI targeting RET-mutated solid tumors under development currently in clinical trials. As research continues, more RET-TKIs are likely to be approved and marketed in the future, and the market size of RET-TKI will experience further growth.
Expansion of Indications	• As an important RET-TKI, Selpercatinib has gained FDA approval primarily for adult patients with RET fusion-positive tumors in 2019. In 2020, its indications significantly expanded to include MTC, both in previously treated and untreated patients. Besides, there are several RET-TKI drugs under development worldwide, and their indications encompass not only NSCLC or medullary thyroid carcinoma (MTC) but also gastrointestinal, breast, gynecological, genitourinary, and histiocytic cancers. In this dynamic market, RET-TKI drugs are expected to continue expanding their indications as research progresses.
Rising penetration rate of RET-TKIs	• The RET-TKI market is undergoing a transformative phase marked by the emergence of innovative RET targets. Drawing parallels to the historical progression seen in other targeted therapy markets, the growing clinical experience and identification of novel RET alterations are reshaping the treatment landscape. As diagnostic technologies advance, the discovery of diverse RET alterations is expected to expand, contributing to the increased adoption and integration of RET-TKIs across various cancers.
Combination Therapy with RET Inhibitors and Chemotherapy	• Mechanisms of resistance arising from a single targeted drug can be addressed by drug combinations. The side effect damage of cancer spread and resistance mechanism is prevented by interfering with molecular targets through the combination of multiple drugs including RET-TKI. Currently, the combination of RET-TKI and EGFR-TKI has achieved excellent results in the treatment of RET fusion arising from EGFR resistance. In the future, drug combination therapy with RET-TKI will be more widely used in oncology treatment and it is the future trend of RET-TKI market.

Source: Public data, Frost & Sullivan analysis

Competitive Landscape: RET-TKI Approved by FDA

- To date, there are 2 RET-TKIs gained approval from FDA.

Drug Name	Brand Name	Target	Company	Indications	Approval Date	Global Sales (2023) (million USD)
Pralsetinib	Gavreto	RET	Blueprint & Roche	NSCLC	2020-09-04	NA
Selpercatinib	Retevmo	RET	Eli Lilly	RET fusion-positive NSCLC, advanced/metastatic RET-mutant MTC	2020-05-08	253.6

*Note: Approval date: First approval date; NSCLC = Non Small Cell Lung Cancer; MTC = medullary thyroid cancer; as of August 2,2024

Source: FDA, Frost & Sullivan Analysis

Competitive Landscape: RET-TKI Approved by NMPA

- To date, there are 2 RET-TKI gained approval from NMPA.

Drug Name	Brand Name	Target	Company	Indications	Approval Date
Pralsetinib 普拉替尼	Gavreto	RET	Blueprint & Cstone pharmaceuticals	RET fusion-positive NSCLC, advanced/metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory	2021-03-23
Selpercatinib 塞普替尼	Retevmo	RET	Eli Lilly and Company	RET fusion-positive NSCLC, advanced/metastatic RET-mutant MTC, advanced/metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory	2022-09-30

*Note: Approval date: First approval date; NSCLC = Non Small Cell Lung Cancer; MTC = medullary thyroid cancer;
as of August 2,2024

Source: NMPA, Frost & Sullivan Analysis

Competitive Landscape of Global RET-TKI Pipeline (1/2)

- To date, there are 14 RET-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
SY-5007	RET	Shouyao Holdings (Beijing) Co. LTD	III	locally advanced or metastatic RET-positive NSCLC	2023/9/11
			I/II	NSCLC, MTC, Solid Tumor	2022/3/14
BOS-589	RET	Boston Pharmaceuticals	II	Diarrhea-predominant Irritable Bowel Syndrome	2019/6/6
			I	Advanced Nonhaematologic Malignancies	2018/12/19
TY-1091	RET	TYK Medicines, Inc	I/II	RET-altered NSCLC, MTC, RET-altered Papillary Thyroid Cancer, Neoplasms	2023/1/9
HEC169096	RET	Sunshine Lake Pharma Co., Ltd.	I/II	Advanced Solid Tumor	2022/7/11
EP0031	RET	Ellipses Pharma	I/II	Advanced Solid Tumor	2022/7/5
KL590586	RET	Sichuan Kelun Pharmaceutical Research Institute Co., Ltd.	I/II	Advanced Solid Tumor	2022/3/3
HS-10365	RET	Jiangsu Hansoh Pharmaceutical Co., Ltd.	II	NSCLC	2023/11/27

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; MTC = medullary thyroid cancer; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global RET-TKI Pipeline (2/2)

- To date, there are 14 RET-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
TAS0953/HM06	RET	Helsinn Healthcare SA	I/II	RET-altered NSCLC, RET-altered Solid Tumors	2020/12/24
FHND5071	RET	Jiangsu Chia Tai Fenghai Pharmaceutical Co., Ltd.	I	Advanced Solid Tumors	2023/4/19
APS03118	RET	Applied Pharmaceutical Science, Inc.	I	RET-altered Solid Tumors	2022/12/16
LOXO-260	RET	Eli Lilly and Company	I	Carcinoma, NSCLC, Thyroid Neoplasms	2022/2/16
HS269	RET	Zhejiang Hisun Pharmaceutical Co. Ltd.	I	Advanced Solid Tumor	2021/9/27
GSK3352589	RET	GlaxoSmithKline	I	Irritable Bowel Syndrome	2017/5/15
GSK3179106	RET	GlaxoSmithKline	I	Irritable Bowel Syndrome	2016/6/14

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; MTC = medullary thyroid cancer; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of RET-TKI Pipeline in China

- According to CDE, there are 7 RET-TKI under development in China, mainly used to treat NSCLC.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
SY-5007	RET	ShouYao Holding (Beijing) Co., Ltd	III	NSCLC	2023-07-05
HS-10365	RET	Jiangsu Hansoh Pharmaceutical Co., Ltd.	II	NSCLC with RET fusion	2023-08-02
			I	NSCLC, Thyroid Cancer	2023-06-12
			I	Locally advanced or metastatic solid tumor	2023-09-11
TY-1091	RET	TYK Medicines,Inc	I/II	NSCLC	2022-12-23
APS03118	RET	Beijing Applied Pharmaceutical Science Co., Ltd	I	Locally advanced or metastatic solid tumors	2022-09-27
FHND5071	RET	Jiangsu Chia Tai Fenghai Pharmaceutical Co.Ltd	I	Advanced tumor with RET mutations	2022-08-31
KL590586	RET	Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd	I	NSCLC with RET fusion, Advanced solid tumor	2023-09-07
HS269	RET	Zhejiang Hisun Pharmaceutical Co.Ltd	I	Advanced solid tumor	2021-10-13

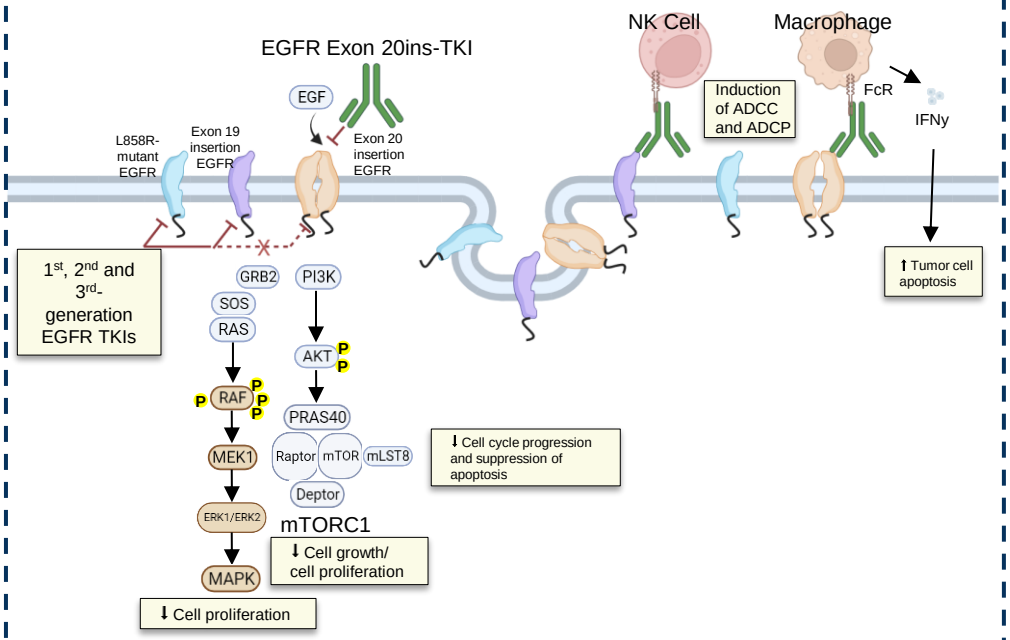
*Note: First posted date: 首次公示日期;
NSCLC= Non Small Cell Lung Cancer;
as of August 2,2024

Source: CDE, Frost & Sullivan Analysis

Overview and Mechanism of EGFR/HER2 Exon 20ins-TKI (1/2)

- EGFR exon 20 insertion (ex20ins) is the third common mutation in NSCLC. Among NSCLC patients with EGFR mutations, approximately 10% of patients have EGFR ex20ins mutations. Patients with ex20ins mutations are associated with de novo resistance to targeted EGFR-TKIs and correlate with a poor patient prognosis. In recent years, progress in EGFR/HER ex20ins TKI brings new hope for the treatment of these patients.

Mechanism of EGFR Exon 20ins-TKI



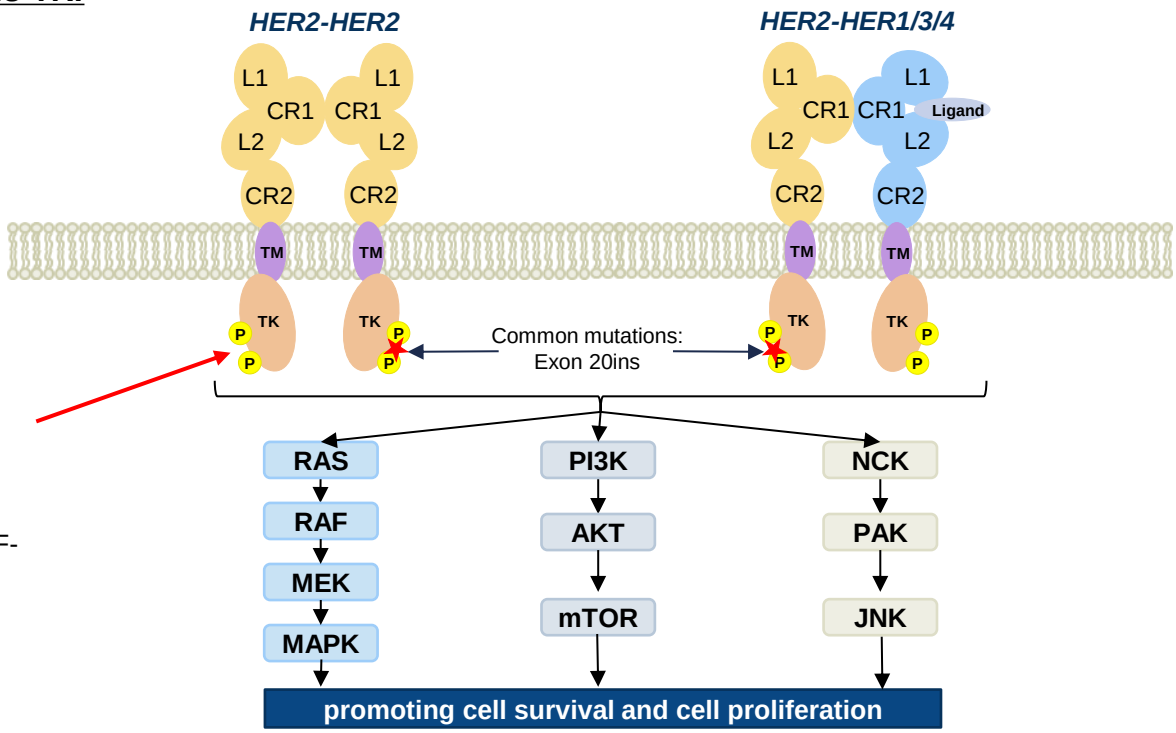
- Activated EGFR leads to downstream activation of proliferative pathways, including the MAPK and PI3K–AKT–mTOR signaling pathways. In cancers, predominantly NSCLC, classic EGFR exon 19 insertions and exon 21 (L858R) mutations and non-classic EGFR exon 20 insertions result in constitutive activation of these pathways and thus drive tumor development and progression.
- First-generation and second-generation EGFR-TKIs are effective treatments for NSCLC harboring the classic EGFR mutations, 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 harboring EGFR exon 20 insertions. **EGFR Exon 20ins-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 induction of Fc receptor (FcR) signaling and antibody- dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

Source: Literature Review, Frost & Sullivan Analysis

Overview and Mechanism of EGFR/HER2 Exon 20ins-TKI (2/2)

- Ex20ins mutations are also found in HER2 which is another member of 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. Additionally, HER2 may form homodimers when it is highly expressed. Ex20ins mutations are the most dominant type of HER2 aberration in NSCLC by far, representing greater than 90% of all observed HER2 mutations. Dysregulation of HER2 signaling is associated with HER2 amplification, overexpression, or mutation, and is a common oncogenic driver in a variety of tumors.
- HER2 exon 20ins-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 play anti-tumor effects.

Mechanism of HER2 Exon 20ins-TKI



HER2 Exon 20ins Inhibitors:
HER2 Exon 20ins TKIs inhibit the activation of downstream signaling pathways which are related to cell survival and cell proliferation, such as RAS-RAF-MEK-ERK pathway and PI3K-AKT-mTOR pathway, to play anti-tumor effects.

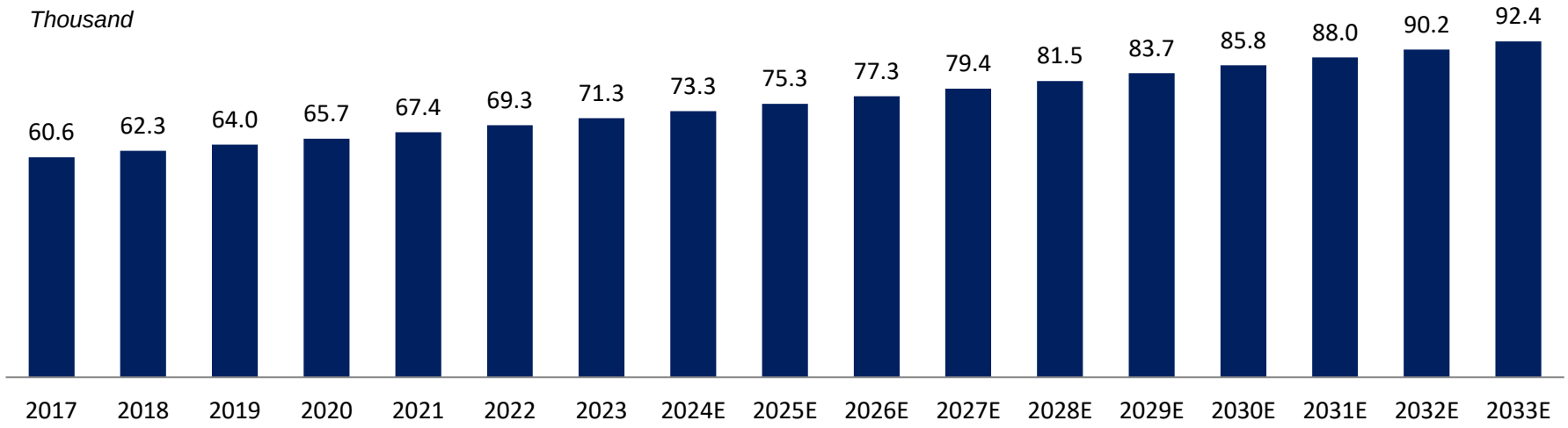
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of NSCLC patients with EGFR Exon 20 insertion mutations, 2017-2033E

- From 2017 to 2023, the number of new cases of NSCLC with EGFR Exon 20 insertion mutations worldwide increased from 60.6 thousand to 71.3 thousand, representing a compound annual growth rate of 2.7%. It is estimated that by 2027 and 2033, the number of new patients of NSCLC with EGFR Exon 20 insertion mutations worldwide will reach 79.4 thousand and 92.4 thousand respectively.

Global incidence of patients with EGFR Exon 20 insertion mutations, 2017-2033E

Period	CAGR
2017-2023	2.7%
2023-2027E	2.7%
2027E-2033E	2.6%



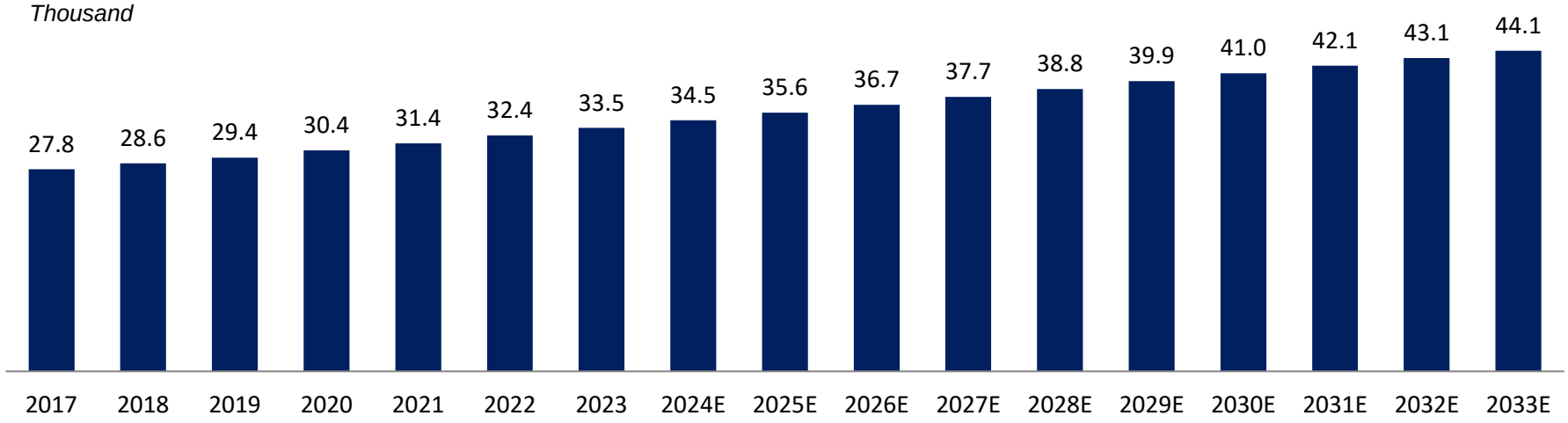
Source: NCCR, Frost & Sullivan analysis

Incidence of NSCLC patient with EGFR Exon 20 insertion mutations in China, 2017-2033E

- From 2017 to 2023, the number of new cases of NSCLC with EGFR Exon 20 insertion mutations in China increased from 27.8 thousand to 33.5 thousand, representing a compound annual growth rate of 3.1%. It is estimated that by 2027 and 2033, the number of new patients of NSCLC with EGFR Exon 20 insertion mutations in China will reach 37.7 thousand and 44.1 thousand respectively.
- EGFR exon 20 insertion is the third common mutation in NSCLC, and among NSCLC patients with EGFR mutations, approximately 7.7% of patients have EGFR exon 20 insertion mutations. Patients with exon 20 insertion mutations are associated with primary resistance to targeted EGFR-TKIs and correlate with a poor patient prognosis.

Incidence of NSCLC patient with EGFR Exon 20 insertion mutations in China, 2017-2033E

Period	CAGR
2017-2023	3.1%
2023-2027E	3.0%
2027E-2033E	2.6%



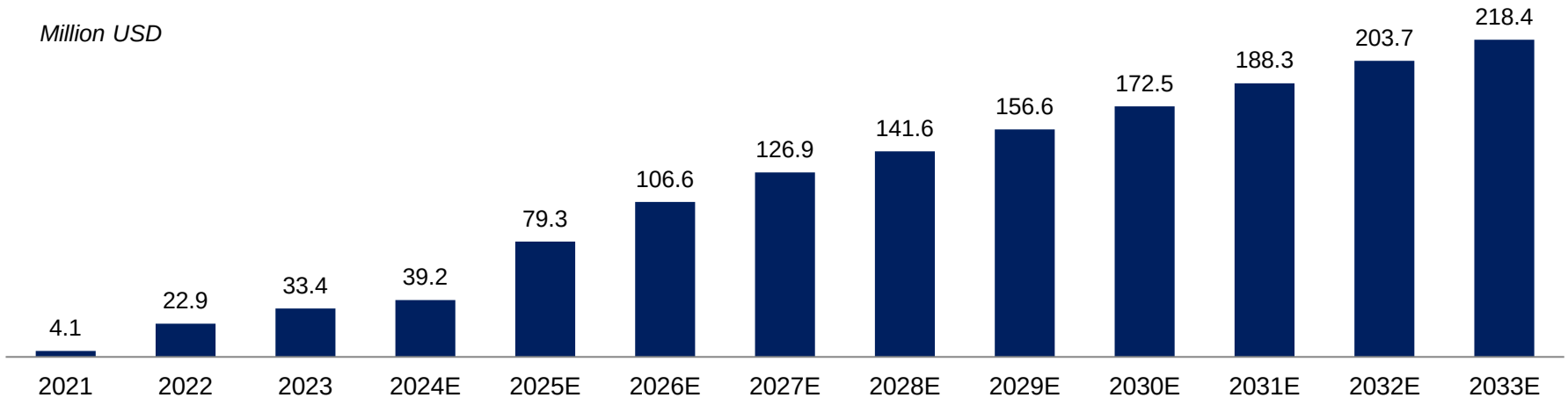
Source: NCCR, Frost & Sullivan analysis

Global Market size of EGFR Exon 20ins-TKI, 2021-2033E

- Revenue generated by global market of EGFR Exon 20ins-TKI reached USD33.4 million in 2023, and it is expected to reach USD126.9 million with a compound annual growth rate of 76.8% from 2021 to 2027 and reach USD218.4 million with a compound annual growth rate of 9.5% from 2027 to 2033.

Global market size and forecast of EGFR Exon 20ins-TKI, 2021-2033E

Period	CAGR
2021-2027E	76.8%
2027E-2033E	9.5%



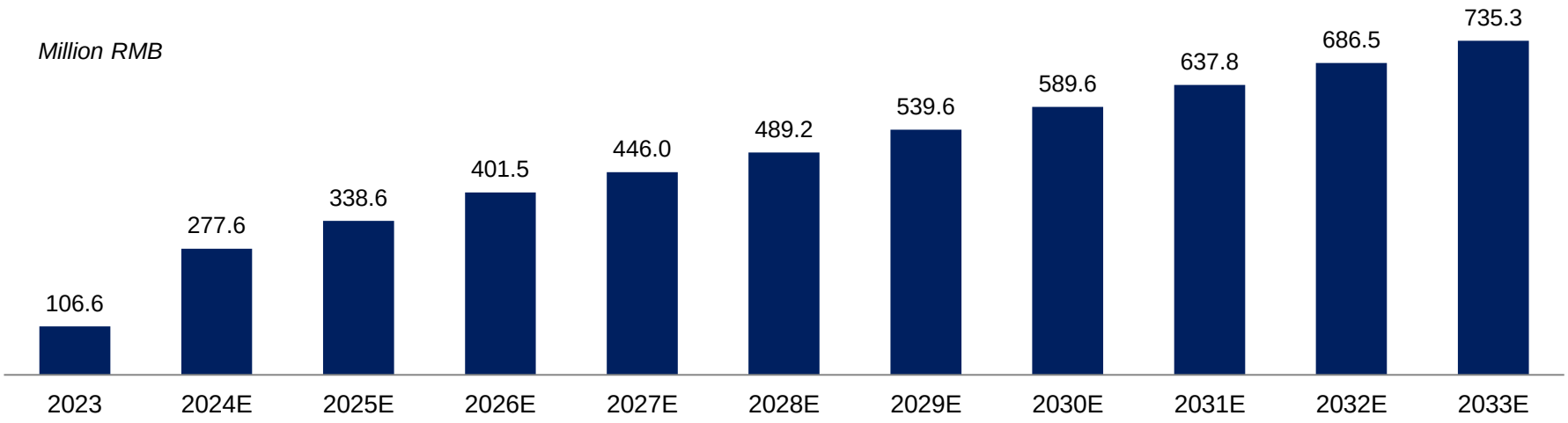
Source: Frost & Sullivan analysis

Market size of EGFR Exon 20ins-TKI in China, 2023-2033E

- It is estimated that revenue generated by market of EGFR Exon 20ins-TKI in China will reach RMB106.6 million in 2023, and it is expected to reach RMB446.0 million with a compound annual growth rate of 43.0% from 2023 to 2027 and reach RMB735.3 million with a compound annual growth rate of 8.7% from 2027 to 2033.

Market size and forecast of EGFR Exon 20ins-TKI in China, 2023E-2033E

Period	CAGR
2023-2027E	43.0%
2027E-2033E	8.7%



Source: Frost & Sullivan analysis

Competitive Landscape of EGFR/HER2 Exon 20ins-TKI Approved by NMPA

- To date, there are no EGFR/HER Exon 20ins-TKI gained approval from FDA. There is one EGFR/HER Exon 20ins-TKI gained approval from NMPA, which can be used in the treatment of NSCLC. Mobocertinib (Exkivity) of Takeda pharmaceuticals was approved for marketing by FDA on September 15, 2021 and approved for marketing by NMPA on January 10, 2023. However, Takeda pharmaceuticals voluntarily withdrew Exkivity from the U.S. market and the PRC market in October 2023 and April 2024 respectively since the phase 3 confirmatory study of Exkivity did not meet its primary endpoint. According to the public information released by Dizal Pharma, the sales revenue of Sunvozertinib (舒沃哲), approved by NMPA in August 23, 2023, reached RMB40.1 million by September 30, 2023.

EGFR/HER Exon 20ins-TKI Approved by NMPA

Drug Name	Brand Name	Target	Company	Indications	Approval Date
Sunvozertinib**	舒沃哲	EGFR-Ex20Ins, HER2-Ex20Ins	Dizal Pharmaceutical Co.,Ltd	NSCLC	2023-08-22

*Note: Approval date: First approval date; NSCLC= Non Small Cell Lung Cancer
**Note: Takeda pharmaceuticals voluntarily withdrew Exkivity from the U.S. market and the PRC market in October 2023 and April 2024 respectively since the phase 3 confirmatory study of Exkivity did not meet its primary endpoint.
as of August 2, 2024

Source: FDA, NMPA, Frost & Sullivan Analysis

Competitive Landscape of Global EGFR/HER2 Exon 20ins-TKI Pipeline (1/2)

- To date, there are 9 EGFR/HER Exon 20ins-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
Poziotinib	HER4, HER2-Ex20Ins, EGFR-Ex20Ins, EGFR, HER2	Spectrum Pharmaceuticals, Inc	II	BC	2016-1-20
			II	EGFR exon 20 mutation, ERBB2 gene mutation, recurrent lung non-small cell carcinoma, stage IV NSCLC AJCC v7	2017-02-28
		Hanmi Pharmaceutical Company Limited	II	Metastatic BC	2015-04-16
			II	Lung adenocarcinoma patients with acquired resistance to prior EGFR TKIs	2012-10-31
			I/II	HER2 positive advanced GC	2012-12-11
Zipalertinib	EGFR-Ex20Ins	Taiho Oncology, Inc.	II	Advanced or metastatic NSCLS with exon 20 ins	2023-08-11
Zipalertinib** (drug combination)			III		2023-08-03
DZD9008***	EGFR-Ex20Ins, HER2-Ex20Ins	Dizal Pharmaceuticals	III	Locally advanced or metastatic NSCLC harboring EGFR Exon 20 insertion mutation	2022-12-13

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; BC= Breast Cancer; GC= Gastric Cancer
**Note: Zipalertinib is in combination with standard chemotherapy with pemetrexed and a platinum agent (either carboplatin or cisplatin).
***Note: DZD9008 has been approved for marketing by the NMPA in China as sunvozertinib.
as of August 2, 2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global EGFR/HER2 Exon 20ins-TKI Pipeline (2/2)

- To date, there are 9 EGFR/HER Exon 20ins-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
BAY 2927088	EGFR-Ex20Ins、HER2-Ex20Ins、EGFR-C797S	Bayer	III	Locally advanced or metastatic NSCLC with HER2-activating mutations	2024/6/11
FWD1509	EGFR-Ex20Ins、HER2	Forward Pharmaceuticals Co., Ltd.	I/II	Advanced NSCLC	2021/10/5
HS-10376	EGFR-Ex20Ins、HER2-Ex20Ins	Jiangsu Hansoh Pharmaceutical Co., Ltd.	I/II	Advanced NSCLC	2022/6/28
ABSK112	EGFR-Ex20Ins	Abbisko Therapeutics Co, Ltd	I	NSCLC	2024/1/26
ORIC-114	EGFR-Ex20Ins、HER2-Ex20Ins	ORIC Pharmaceuticals	I	Solid tumor	2022/4/7
BI 1810631	HER2-Ex20Ins	Boehringer Ingelheim	I	Neoplasm metastasis; NSCLC	2021/5/14

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; BC= Breast Cancer; GC= Gastric Cancer
as of August 2, 2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of EGFR/HER2 Exon 20ins-TKI Pipeline in China

- According to CDE, there are 9 EGFR/HER Exon 20ins-TKI under development in China, used to treat NSCLC.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
YK-029A	EGFR-T790M, EGFR-Ex20Ins	Hainan Yuekang Biopharmaceutical Co., Ltd	III	EGFR exon 20ins-positive advanced/metastatic NSCLC	2023-03-23
PLB1004	EGFR-T790M, EGFR-Ex20Ins, EGFR-L858R	Beijing Avistone Biotechnology Co., Ltd	III	EGFR exon 20ins-positive locally advanced/metastatic non-squamous NSCLC	2024-01-09
BEBT-109	EGFR-T790M, EGFR-Ex20Ins, EGFR-L858R, EGFR-Ex19del, EGFR-G719X	Guangzhou BeBetter Med Co., Ltd	II	EGFR exon 20ins-positive advanced/metastatic NSCLC	2021-12-31
AP-L1898	EGFR-Ex20Ins	Suzhou Junjing Biopharmaceutical Technology Co., Ltd	I/II	EGFR positive locally advanced/metastatic NSCLC	2021-06-15
ABSK112	EGFR-Ex20Ins	Shanghai Abbisko Therapeutics Co., Ltd	I	NSCLC	2024-01-09
NIP142	EGFR-Ex20Ins, HER2-Ex20Ins	National institutes of pharmaceutical Research and Development Co., Ltd	I	EGFR positive locally advanced/metastatic NSCLC	2022-04-31
BAY2927088	EGFR-Ex20Ins, HER2-Ex20Ins	Bayer, Patheon pharma services	I	Advanced NSCLC	2022-03-04
HS-10376	EGFR-Ex20Ins, HER2-Ex20Ins	Jiangsu Hansoh Pharmaceutical Co., Ltd.	I	Advanced NSCLC	2021-10-11
FWD1509 MsOH	HER2,EGFR-Ex20Ins	Shenzhen Fuwo Pharmaceutical Co., Ltd	I	EGFR positive locally advanced/metastatic NSCLC	2021-07-23

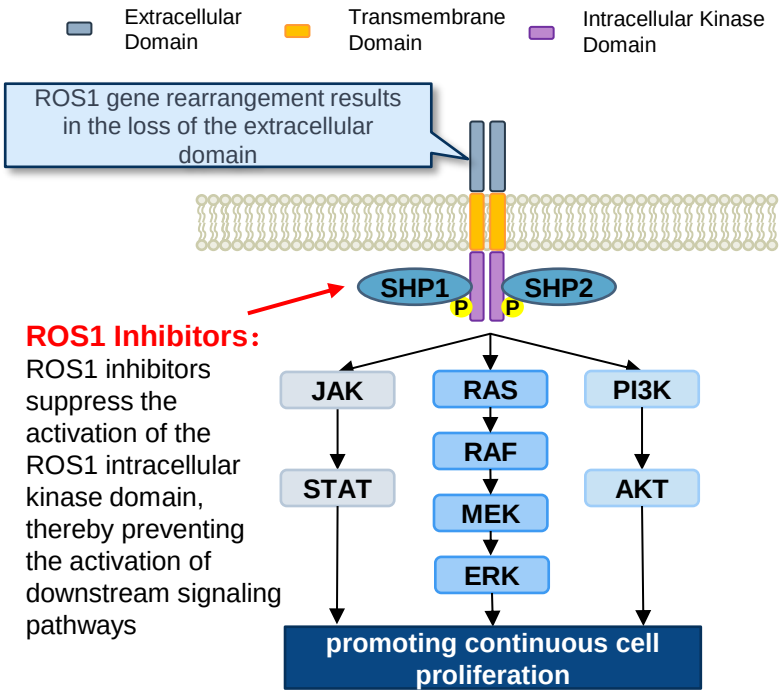
*Note: First posted date: 首次公示日期;
NSCLC= Non Small Cell Lung Cancer;
as of August 2, 2024

Source: CDE, Frost & Sullivan Analysis

Overview and Mechanism of ROS1-TKI (1/2)

- 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 anti-tumor effects. Up to 36% of patients with ROS1 fusion-positive NSCLCs have brain metastases at the diagnosis of advanced disease, and many others will subsequently develop intracranial metastases.

Mechanism of ROS1-TKI

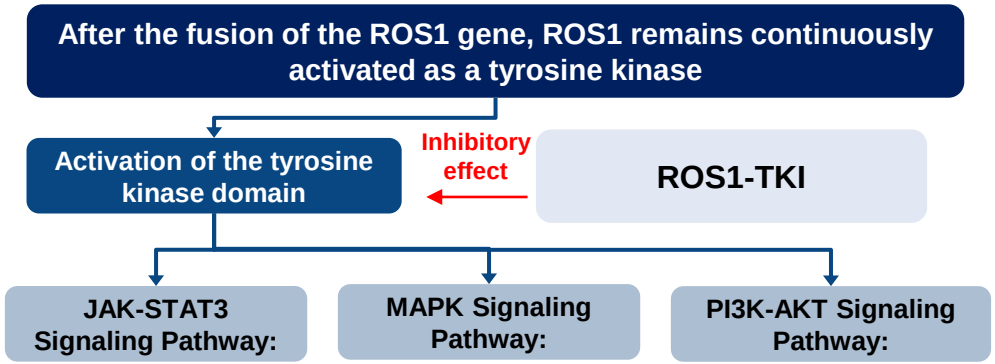


Source: Literature Review, Frost & Sullivan Analysis

Overview and Mechanism of ROS1-TKI (2/2)

- ROS1 is a pivotal transmembrane receptor protein tyrosine kinase which regulates several cellular processes like apoptosis, survival, differentiation, proliferation, cell migration, and transformation. There is increasing evidence supporting 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 3' region of ROS1 fusing to various partners, the most common of which being CD74. 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.

ROS1-TKI Action Process



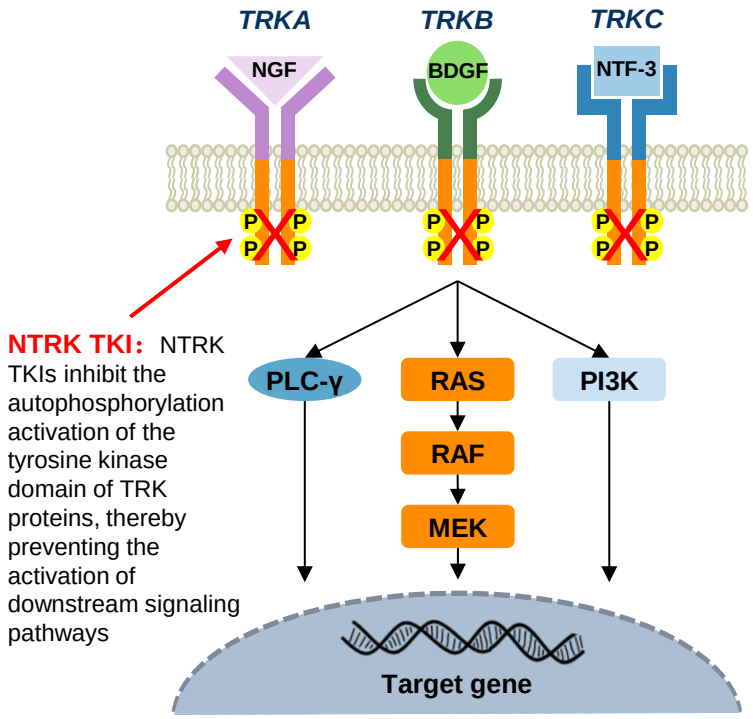
- STAT3 is a major regulatory factor in the balance of cell proliferation and apoptosis. This signaling pathway is involved in regulating various physiological processes such as cell growth, differentiation, and apoptosis.
- MAPK can promote the proliferation of vascular endothelial cells and the generation of new blood vessels; after new blood vessel formation, it can provide more nutrients for tumors, accelerate tumor growth, and promote the spread of cancer cells.
- The PI3K-AKT signal pathway is an intracellular signaling transduction pathway that can respond to extracellular signals, thereby promoting metabolism, proliferation, cell survival, growth, and angiogenesis.

Source: Literature Review, Frost & Sullivan Analysis

Overview and Mechanism of NTRK-TKI (1/2)

- The tropomyosin-related kinase (TRK) protein is a neurotrophic receptor kinase, belonging to the tyrosine kinase family. The TRK family comprises three highly homologous proteins which are TRKA, TRKB, and TRKC. They 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 fusions in NTRK, the extracellular domain of the TRK protein is lost, making it challenging for monoclonal antibodies to bind to the extracellular domain of TRK protein. Therefore, NTRK TKIs have a distinct advantage in clinical applications.

Mechanism of NTRK-TKI

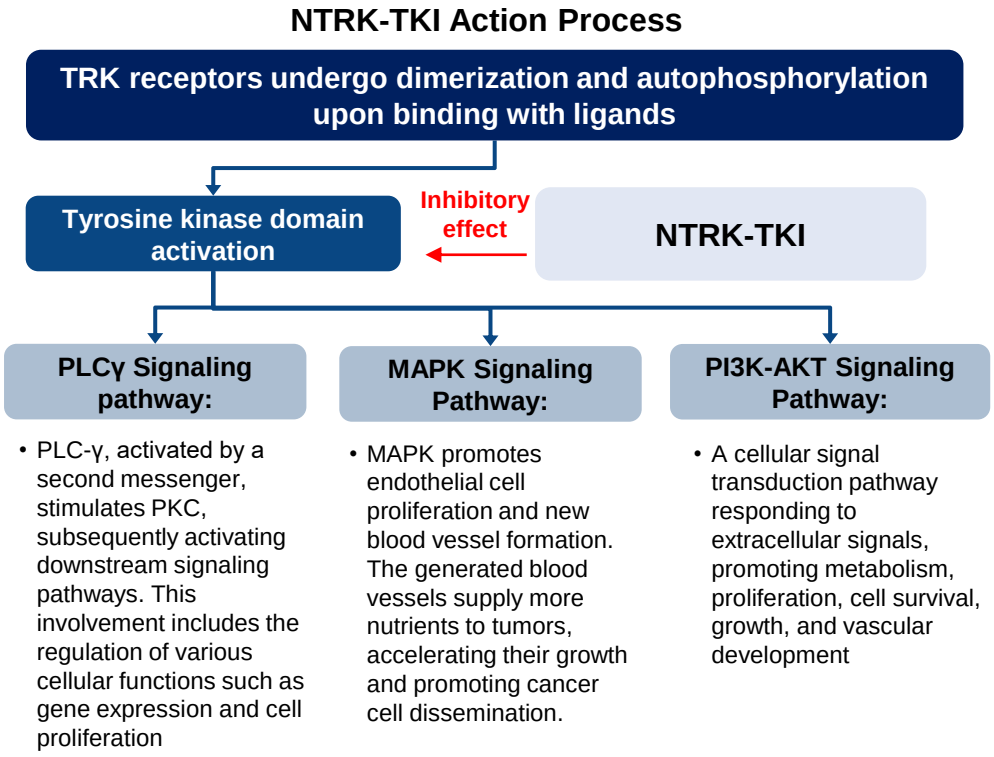


NTRK TKI: NTRK TKIs inhibit the autophosphorylation activation of the tyrosine kinase domain of TRK proteins, thereby preventing the activation of downstream signaling pathways

Source: Literature Review, Frost & Sullivan Analysis

Overview and Mechanism of NTRK-TKI (2/2)

- 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 are approved by the FDA, including Larotrectinib and entrectinib.



- TKIs can be used for the treatment of ROS1/NTRK mutated NSCLCs, and there have been several products, such as crizotinib and entrectinib, that 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 ORR, an intracranial ORR, and a medium PFS of 67.1%, 79.2%, and 15.7 months in locally advanced or metastatic ROS1 fusion-positive NSCLC. While the current treatments demonstrated effectiveness, the development of the next generation of ROS1/NTRK Inhibitors aims to enhance their efficacy, specifically simultaneously targeting both the oncogene and combating drug-resistant mutations.

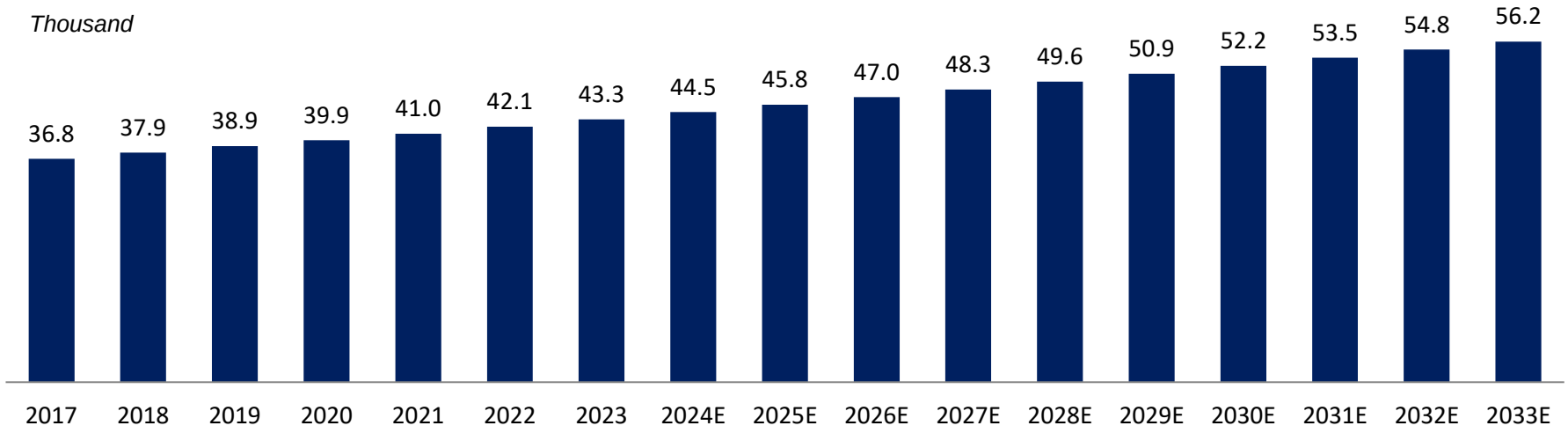
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of NSCLC patients with ROS1 or NTRK mutations, 2017-2033E

- From 2017 to 2023, the number of new cases of NSCLC with ROS1 or NTRK mutations worldwide increased from 36.8 thousand to 43.3 thousand, representing a compound annual growth rate of 2.7%. It is estimated that by 2027 and 2033, the number of new patients of NSCLC with ROS1 or NTRK mutations worldwide will reach 48.3 thousand and 56.2 thousand respectively.

Global incidence of patients with ROS1 or NTRK mutations, 2017-2033E

Period	CAGR
2017-2023	2.7%
2023-2027E	2.7%
2027E-2033E	2.6%



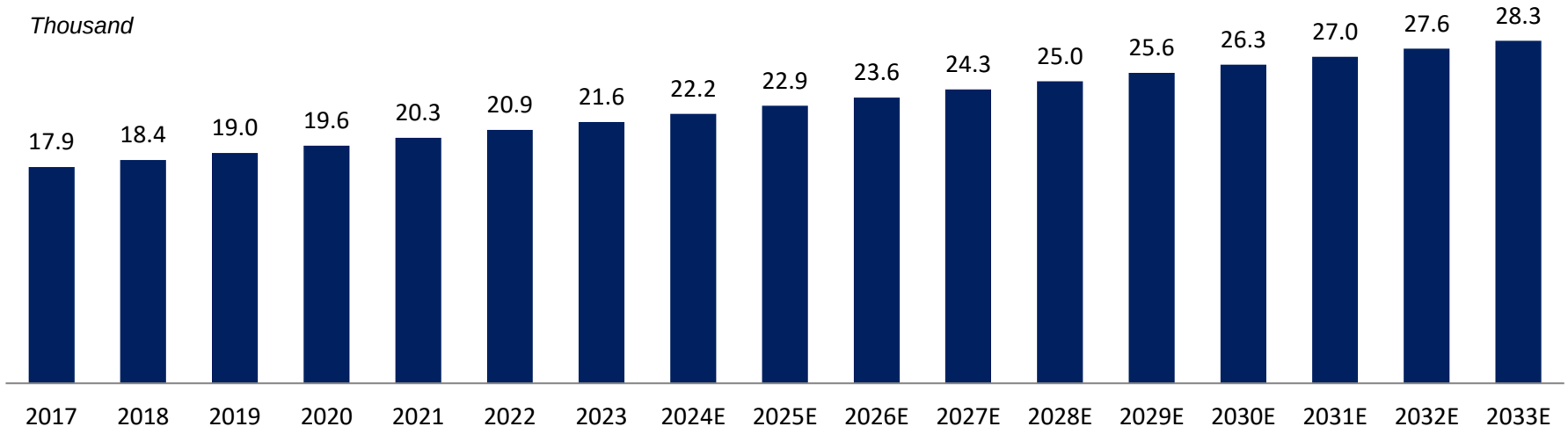
Source: NCCR, Frost & Sullivan analysis

Incidence of NSCLC patient with ROS1 or NTRK mutations in China, 2017-2033E

- From 2017 to 2023, the number of new cases with ROS1 or NTRK mutations in China increased from 17.9 thousand to 21.6 thousand, representing a compound annual growth rate of 3.2%. It is estimated that by 2027 and 2033, the number of new NSCLC patients with ROS1 or NTRK mutations in China will reach 24.3 thousand and 28.3 thousand respectively. ROS1 mutations account for approximately 1.5% of all NSCLC patients, while NTRK mutations account for approximately 1.0% of all NSCLC patients in China.

Incidence of NSCLC patient with ROS1 or NTRK mutations in China, 2017-2033E

Period	CAGR
2017-2023	3.2%
2023-2027E	3.0%
2027E-2033E	2.6%



Source: NCCR, Frost & Sullivan analysis

Analysis of market drives of ROS1/NTRK-TKI

Increasing incidence of cancer patients with these three mutations	• Mutations such as ROS1 and NTRK are relatively common in patients with lung adenocarcinoma and other NSCLCs. From 2017 to 2022, global incidence of NSCLC patients with ROS1/NTRK mutations increased from 36.8 thousand to 42.1 thousand, with a CAGR of 2.7%. Chinese patients account for about 25% of the global population and continue to increase at a CAGR of 3.0% from 2022 to 2027E. The huge number of patients with ROS1/NTRK mutations will drive the clinical demand for ROS1/NTRK TKIs, thereby driving the market.
Advantages of multiple targeted drugs	• Clinical practice shows that when single-target drugs treat multi-factor diseases such as tumors, it is often difficult to achieve good therapeutic effects, and even serious adverse reactions may occur. Multi-target drugs can simultaneously regulate multiple links of disease, improve efficacy, reduce adverse reactions, and improve drug resistance. They are ideal drugs for treating complex diseases, and therefore have become the main direction of drug development. ROS1/NTRK-TKI is an oral small molecule inhibitor that targets NTRK and ROS1, which is an important therapeutic option. It can overcome the drug resistance of ROS1 and NTRK and is clinically effective with rare side effects. These advantages will contribute to the tremendous growth of the ROS1/NTRK-TKI market.
Rapid development of molecular diagnosis	• There is increasing evidence that target-based drugs are only active in a population of selected molecules. Therefore, the identification of predictive biomarkers has become a necessary condition for improving the clinical development of these novel drugs. With the help of molecular diagnostic technology, specific mutations of cancer can be detected, and then the corresponding TKIs can be used for efficient treatment. Development of molecular diagnostic technology is helpful to individualize oncology treatments. It can also improve the development of ROS1/NTRK TKI markets.
Favorable Policies	• China and U.S. government promulgated a series of policies to shorten the review and approval time span for innovative drugs IND and NDA applications, which will accelerate getting to the market process for drugs with potential to address the urgently clinical needs. Patent protection is greatly enhanced as well. All these reforms will attract TKI pharma to launch more global innovative drugs in ROS1/NTRK-TKI market. Furthermore. Government has issued favorable policies in terms of tax reduction, talents incentive program and special public R&D fund to support R&D activities of domestic companies in particular.

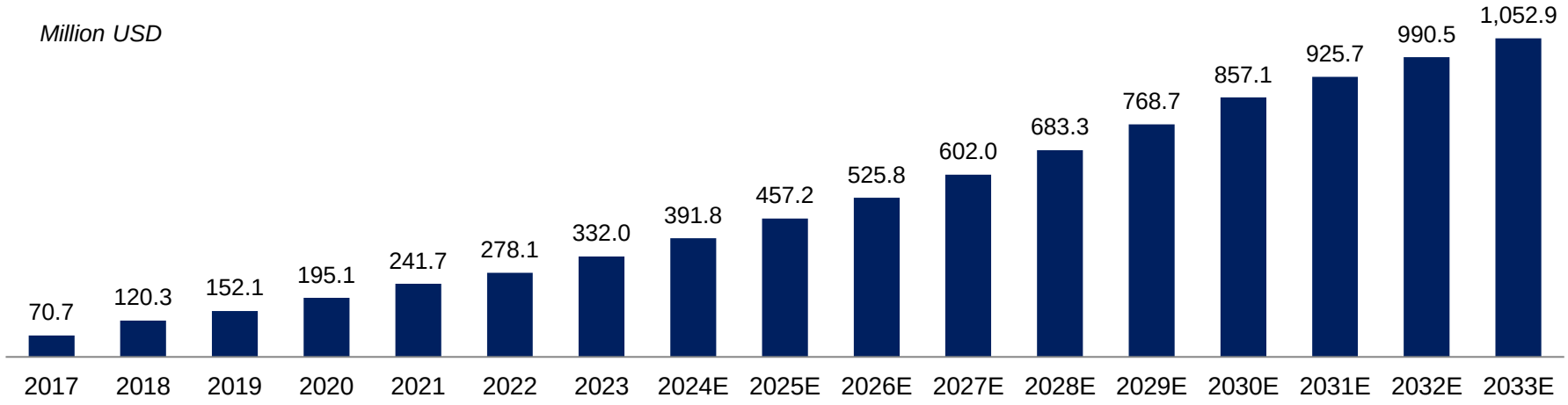
Source: Public data, Frost & Sullivan analysis

Global Market size of ROS1/NTRK-TKI, 2017-2033E

- Global ROS1/NTRK-TKI market has experienced a steady growth, increasing from USD70.7 million in 2017 to USD332.0 million in 2023, and it is expected to reach USD602.0 million with a compound annual growth rate of 16.0% from 2023 to 2027 and reach USD1,052.9 million with a compound annual growth rate of 9.8% from 2027 to 2033.

Global market size and forecast of ROS1/NTRK-TKI, 2017-2033E

Period	CAGR
2017-2023	29.4%
2023-2027E	16.0%
2027E-2033E	9.8%



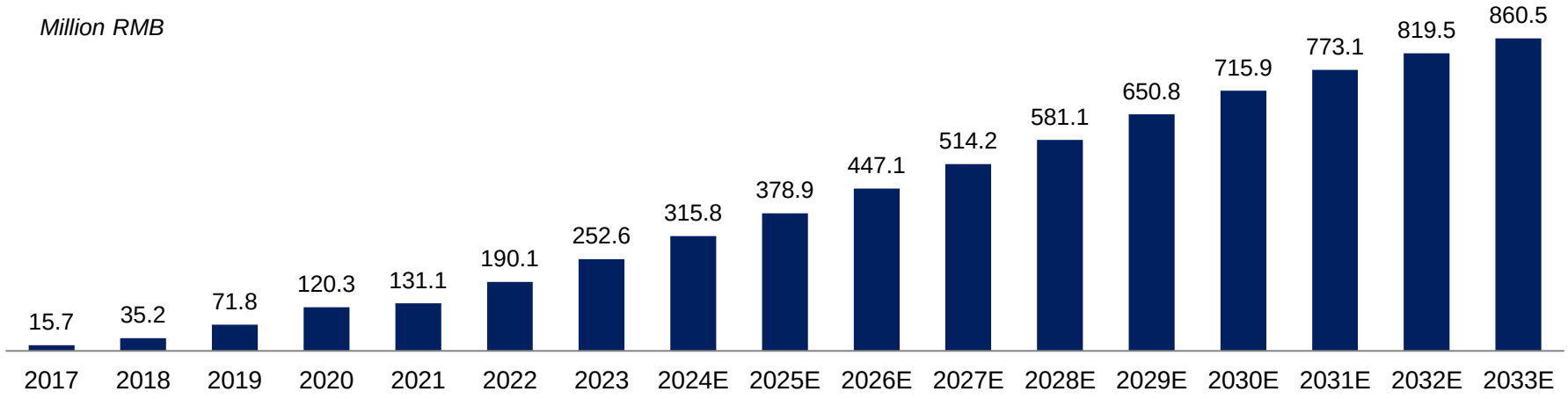
Source: Frost & Sullivan analysis

Market size of ROS1/NTRK-TKI in China, 2017-2033E

- ROS1/NTRK-TKI market in China has increased significantly from RMB15.7 million in 2017 to RMB252.6 million in 2023 with a CAGR of 58.8%. It is estimated that revenue generated by market of ROS1/NTRK-TKI in China will reach RMB514.2 million with a CAGR of 19.4% from 2023 to 2027 and reach RMB860.5 million with a CAGR of 9.0% from 2027 to 2033.

Market size and forecast of ROS1/NTRK-TKI in China, 2017-2033E

Period	CAGR
2017-2023	58.8%
2023-2027E	19.4%
2027E-2033E	9.0%



Source: Frost & Sullivan analysis

Competitive Landscape：ROS1/NTRK-TKI Approved by FDA

- To date, there are 4 ROS1/NTRK-TKI gained approval from FDA.

Drug Name	Brand Name	Target	Company	Indications	Approval Date	Global sales 2023 (million USD)
Entrectinib	Rozlytrek	NTRK, ROS1, ALK	Roche	ROS1-positive NSCLC, NTRK-positive Solid Tumors	2019-08-15	NA
Crizotinib	Xalkori	ALK, MET, ROS1	Pfizer	ALK-positive locally advanced or metastatic NSCLC	2011-08-26	374
				ROS1-positive metastatic NSCLC	2016-03-11	
				ALK-positive systemic ALCL	2021-01-14	
				ALK-positive unresectable IMT	2022-07-14	
Larotrectinib	Vitrakvi	NTRK	Bayer	NTRK-positive solid tumor	2018-11-26	NA
Repotrectinib	Augtyro	NTRK, ROS1, ALK, JAK2, SRC, FAK	BMS	locally advanced or metastatic ROS1-positive NSCLC	2023-11-15	NA

*Note: Approval date: First approval date; NSCLC = Non Small Cell Lung Cancer; ALCL= anaplastic large cell lymphoma; IMT=inflammatory myofibroblastic tumor
as of August 2,2024

Source: FDA, Frost & Sullivan Analysis

Competitive Landscape：ROS1/NTRK-TKI Approved by NMPA

- There are 5 ROS1/NTRK-TKI innovative drugs approved from NMPA. No generic drugs of entrectinib and larotrectinib have been approved in China. One generic drug of crizotinib gained approval from NMPA in November 2023.

ROS1/NTRK-TKI Approved by NMPA (Innovative Drugs)

Drug Name	Brand Name	Target	Company	Approved Indications	Approval Date	Whether is covered by the NRDL	End user price (RMB/box)	Treatment cost (RMB/month)
Entrectinib	Rozlytrek	NTRK, ROS1, ALK	Roche	ROS1-positive NSCLC; NTRK-positive solid tumor	2022-7-26	YES**	~15,120	~15,120
Crizotinib	Xalkori	ALK, MET, ROS1	Pfizer	ALK-positive locally advanced or metastatic NSCLC; Advanced ROS1-positive NSCLC	2013-1-22	YES	~10,296	~10,296
Larotrectinib	Vitrakvi	NTRK	Bayer	NTRK-positive solid tumor	2022-4-08	NO	~62,600	~65,000
Repotrectinib	Augtyro	NTRK, ROS1, ALK, JAK2, SRC, FAK	BMS	locally advanced or metastatic ROS1-positive NSCLC	2024-5-8	NO	NA	NA
Unecritinib	安柏尼	ALK, MET, ROS1	Chiatai Tianqing Pharmaceutical Group	ROS1-positive locally advanced or metastatic NSCLC	2024-4-24	NO	NA	NA

ROS1/NTRK-TKI Approved by NMPA (Generic Drugs)

Drug Name	Target	Company	Approval Date
Crizotinib	ALK, MET, ROS1	Jiangsu Wanbang Biopharmaceuticals	2023-11-21

*Note: Approval date: First approval date; NSCLC = Non Small Cell Lung Cancer
**Note: Entrectinib was added in NRDL for the first time on 1st January 2024.
as of August 2,2024

Source: NMPA, Frost & Sullivan Analysis

Competitive landscape of global ROS1/NTRK-TKI pipeline: Indications that are under development of approved drugs

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
Entrectinib	NTRK, ROS1, ALK	Roche	Phase 1/2	NTRK positive or ROS1 positive solid tumours and CNS tumours	2016-01-08
			Phase 2	Patients with solid tumors that harbor an NTRK, ROS1, or ALK gene fusion	2015-10-05
Repotrectinib	NTRK, ROS1, ALK, JAK2, SRC, FAK	BMS	Phase 1/2	Advanced or metastatic malignancies harboring ROS1 or NTRK alterations	2019-09-19
Iruplinalkib**	ALK , ROS1	Qilu Pharmaceutical Co., Ltd.	Phase 2	ALK -positive, or ROS1-positive NSCLC	2020-11-24
			Phase 1/2	ALK/ROS1-positive solid tumor; ALK -positive NSCLC	2018-01-04
Lorlatinib**	ALK , ROS1	CStone Pharmaceuticals; Pfizer	Phase 2	ROS1-positive NSCLC	2022-04-28

*Note: Approval date: First approval date; NSCLC = Non Small Cell Lung Cancer
**Note: Iruplinalkib and Lorlatinib are usually considered as ALK-TKIs since their approval indications are ALK-positive NSCLC.
as of August 2,2024

Source: NMPA, Frost & Sullivan Analysis

Competitive Landscape of ROS1/NTRK-TKI Pipeline in China: Indications that are under development of approved drugs

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
Entrectinib	NTRK, ROS1, ALK	Roche	Phase 2	NTRK positive or ROS1 positive solid tumors and CNS tumors	2020-09-25
			Phase 2	Patients with solid tumors that harbor an NTRK, ROS1, or ALK gene fusion	2019-10-16
Iruplinalkib**	ALK , ROS1	Qilu Pharmaceutical Co., Ltd.	Phase 2	ALK -positive, or ROS1-positive NSCLC	2019-04-28
Lorlatinib**	ALK , ROS1	CStone Pharmaceuticals; Pfizer	Phase 2	ROS1-positive locally advanced or metastatic NSCLC	2022-03-22

*Note: Approval date: First approval date; NSCLC = Non Small Cell Lung Cancer
**Note: Iruplinalkib and Lorlatinib are usually considered as ALK-TKIs since their approval indications are ALK-positive NSCLC.
as of August 2,2024

Source: NMPA, Frost & Sullivan Analysis

Competitive Landscape of Global ROS1/NTRK-TKI Pipeline (1/4)

- To date, there are 30 ROS1/NTRK-TKI under development globally. TY-2136b is a potential best-in-class, oral inhibitor of ROS1/NTRK for the treatment of NSCLC.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
Taletrectinib	NTRK, ROS1	AnHeart Therapeutics Inc.	II	NSCLC	2021-06-09
			II	Metastatic CDH1-mutated invasive lobular cancer of the breast	2024-4-25
XZP-5955	NTRK, ROS1	Xuanzhu Biopharmaceutical Co., Ltd.	I/II	Locally Advanced/Metastatic solid tumor/NSCLC	2021-08-09
TY-2136b	NTRK, ROS1	TYK Medicines, Inc	I	Locally advanced/metastatic solid tumor	2023-03-15
SIM1803-1A	NTRK, ROS1, ALK	Jiangsu Simcere Pharmaceutical Co., Ltd.	I	Advanced/metastatic solid tumors harboring NTRK, ROS1 or ALK Gene Fusion	2020-12-17
TSR-011	ALK, NTRK	Tesaro, Inc.	I/II	Solid tumor; Lymphomas	2014-01-29
TGRX-326	ALK, ROS1	Shenzhen TargetRx Biopharmaceutical Co., Ltd	III	NSCLC	2023-10-13
XZP-3621	ALK, ROS1	Xuanzhu Biopharmaceutical Co., Ltd.	III	Treatment-naive ALK-positive advanced NSCLC	2022-01-24
Alkotinib	ALK, ROS1	Suzhou Zelgen Biopharmaceuticals Co.,Ltd	II	ALK-positive NSCLC	2019-12-26

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global ROS1/NTRK-TKI Pipeline (2/4)

- To date, there are 30 ROS1/NTRK-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
SAF-189s	ALK, ROS1	Shanghai Fosun Pharmaceutical Industrial Development Co. Ltd.	I/II	Advanced solid tumor, NSCLC	2020-01-23
APG-2449	ALK, ROS1, FAK	Ascentage Pharma Group Inc.	I	Advanced solid tumor	2019-04-16
Unecritinib	ALK, MET, ROS1	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	II	ROS1-positive Non-Small Cell Lung Cancer	2019-06-03
TL-118	NTRK	Teligene US	II	Solid tumor	2023-08-24
SNA-120	NTRK	Sienna Biopharmaceuticals	II	Pruritus; Psoriasis	2018-02-27
CT327	NTRK	Creabilis SA	II	Atopic dermatitis	2013-03-11
			II	Psoriasis vulgaris	2011-11-04
ICP-723	NTRK	InnoCare Pharma Inc.	I/II	Advanced solid tumor/primary CNS tumor harboring NTRK fusion	2023-02-27

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global ROS1/NTRK-TKI Pipeline (3/4)

- To date, there are 30 ROS1/NTRK-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
PBI-200	NTRK	Pyramid Biosciences	I/II	Solid tumor; Primary brain tumor; Desmoplastic small round cell tumor	2021-05-26
VC004	NTRK	Jiangsu vcare pharmaceutical technology co., LTD	I/II	Locally advanced/metastatic solid tumor	2020-11-04
BEN2293	NTRK	BenevolentAI Bio	I/II	Atopic dermatitis	2021-02-03
TQB3558	NTRK	Chia Tai Tianqing Pharmaceutical Group Co., Ltd.	I	Advanced solid tumor	2020-05-29
TQB3811			I	Solid tumor	2021-9-16
BPI-28592	NTRK	Betta Pharmaceuticals Co., Ltd.	I	Neoplasm metastasis	2022-03-31
TGRX-1942	NTRK	Shenzhen TargetRx, Inc.	I	NSCLC, advanced solid tumor, hematologic malignancy	2024-7-3
ND-003	RET, NTRK	Shenzhen NewDEL Biotech, Co., Ltd; Shenzhen Innovation Center for Small Molecule Drug Discovery Co., Ltd.	I	Advanced solid tumor	2023-12-13

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global ROS1/NTRK-TKI Pipeline (4/4)

- To date, there are 30 ROS1/NTRK-TKI under development globally.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
FCN-011	NTRK	Fochon Pharmaceuticals, Ltd.	I	Advanced solid tumor	2020-12-29
FCN-098	NTRK		I	Solid tumor	2022-1-28
Selitrectinib	NTRK	Bayer	I	Solid tumors harboring NTRK fusion	2017-7-12
NOV1601	NTRK	Handok Inc.	I	Adult solid tumor	2019-7-10
ONO-4474	NTRK	Ono Pharmaceutical Co. Ltd	I	Osteoarthritis	2015-5-27
NVL-520	ROS1	Nuvalent Inc.	I/II	Locally advanced solid tumor; Metastatic solid tumor	2021-11-12
JYP0322	ROS1	Guangzhou JOYO Pharma Co., Ltd	I	ROS1-positive locally advanced/metastatic solid tumor	2023-11-13

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of ROS1/NTRK-TKI Pipeline in China (1/3)

- According to CDE, there are 23 ROS1/NTRK-TKI under development in China.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
AB-106	ROS1, NTRK	Baoyuan Biopharmaceutical Technology (Hangzhou) Co., Ltd	II	Malignant tumor	2023-08-30
			II	ROS1-positive locally advanced/metastatic NSCLS; NTRK-positive solid tumors	2020-05-15
HS301	ROS1, NTRK	Hanhui Pharmaceuticals Co., Ltd	I/II	Locally advanced/metastatic solid tumor harboring NTRK/ROS1/ALK fusion	2022-05-19
HG030	ROS1, NTRK	Chengdu HitGen Pharmaceutical Development Co., Ltd	I	Advanced solid tumor	2021-02-09
XZP-5955	ROS1, NTRK	Xuanzhu Biopharmaceutical Co., Ltd.	I/II	Locally advanced/metastatic tumor harboring NTRK/ROS1/ALK fusion and mutation	2021-08-13
			I	ALK-positive NSCLC	2023-04-23
TL139	ALK, ROS1, NTRK	Suzhou Teligene Biopharmaceutical Co., Ltd	I/II	Locally advanced or metastatic tumor harboring NTRK/ROS1/ALK fusion	2020-12-23
LZ001	ALK, ROS1, NTRK	Livzon Pharmaceutical Group Inc	I	Advanced solid tumor harboring NTRK1/2/3, ROS1 or ALK gene fusion	2022-07-26

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; as of August 2,2024

Source: CDE, Frost & Sullivan Analysis

Competitive Landscape of ROS1/NTRK-TKI Pipeline in China (2/3)

- According to CDE, there are 23 ROS1/NTRK-TKI under development in China.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
XZP-3621	ALK, ROS1	Xuanzhu Biopharmaceutical Co., Ltd	III	ALK-positive advanced NSCLC	2021-12-21
TGRX-326	ALK, ROS1	Shenzhen TargetRx, Inc.	III	NSCLC	2023-11-07
Furetinib succinate	ALK, ROS1	Chongqing Fuchuang Pharmaceuticals Research Co.,Ltd.	III	ALK-positive NSCLC	2021-12-01
SAF-189s	ALK, ROS1		I	ALK/ROS1-positive NSCLC	2022-10-21
Alkotinib	ALK, ROS1	Suzhou Zelgen Biopharmaceuticals Co., Ltd.	II	ALK-positive advanced NSCLC	2019-11-04
JYP0322	ROS1	Guangzhou Joyo Pharmaceutical Technology Co., Ltd	I	ROS1-positive advanced tumor	2022-03-30
APG-2449	ALK, FAK, ROS1	Suzhou Ascentage Pharma Co.,Ltd.	I	Advanced solid tumor	2019-04-09
TL118	NTRK	Suzhou Teligene Biopharmaceutical Co., Ltd	II	Advanced tumors harboring NTRK fusion	2020-10-11

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer;
as of August 2,2024

Source: CDE, Frost & Sullivan Analysis

Competitive Landscape of ROS1/NTRK-TKI Pipeline in China (3/3)

- According to CDE, there are 23 ROS1/NTRK-TKI under development in China.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
ICP-723	NTRK	Beijing InnoCare Pharma Tech Co., Ltd.	II	NTRK-positive advanced tumor; Primary tumor of central nervous system	2022-12-22
VC004	NTRK	Jiangsu Vcare Pharmatech Co., Ltd.	I/II	Solid tumor harboring NTRK fusion	2020-08-28
CG001419	NTRK	Cullgen Shanghai	I/II	Advanced/metastatic solid tumor harboring NTRK fusion or mutation	2022-10-24
FCN-011	NTRK	Chongqing Fuchuang Pharmaceuticals Research Co.,Ltd.	I/II	Solid tumor harboring NTRK fusion	2020-11-27
TQB3811	NTRK	Jiangsu Chia Tai-tianqing Pharmaceutical Co., Ltd.	I	Solid tumor	2021-08-27
TQB3558			I	Advanced malignant solid tumor	2020-04-29
BPI-28592	NTRK	Betta Pharmaceuticals Co.Ltd	I	Solid tumor harboring NTRK mutation	2020-12-11
TGRX-1942	NTRK	Shenzhen TargetRx, Inc.	I	Advanced solid tumor, hematologic malignancy	2024-6-11
ND-003	RET, NTRK	Shenzhen Innovation Center for Small Molecule Drug Discovery Co., Ltd.; Shenzhen NewDEL Biotech Co., Ltd.	I	Advanced solid tumor	2023-11-21

*Note: First posted date: 首次公示日期; NSCLC= Non Small Cell Lung Cancer; as of August 2,2024

Source: CDE, Frost & Sullivan Analysis

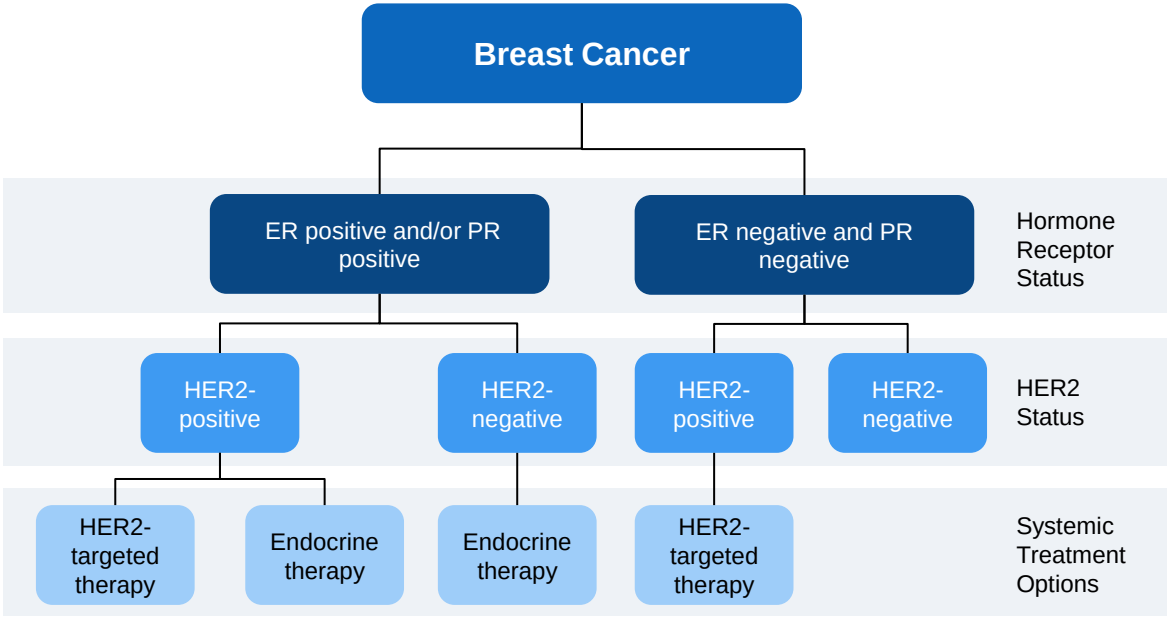
Table of Contents

Overview of Breast Cancer

- Breast cancer is the most common cancers in women, and the incidence increases year by year. Breast cancer mostly occurs in women aged over 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.
- There are different types of treatment for patients with breast cancer. Six types of standard treatment are used: surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy and immunotherapy.
- Chemotherapy may be given before surgery to remove the tumor. When given before surgery, chemotherapy will shrink the tumor and reduce the amount of tissue that needs to be removed during surgery. Treatment given before surgery is called preoperative therapy or neoadjuvant therapy. Breast cancer is the most common cancer in women, and its incidence rises with age, increasing year by year as women age

Risk Factors

- Genetic predisposition (BRCA1 or BRCA2 mutations)
- Estrogen and progesterone exposure
- Oral contraceptives or birth control drugs
- Atypical hyperplasia of the breast
- Lobular carcinoma in situ
- Lifestyle factors (weight, food, alcohol, physical activity)
- Breast density (dense breast tissue)
- Family history of breast cancer



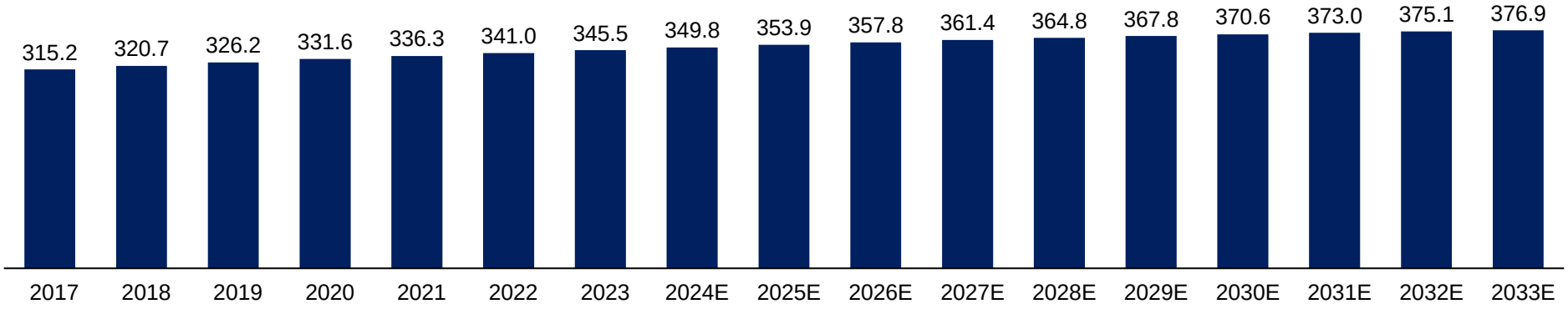
Source: NCCN Guidelines, Literature Review, Frost & Sullivan analysis

Incidence of breast cancer in China，2017-2033E

- Breast cancer is one of the top 10 cancers in terms of incidence in China and the U.S. In 2017, there were 315.2 thousand new cases of breast cancer in China. By 2023, this number will increase to 345.5 thousand, representing a CAGR of 1.5% from 2017 to 2023. It is projected to reach 361.4 thousand and 376.9 thousand in 2027 and in 2033 respectively, with a CAGR of 1.1% from 2023-2027 and 0.7% from 2027-2033.
- The incidence of breast cancer varies greatly geographically due to differences in natural environment, economic conditions and lifestyles. Generally speaking, developed countries, such as the United States and some European countries, have higher rates of new cases, while developing countries, including China, have relatively lower incidence rates.
- The increase in incidence rate has slowed down year by year, which is related to the increased awareness of cancer management. In addition, the system for controlling risk factors for breast cancer will become more complete, which will be helpful in controlling the incidence rate of cancer.

Incidence of breast cancer in China，2017-2033E

Period	CAGR
2017-2023	1.5%
2023-2027E	1.1%
2027E-2033E	0.7%



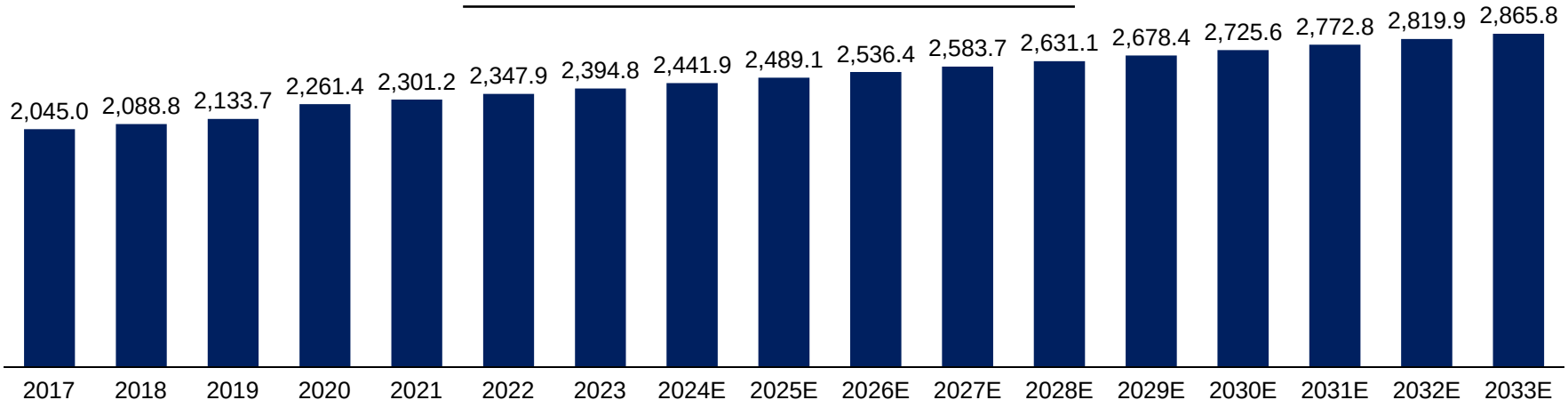
Source: NCCR,IARC,Frost & Sullivan Analysis

Global incidence of breast cancer，2017-2033E

- From 2017 to 2023, the global number of breast cancer identified increased from 2045.0 thousand to 2394.8 thousand. By 2027 and 2033, the number of breast cancer cases will reach 2,583.7 thousand and 2,865.8 thousand with a CAGR of 1.9% and 1.7%, respectively.
- With increasing pressure and changing lifestyles, breast cancer patients tend to be younger, leading to a rising incidence rate. In addition, due to work pressure and cultural changes, many women choose to give birth to their first child after the age of 35, thus increasing the risk of breast cancer.

Global incidence of breast cancer，2017-2033E

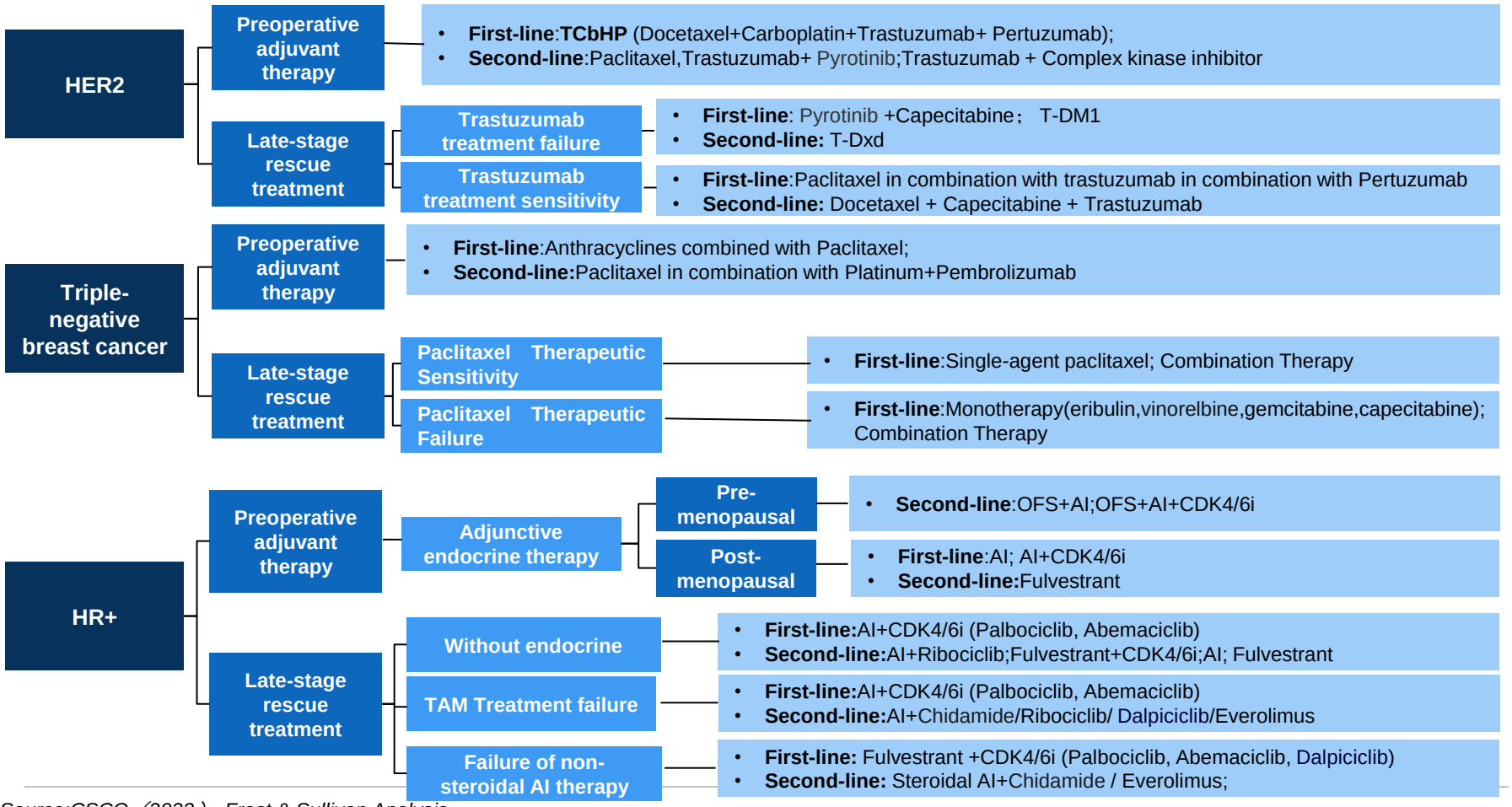
Period	CAGR
2017-2023	2.7%
2023-2027E	1.9%
2027E-2033E	1.7%



Source: NCCR,IARC,Frost & Sullivan Analysis

Treatment Paradigm of Breast Cancer in China

- CDK4/6 inhibitors are novel targeted therapeutic agents, which are mainly used for HR+/HER2- breast cancer patients, making a breakthrough in related endocrine treatment modalities. Compared with traditional endocrine therapy alone, CDK4/6 inhibitors combined with endocrine therapy significantly prolonged the progression-free survival of breast cancer patients and was well tolerated.



Source:CSCO（2023）, Frost & Sullivan Analysis

Overview of Triple Negative Breast Cancer

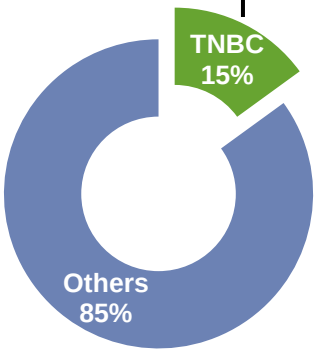
- Triple negative breast cancer(TNBC) is a type of breast cancer based on immunohistochemistry (IHC) is estrogen receptor (ER) negative, progesterone receptor (PR) negative and human epidermal growth factor receptor 2 (HER2) negative, which accounted for approximately 15% of the total breast cancer population globally. TNBC is typically diagnosed more frequently in younger and premenopausal women. TNBC has the worst prognosis among the subtypes of breast cancer, with no targeted therapy available. TNBC is characterized by the lack of estrogen and progesterone receptor expression and lacks HER2 over-expression or gene amplification, It is a biologically aggressive tumor, characterized by moderate/high grade and highly proliferative cancer cells

Triple Negative Breast Cancer

ER Negative	PR Negative	HER2 Negative
No response to hormonal therapy (such as tamoxifen or aromatase inhibitors)		No response to target HER2 receptors treatment, such as Herceptin

Risk Factors

1	**General**	Age： 50-year-old and over Race: African-American & Hispanic
2	**BRCA Mutations**	A mutation in BRCA1, BRCA2, or both genes
3	**Physiological status**	Early menarche, higher parity, younger age at full term pregnancy, shorter duration of breast feeding, higher body mass index, higher waist to hip ratio.



- TNBC is an aggressive, difficult–to-treat cancer.
- About **15%** of breast cancers are TNBC.

Clinical Characteristics

- TNBC is aggressive behaviors and characterized by onset at a younger age, high mean tumor size, higher grade tumors as well as a higher rate of node positivity.
- TNBC shows an early peak of recurrence between the first and third year after diagnosis, and it is known for more aggressive metastases which are more likely to occur in viscera, particularly in the lungs and brain.

Source: Triple Negative Breast Cancer – An Overview, Triple-Negative Breast Cancer:: Clinical Features, Frost & Sullivan analysis

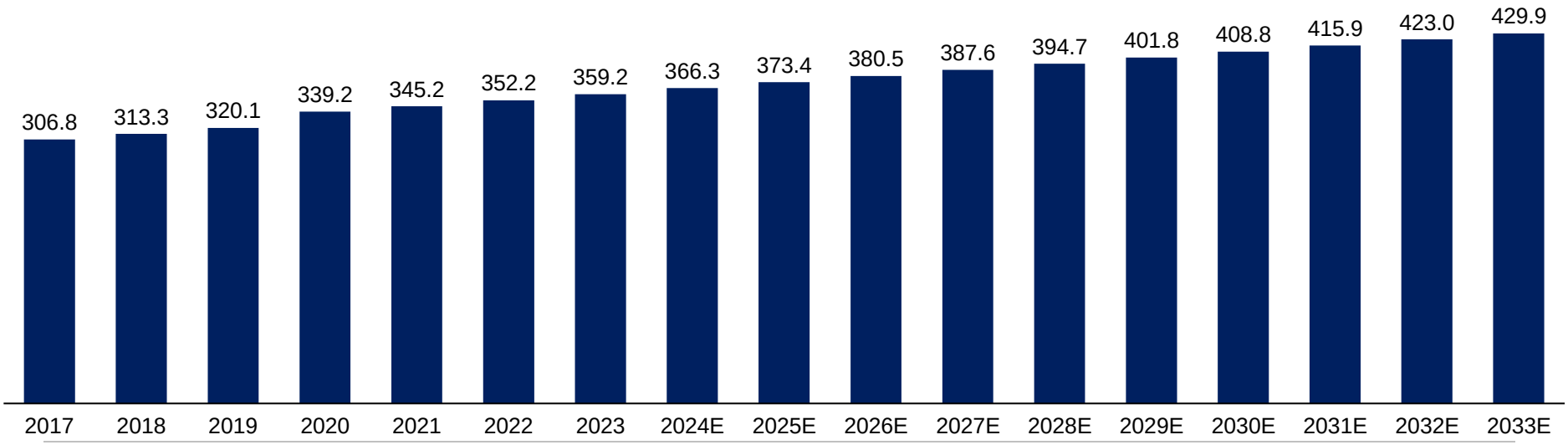
Global incidence of TNBC，2017-2033E

- The number of new TNBC cases increased from 306.8 thousand in 2017 to 359.2 thousand in 2023, exhibiting a CAGR of 2.7% during this period. The number is forecasted to reach 387.6 thousand by 2027 with a CAGR of 1.9% from 2023 to 2027. It is expected to further reach 429.9 thousand in 2033, representing a CAGR of 1.7% from 2027 to 2033.

Global incidence of TNBC，2017-2033E

Period	CAGR
2017-2023	2.7%
2023-2027E	1.9%
2027E-2033E	1.7%

Thousand



Source: American Cancer Society, Globocan2018, Frost & Sullivan analysis

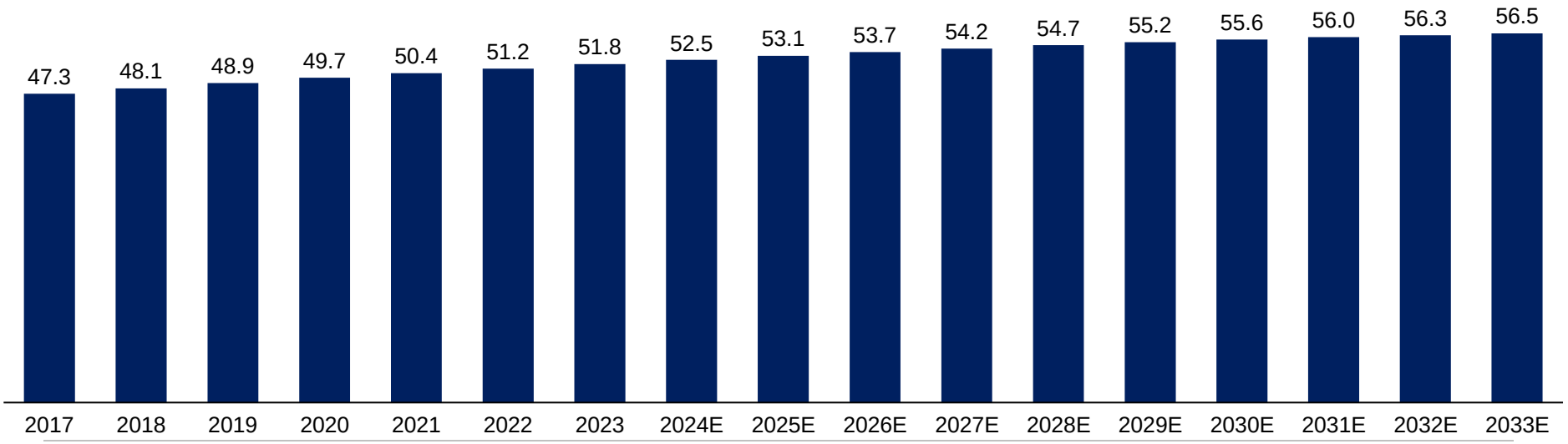
Incidence of TNBC in China, 2017-2030E

- The number of new TNBC cases increased from 47.3 thousand in 2017 to 51.8 thousand in 2023, exhibiting a CAGR of 1.5% during this period.The number is forecasted to reach 54.2 thousand by 2027 with a CAGR of 1.1% from 2023 to 2027. It is expected to further reach 56.5 thousand in 2033, representing a CAGR of 0.7% from 2027 to 2033.

Incidence of TNBC in China, 2017-2033E

Period	CAGR
2017-2023	1.5%.
2023-2027E	1.1%
2027E-2033E	0.7%

Thousand



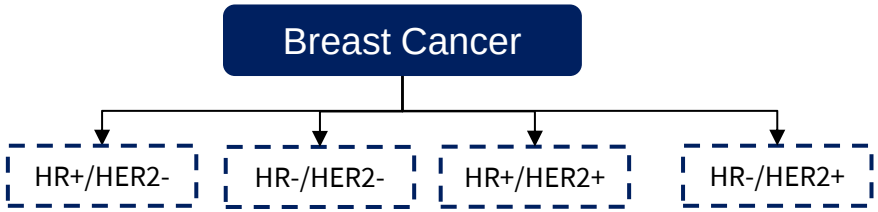
Source: NCCR, Frost & Sullivan analysis

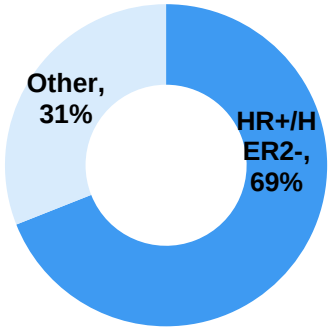
Overview of HR+/HER2−Breast Cancer

- HR+/HER2- refers to the tumor tested positive for estrogen and progesterone receptors and negative for HER2. This subtype accounts for most cases of breast cancer. CDK2 inhibition represents a promising, novel therapeutic approach to treat or prevent CDK4/6 inhibitor resistance in HR+/HER2− breast cancer.
- The results of the related study showed that CDK4/6 inhibitors in combination with endocrine therapy extended the preferred indications for endocrine therapy and provided benefits for HR+/HER2- patients.
- In HR+ breast cancer, it typically involves the simultaneous expression of both estrogen receptors and progesterone receptors. About 80 percent of all HR+ breast cancers are ER+ or ER/PR+.

HR+/HER2-Breast Cancer

There are four main female breast cancer subtypes, including the following in order of prevalence:





- The breast cancer subtype HR+/HER2- is the most common subtype
- About **69%** of breast cancers are HR+/HER2-.

Clinical Characteristics

- HR+ breast cancer is characterized by delayed recurrence, with a chance of recurrence ten or more years after healing.
- HER2+ breast cancer is more malignant and has a higher chance of spreading and recurrence. In addition, these patients are usually relatively young, so long-term surveillance and the use of drugs to reduce the risk of recurrence are necessary.
- Approximately 70% of women with breast cancer worldwide receive a diagnosis of ER-positive/HER2-negative disease. Recurrence-free survival of the node-negative population of these women is approximately 85%, and most are treated with endocrine chemotherapy. Endocrine treatment for ER-positive/HER2-negative early breast cancer is a major treatment strategy.
- 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 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 target of rapamycin inhibitors, leading to the emergence of CDK2/4/6 inhibitors as a novel therapeuticavenue to curb cancer cell proliferation.

Source: NATIONAL CANCER INSTITITE(NIH), Frost & Sullivan analysis

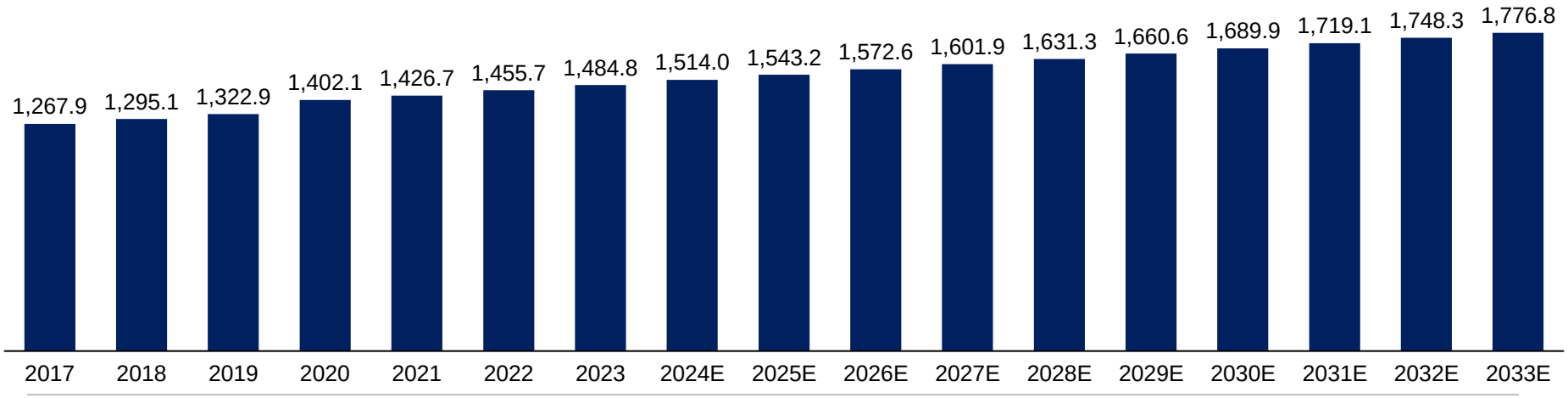
Global incidence of HR+/HER2−Breast Cancer, 2017-2033E

- In China, the number of new cases increased from 1267.9 thousand in 2017 to 1484.8 thousand in 2023, exhibiting a CAGR of 2.7% during this period**.** From 2023 to 2027, the number of new cancer cases is expected to grow at an annual rate of 1.9% and would reach 1601.0 thousand by 2027. By 2033, the number of HR+/HER2− breast cancer cases is expected to reach 1776.8 thousand, representing a CAGR of 1.7%.

Global incidence of HR+/HER2−Breast Cancer, 2017-2033E

Period	CAGR
2017-2023	2.7%
2023-2027E	1.9%
2027E-2033E	1.7%

Thousand



Source: Breast Cancer Treatment: A Review. JAMA. 2019,Frost & Sullivan analysis

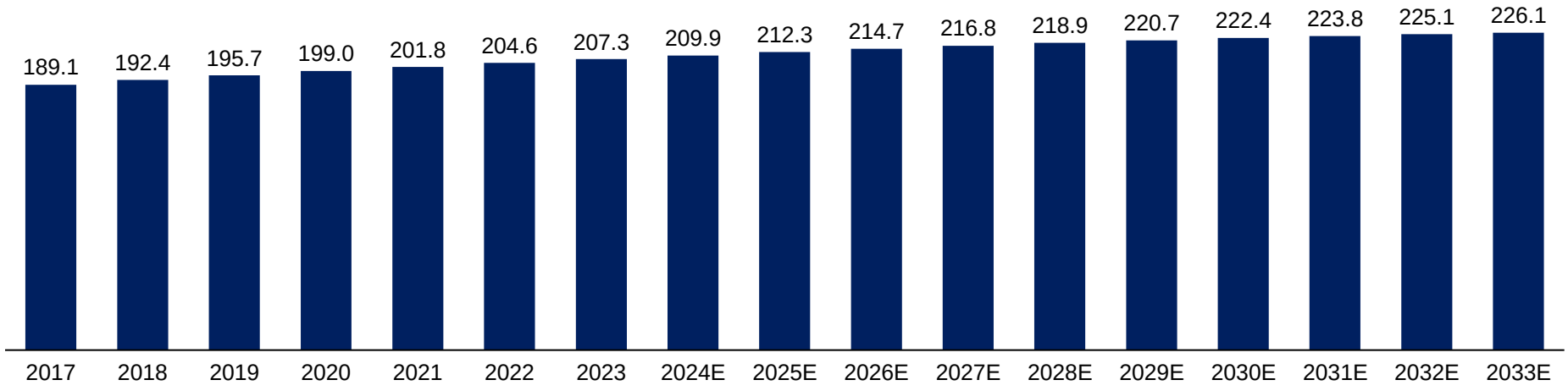
Incidence of HR+/HER2−Breast Cancer in China, 2017-2033E

- In China, the number of new HR+/HER2-breast cancer cases increased from 189.1 thousand in 2017 to 207.3 thousand in 2023, exhibiting a CAGR of 1.5% during this period. The number is set to grow to 216.8 thousand by 2027 with a CAGR of 1.1% from 2023 to 2027. It is expected to reach 226.1 thousand in 2033, representing a CAGR of 0.7% from 2027 to 2033.

Incidence of HR+/HER2−Breast Cancer in China, 2017-2033E

Period	CAGR
2017-2023	1.5%
2023-2027E	1.1%
2027E-2033E	0.7%

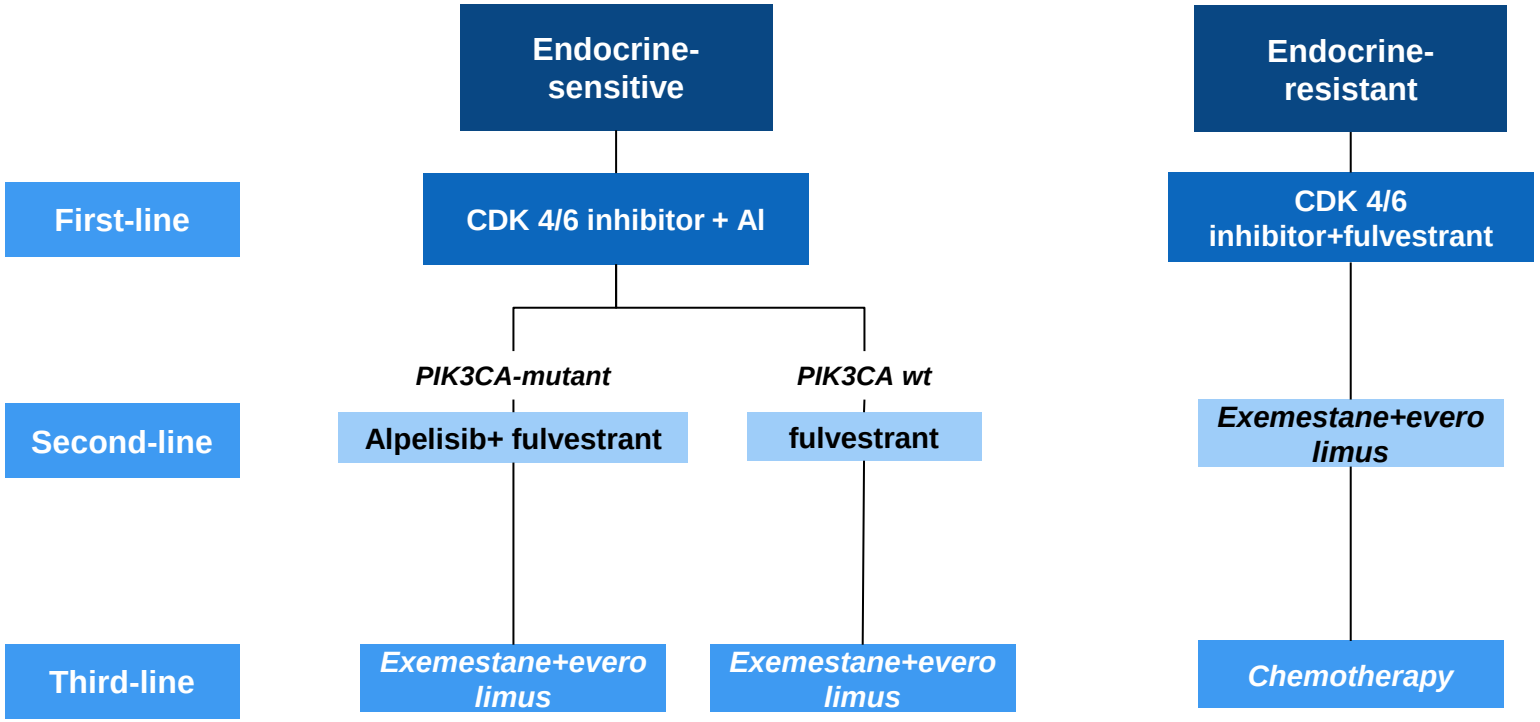
Thousand



Source: NCCR, Frost & Sullivan analysis

Treatment Paradigm of HR+/HER2-Breast Cancer in China

- 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.



Source: JCO Oncology Practice, *Frost & Sullivan analysis*

Breast Cancer Treatment – Unmet Needs(1/2)

Recurrence/ metastatic diseases for HR+/HER2- patients	Limited Treatment Options in the Late-Stage Setting	Limited treatment options for HR+/HER2 and TNBC 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, whilst limiting the impact of side effects on patients' QoL. While survival for metastatic breast cancer has improved, patients eventually require chemotherapy and meaning additional side effects. More advances are required to delay disease progression and continue day-to-day lives.	• CDK4/6 inhibitors have dramatically changed the therapeutic landscape for HR+/HER2-advanced breast cancer. Combination of CDK4/6 inhibitors with ET significantly improves patients' PFS and OS, and 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 cure for HR+/HER2- metastatic breast cancer. There is a significant need for new and effective HR+/HER2- therapeutics that can be administered to patients.	• HR+/HER2- breast cancer patients are facing much fewer treatment options, especially targeted therapies. • HR+/HER2- BC is the most common form of breast cancer in China, representing over 60% of all breast cancer cases, but almost all HR+/HER2- metastatic breast cancer would become refractory to hormone therapies. • 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.

Scharl A, et al. The Right Treatment for the Right Patient – Personalised Treatment of Breast Cancer. Geburtshilfe Frauenheilkd. 2015;75(7)683-91.

Source: Frost & Sullivan Analysis

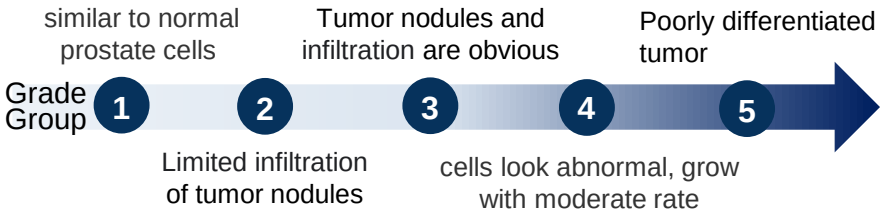
Overview of Prostate Cancers

- Prostate cancer is an epithelial malignant tumor occurring 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.
- Prostate cancer progresses slowly and is usually asymptomatic in the early stages. Once metastasis or migration, the condition becomes more serious, which brings heavy disease burden to the patient's life.

Risk Factors of PC

- The peak age of prostate cancer mostly onset is 65-80 years old.
- If 2 or more immediate family members suffer from prostate cancer, the risk of developing prostate cancer will increase by 5-11 times

Pathology Stages and Grades



- Pathologists grade prostate cancers using numbers from 1 to 5 based on how much the cells in the cancerous tissue look like normal prostate tissue under the microscope. This is called the Gleason system.

Symptom:

- Early prostate cancer usually has no clear symptoms, often similar to those of benign prostatic hyperplasia.
- Metastatic prostate cancer (especially bone metastasis) can cause symptoms, such as：

Difficulty maintaining stream of urine	Frequent urination
Bone pain	Dysuria (painful urination)
Hematuria	Difficulty erection

Diagnostic criteria

Metastatic castrate-resistant prostrate cancer (mCRPC) is diagnosed by:

Level of serum testosterone.	PSA blood test	Imaging test

Source: Frost & Sullivan Analysis

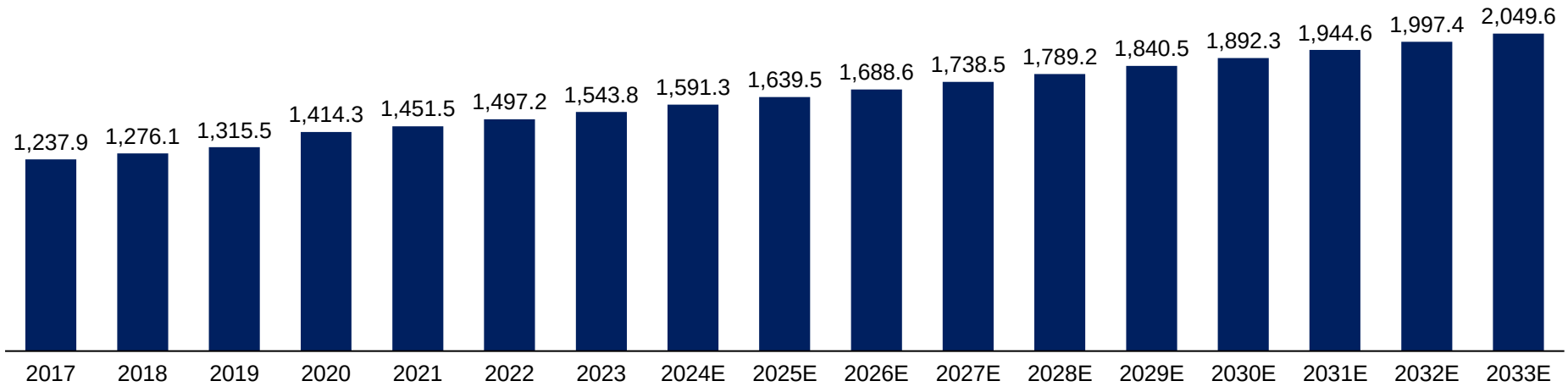
Global incidence of Prostate cancer， 2017-2033E

- Prostate cancer is the second most prevalent and fifth most deadly cancer worldwide for men, posing a serious threat to men's health and quality of life. The number of new prostate cancer cases globally grew from 1,237.9 thousand in 2017 to 1,543.8 thousand in 2023, with a compound annual growth rate of 3.8%. This number is expected to grow and reach 1,738.5 thousand in 2027 and 2,049.6 thousand in 2033, representing CAGRs of 3.0% from 2023-2027 and 2.8% from 2027-2033, respectively.

Global incidence of prostate cancer， 2017-2033E

Period	CAGR
2017-2023	3.8%
2023-2027E	3.0%
2027E-2033E	2.8%

Thousand



Source: NCCR,IARC,Frost & Sullivan Analysis

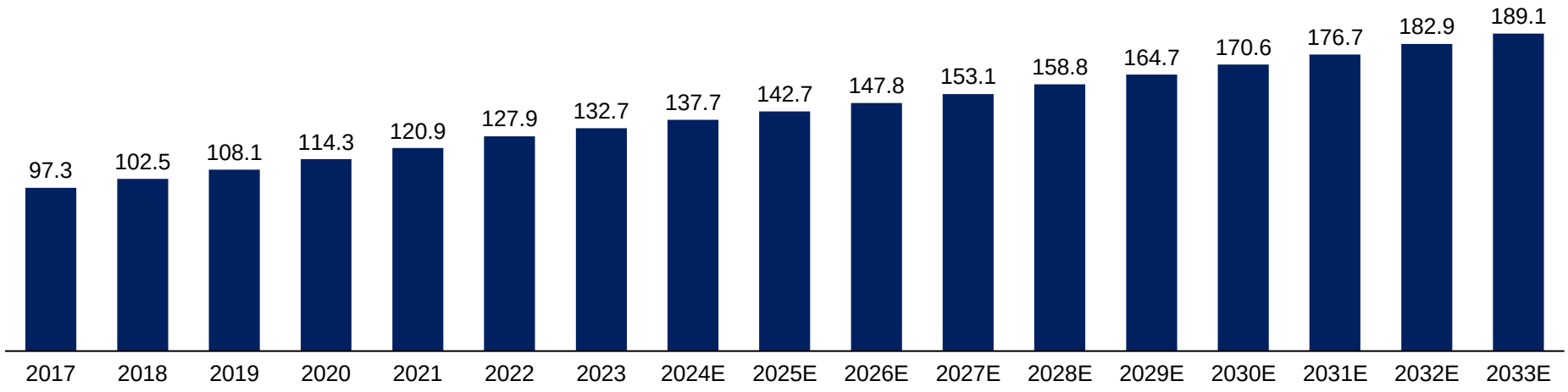
Incidence of Prostate cancer in China，2017-2033E

- Along with the rising economic level in China, improving living standards and lengthening life expectancy, the incidence of prostate cancer in China has shown an upward trend and is gradually becoming an important disease affecting the health of middle-aged and elderly men in China. The number of new prostate cancer cases in China grew from 97.3 thousand in 2017 to 132.7 thousand in 2023, with a compound annual growth rate of 5.3%. This number will continue to grow and reach 153.1 thousand in 2027 and 189.1 thousand in 2033, with CAGRs of 3.6% from 2023-2027 and 3.6% 2027-2033, respectively.

Incidence of prostate cancer in China，2017-2033E

Period	CAGR
2017-2023	5.3%
2022-2027E	3.6%
2027E-2033E	3.6%

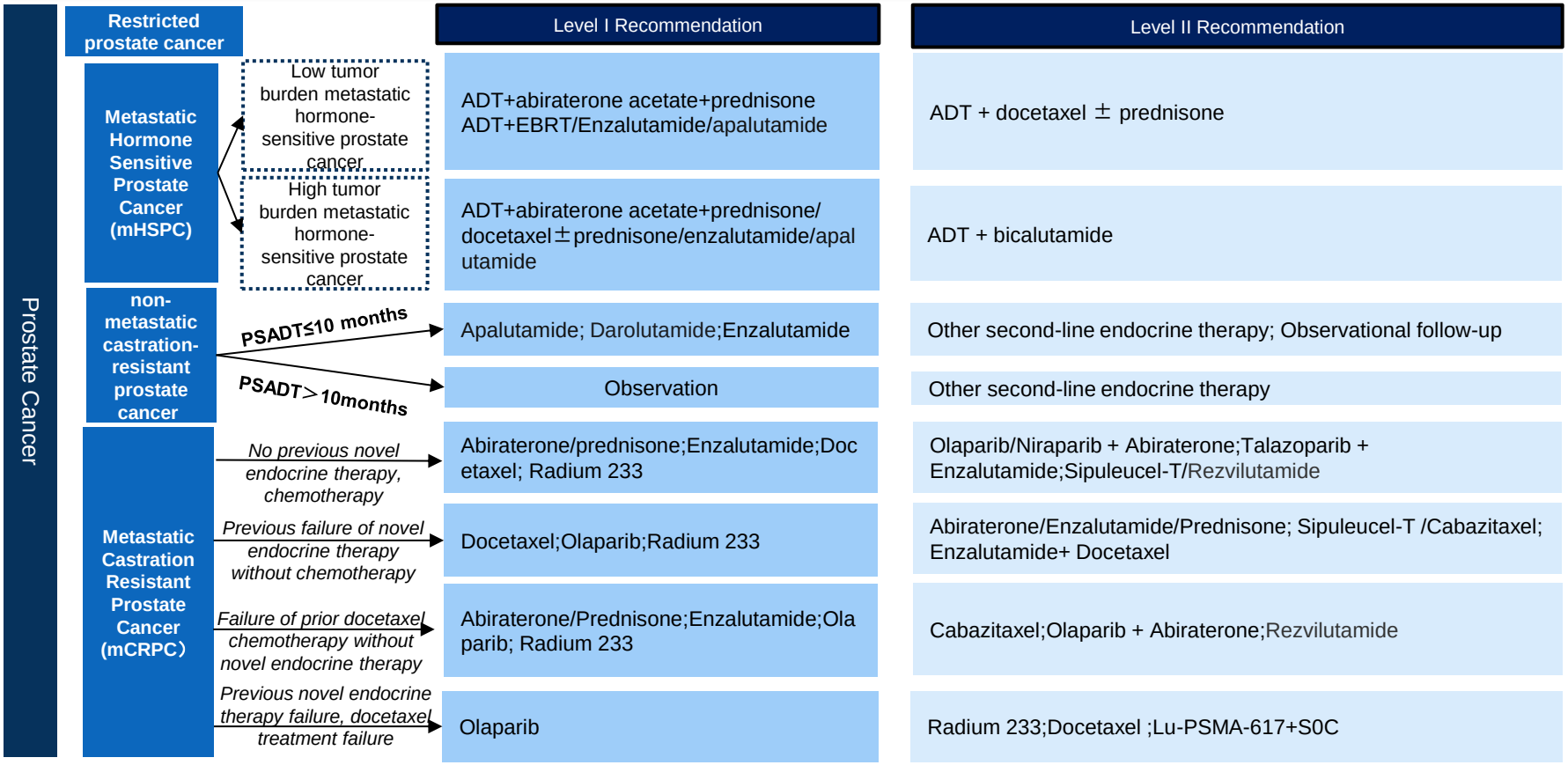
Thousand



Source: NCCR,IARC,Frost & Sullivan Analysis

Treatment Paradigm of Prostate Cancer in China

- Currently, abiraterone acetate has been unanimously recommended by national guidelines for the first-line treatment of patients with Metastatic Castration Resistant Prostate Cancer (mCRPC). Prostate cancer is an androgen-sensitive tumor, and androgens play a key role in prostate carcinogenesis through their interaction with the androgen receptor (AR). 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 dysregulated and resistant in prostate cancer after abiraterone treatment, and new therapeutic options are urgently needed in the clinic. 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 will have potential synergistic anti-tumor efficacy in prostate cancer.



Source: CSCO,Frost & Sullivan Analysis

Overview of Metastatic Castration Resistant Prostate Cancer

- Castration-resistant prostate cancer (CRPC) is a form of advanced prostate cancer. With CRPC, the cancer no longer completely responds to treatments that lower testosterone. It shows signs of growth, like a rising PSA (prostate-specific antigen), even with low levels of testosterone.
- With **Metastatic CRPC (mCRPC),** the cancer stops responding to hormone treatment, and it is found in other parts of the body. It can spread to nearby lymph nodes, bones, the bladder, rectum, liver, lungs, and maybe the brain.
- Almost all advanced prostate cancer patients, after undergoing hormonal therapy, will eventually progress to castration-resistant prostate cancer (CRPC), with metastatic castration-resistant prostate cancer (mCRPC) being the primary cause of patient death. Despite some advancements in existing treatment methods, the 5-year survival rate for mCRPC patients remains low, highlighting the urgent need for novel treatment approaches.

Symptoms of mCRPC

Metastatic castration-resistant prostate cancer (mCRPC) is a type of prostate cancer that has spread to other parts of your body and is no longer responding to hormone treatment that lowers testosterone.There may be no signs or symptoms at all. If there are symptoms from mCRPC, they depend on the size of the tumors and where the cancer has spread.

- ☐ Signs of mCRPC may begin with:
- ✓ Trouble urinating
- ✓ Pain or blood in urine
- ✓ Feeling more tired or weak than normal
- ✓ Weight loss
- ✓ Shortness of breath
- ✓ Bone pain

Risk Factors

- Advancing Age
- Prior Androgen Deprivation Therapy
- Genetic Factors
- Ethnicity
- Elevated PSA Levels

Source: Literature Review, Frost & Sullivan Analysis

Treatment Paradigm of Metastatic Castration Resistant Prostate Cancer

- The main goal for treating mCRPC is to control symptoms and slow progress. Even though androgen deprivation therapy (ADT) or hormone therapy may no longer work completely to stop prostate cancer from growing, most of men with mCRPC remain on ADT because some prostate cancer cells will continue to respond to it. Other cells need additional treatment to keep the cells from forming.

Therapy Regimen	Level I Recommendation	Level II 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/Prednisone • 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

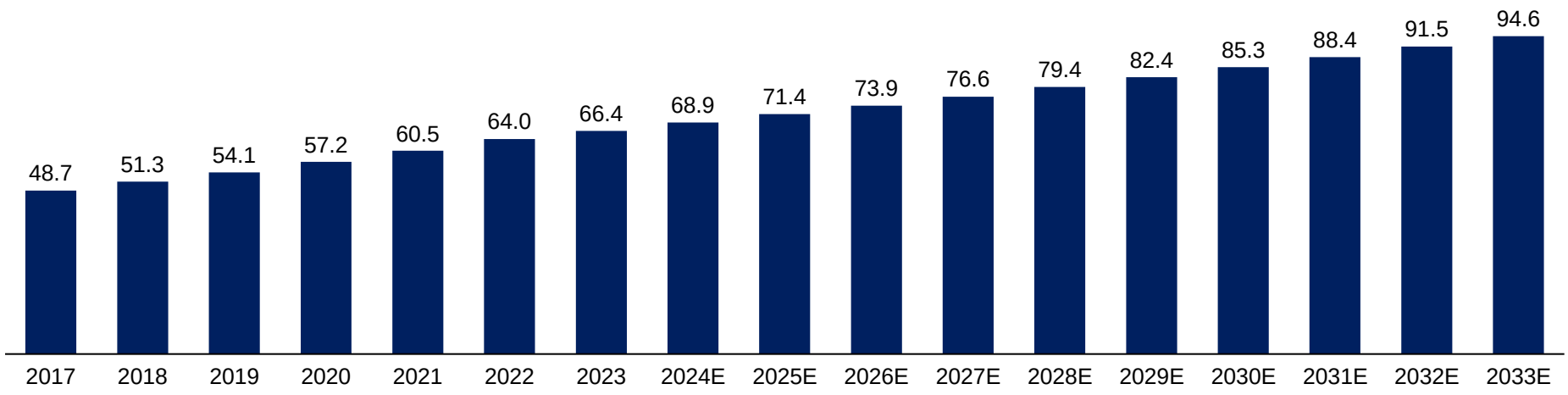
Source: CSCO,Frost & Sullivan Analysis

Incidence of Metastatic Castration Resistant Prostate Cancer in China, 2017-2033E

- In 2017, the incidence of mCRPC in China reached 48.7 thousand, and reached 66.4 thousand in 2023 with a CAGR of 5.3 %. It is predicted that the number will continue to grow, and reach 76.6 thousand by the year of 2027, 94.6 thousand by the year of 2033, with CAGR of 3.6 % and 3.6 % respectively.

Incidence of Metastatic Castration Resistant Prostate Cancer in China, 2017-2033E

Period	CAGR
2017-2023	5.3%
2023-2027E	3.6%
2027E-2033E	3.6%



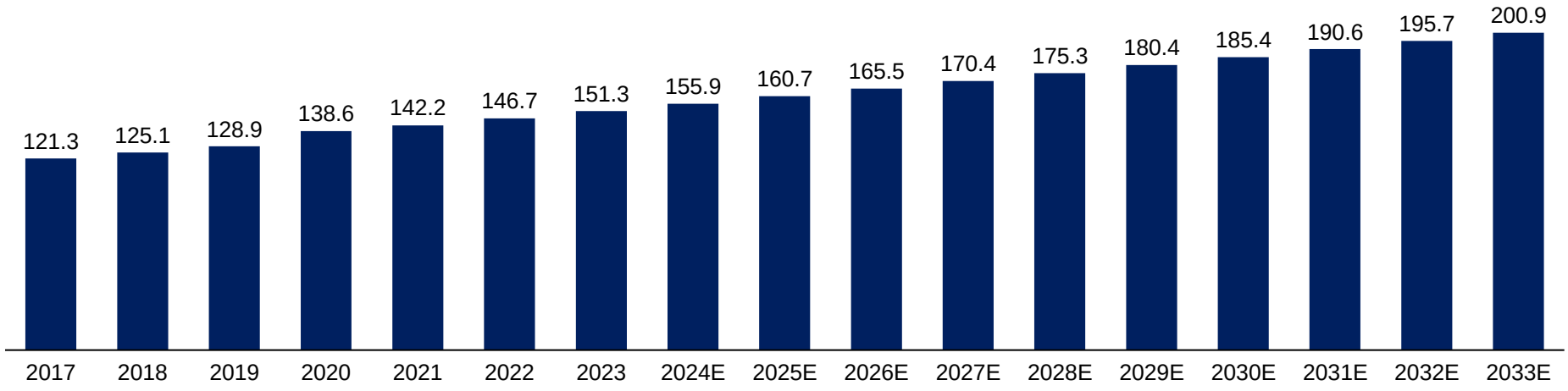
Source:Frost & Sullivan Analysis

Global incidence of Metastatic Castration Resistant Prostate Cancer, 2017-2033E

- In 2017, the global incidence of mCRPC reached 121.3 thousand, and reached 151.3 thousand in 2023 with a CAGR of 3.8%. It is predicted that the number will continue to grow, and reach 170.4 thousand by the year of 2027, 200.9 thousand by the year of 2033, with CAGR of 3.0 % and 2.8 % respectively.

Global incidence of Metastatic Castration Resistant Prostate Cancer, 2017-2033E

Period	CAGR
2017-2023	3.8%
2023-2027E	3.0%
2027E-2033E	2.8%



Source:Frost & Sullivan Analysis

Metastatic Castration Resistant Prostate Cancer Treatment – Unmet Needs(1/2)

- Currently, the unmet clinical need for mCRPC therapy consists mainly of limited therapeutic options in the mCRPC phase and a high incidence of bone metastasis,and addressing drug resistance in mCRPC therapy

Lack of therapeutic options

- Fewer drug treatments available, urgent need for prolonged survival.
- The current approved primary treatment option for adult patients with metastatic depot-resistant prostate cancer (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.

High incidence of bone metastasis

- Long-term androgen deprivation therapy treatment, and tumor bone metastasis all contribute to the development of bone-related events (SREs), including pathologic fractures, spinal cord compression, orthopedic surgical interventions, and palliative radiotherapy for bone metastases. The relative risk of fracture is elevated by 50-70% after endocrine therapy. Bone metastases account for a large proportion of Chinese prostate cancer patients at diagnosis. The proportion of Chinese patients with bone metastases at the time of prostate cancer diagnosis is 54%, and 80% of mCRPC patients with bone metastases experience bone pain.

Source:Frost & Sullivan Analysis

Metastatic Castration Resistant Prostate Cancer Treatment – Unmet Needs(2/2)

- Currently, the unmet clinical need for mCRPC therapy consists mainly of limited therapeutic options in the mCRPC phase and a high incidence of bone metastasis,and addressing drug resistance in mCRPC therapy

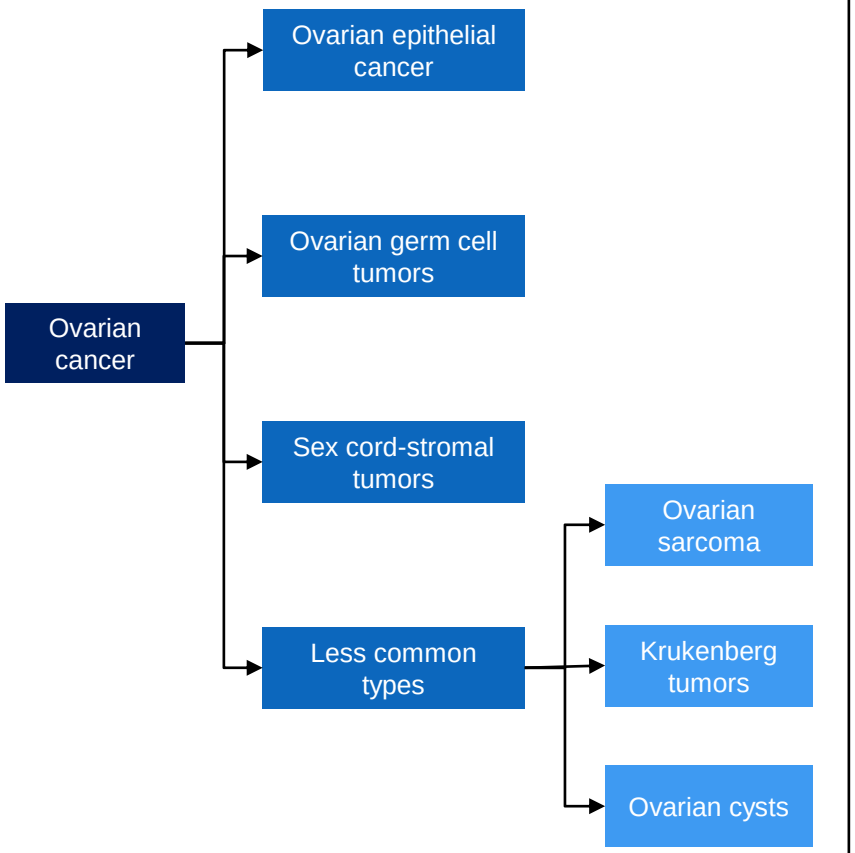
Addressing drug resistance in mCRPC therapy

- The majority of patients with castrate-resistant prostate cancer will have metastatic disease at the time of diagnosis. Investigative efforts on new therapeutics for this patient population have improved with the development of androgen signaling inhibitors and PARP inhibitors to accompany the previously FDA-approved docetaxel, cabazitaxel, sipuleucel-T, and Radium 223. However, new therapeutic strategies are necessary to prolong survival as progression after these agents is inevitable. Unmet clinical needs remain for the management of castrate-sensitive prostate cancer (CSPC) and castrate-resistant prostate cancer (CRPC). Dysregulation of the cyclin-dependent kinase (CDK) pathway can lead to tumorigenesis in prostate cancer cells, and CDK4/6 inhibitors have been shown to disrupt androgen receptor signaling in tumors resistant to antiandrogens. The resistance mechanisms to CDK4/6 inhibitors Optimized the efficacy in the treatment of metastatic castration-resistant prostate cancer (mCRPC)

*Source:Frost & Sullivan Analysis,*Kase AM, Copland Iii JA, Tan W. Novel Therapeutic Strategies for CDK4/6 Inhibitors in Metastatic Castrate-Resistant Prostate Cancer.

Overview of Ovarian Cancer

Category of Ovarian Cancer



Overview

1 Brief Introduction

- Ovarian cancer develops in the ovaries, which are the female reproductive glands that produce eggs during a woman's reproductive years. Ovarian cancer develops when cells in the ovaries begin to grow out of control.

2 Symptom

- Early warning signs: Abdominal bloating, indigestion or nausea, changes in appetite, pressure in the pelvis or lower back, a more frequent or urgent need to urinate and/or constipation, changes in bowel movements, increased abdominal girth, tiredness or low energy, changes in menstruation.
- Advanced: Ovarian cysts, masses or tumors

3 Diagnosis

- CT scan, MRI, PET/CT scan, Ultrasound (Imaging tests)
- Advanced genomic testing, nutrition panel, CA-125 test(lab tests); Pelvic exam

4 Risk Factors

- Age (55&above); Family history
- Genetic mutations (BRCA1&BRCA2)
- Lynch syndrome and Peutz-Jeghers syndrome
- Breast, colorectal or endometrial cancer

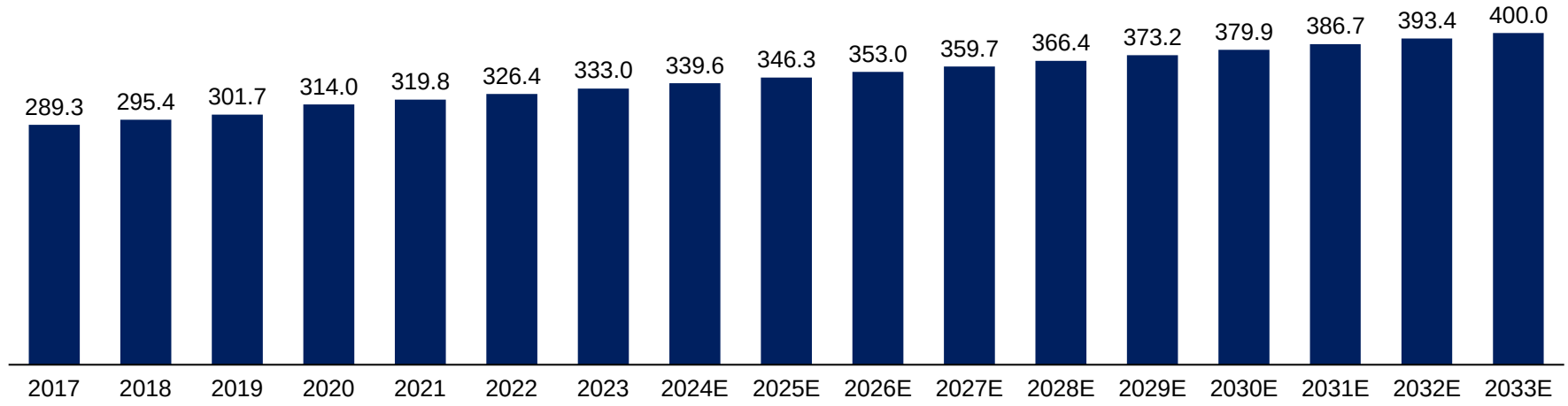
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of Ovarian cancer，2017-2033E

- Ovarian cancer is considered as the most dangerous type of gynecological malignant tumor. Due to the insidious and nonspecific early symptoms of ovarian cancer, about 80% of patients are diagnosed at advanced stages, and the 5-year survival rate is only 40%, so the prognosis is poor. The number of ovarian cancer cases globally grew from 289.3 thousand in 2017 to 333.0 thousand in 2023, with a compound annual growth rate of 2.4%. According to projections, this number will continue to grow and reach 359.7 thousand in 2027 and 400.0 thousand in 2033, with CAGRs of 2.0% and 1.8% between 2023-2027 and 2027-2033, respectively.

Global incidence of ovarian cancer，2017-2033E

Period	CAGR
2017-2023	2.4%
2023-2027E	2.0%
2027E-2033E	1.8%



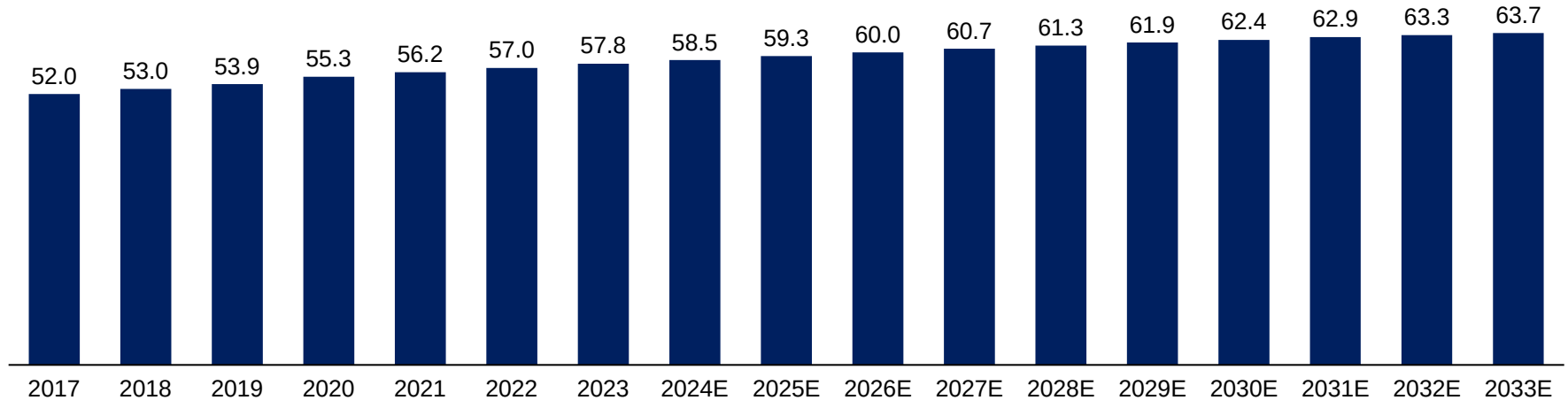
Source: NCCR,IARC,Frost & Sullivan Analysis

Incidence of Ovarian cancer in China，2017-2033E

- Ovarian cancer is one of the common malignant tumors of female reproductive system, which seriously threatens the life and health of women all over the world. Due to the insidious onset of ovarian cancer and the lack of effective screening and early diagnostic methods, most patients are found in advanced stages, so the prognosis is poor. The number of ovarian cancer cases in China increased from 52.0 thousand in 2017 to 57.8 thousand in 2023, with a compound annual growth rate of 1.8%. According to forecasts, this number will continue to grow and reach 60.7 thousand in 2027 and 63.7 thousand in 2033, with CAGRs of 1.2% and 0.8% between 2023-2027 and 2027-2033, respectively.

Incidence of Ovarian cancer in China，2017-2033E

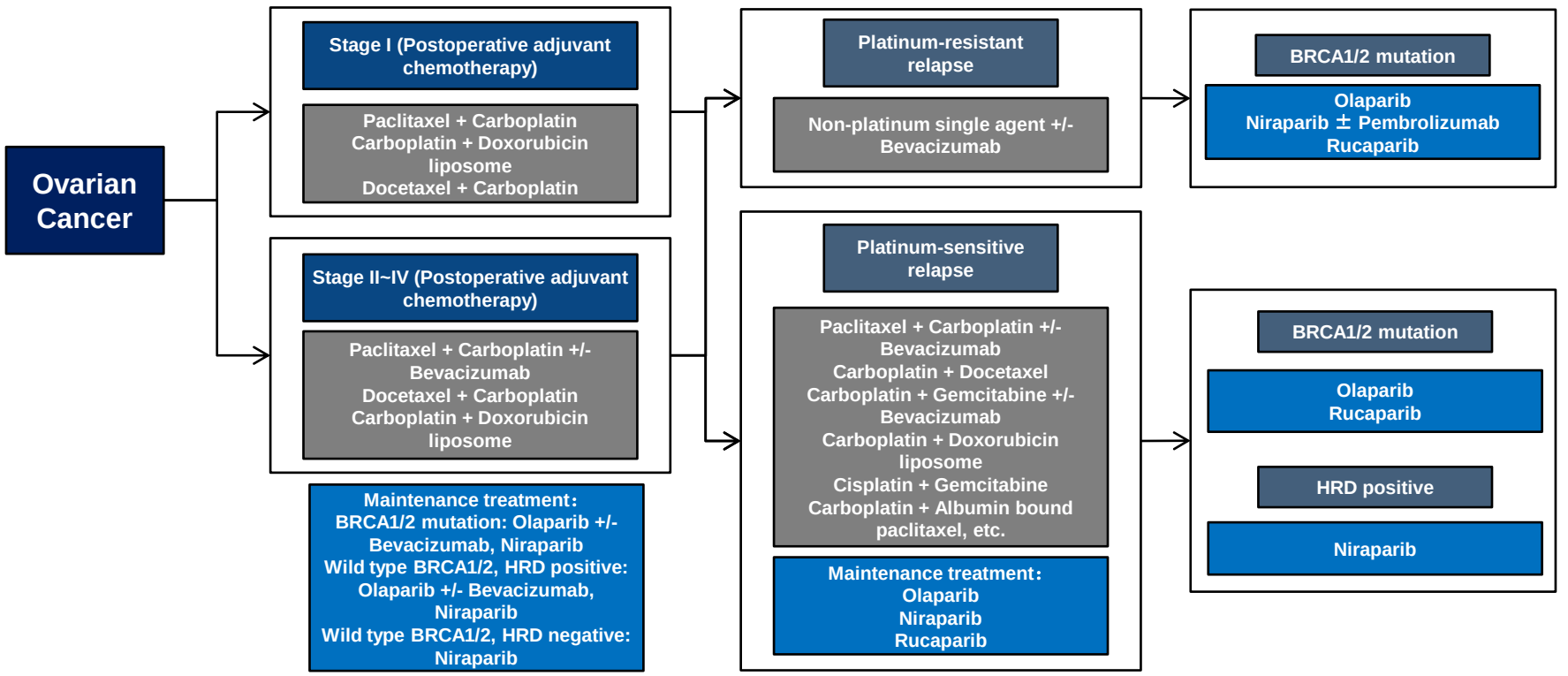
Period	CAGR
2017-2023	1.8%
2023-2027E	1.2%
2027E-2033E	0.8%



Source: NCCR,IARC,Frost & Sullivan Analysis

Treatment Paradigm of Ovarian Cancer in China

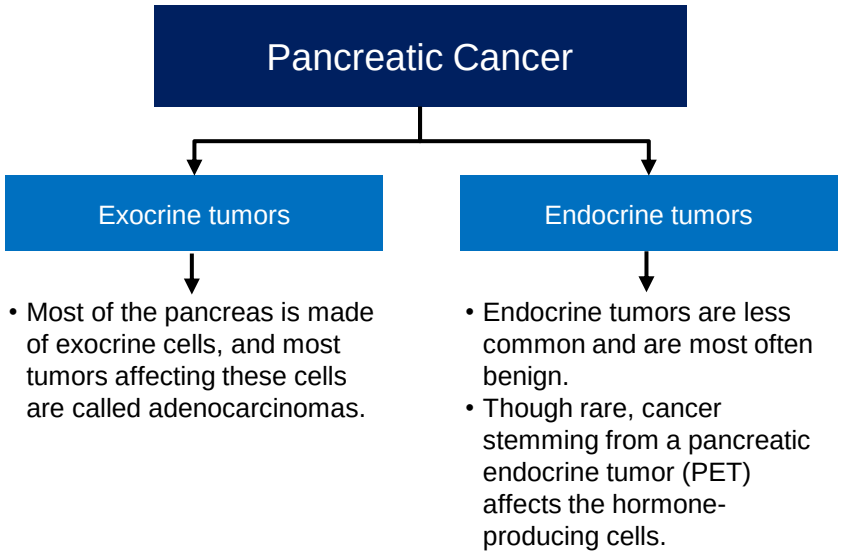
- The previous standard of care in China mainly consists of radical surgery and platinum-based chemotherapy. Although platinum-based chemotherapy is effective at inducing an initial response, an estimated 85% of patients with epithelial ovarian cancer who achieve a full remission following first-line therapy will develop recurrent disease.



Source: Guideline for Diagnosis and Treatment of Ovarian Cancer, Frost & Sullivan Analysis

Overview of Pancreatic Cancer

Category of Pancreatic Cancer



Overview

1 Brief Introduction

Pancreatic cancer is themalignancy with the mortality rate closest to the incidence rate.Pancreatic cancer is caused by the abnormal and uncontrolled growth of cells in the pancreas, a large gland that's part of the digestive system. The 5-year survival rate is around 9-11%..

2 Symptom

- Early warning signs: jaundice, sudden weight loss, dark-colored urine, itchy skin, digestive problems, pain in the upper abdomen, nausea, appetite loss, swollen gallbladder, blood clots, diabetes
- Advanced signs: worsening upper abdomen or back pain, extreme fatigue, swelling, bed sores, recently diagnosed diabetes

3 Diagnosis

- Biopsy; ERCP
- CT scan, MRI, ultrasound, x-ray, angiogram percutaneous transhepatic cholangiography,
- Advanced genomic testing, nutrition panel(Lab tests); Laparoscopy

4 Risk Factors

- Age (55&above); Gender (men>women)
- Obesity, diabetes, chronic pancreatitis, cirrhosis of the liver, H. pylori infection
- Smoking cigarettes; Mutations in Gene PRSS1/NF1/BRCA2/p16

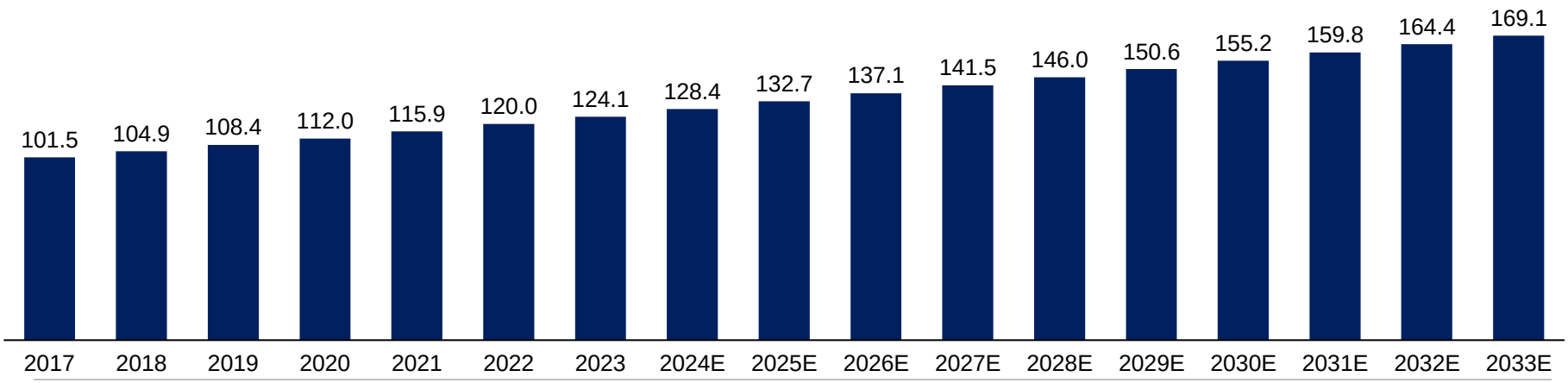
Source: Literature Review, Frost & Sullivan Analysis

Incidence of Pancreatic cancer in China，2017-2033E

- Pancreatic cancer is a tumor produced by cancerous transformation of pancreatic cells, and these tumor cells have the ability to invade other tissues. Pancreatic cancer has insidious onset and atypical early symptoms, which often include dyspepsia, diarrhea, epigastric discomfort or low back pain, and is easily confused with other digestive diseases. Pancreatic cancer in China is characterized by low early diagnosis rate, low surgical resection rate and low drug efficiency. As a digestive tumor with extremely poor prognosis, pancreatic cancer has clinical features such as difficulty in early diagnosis, low surgical resection rate, and easy recurrence and metastasis after surgery, which makes clinical diagnosis and treatment very challenging.
- The number of pancreatic cancer cases in China increased from 101.5 thousand in 2017 to 124.1 thousand in 2023, with a compound annual growth rate of 3.4%. The number is expected to continue to grow and reach 141.5 thousand in 2027 and 169.1 thousand in 2033, with CAGRs of 3.3% and 3.0% between 2023-2027 and 2027-2033, respectively.

Incidence of Pancreatic cancer in China，2017-2033E

Period	CAGR
2017-2023	3.4%
2023-2027E	3.3%
2027E-2033E	3.0%



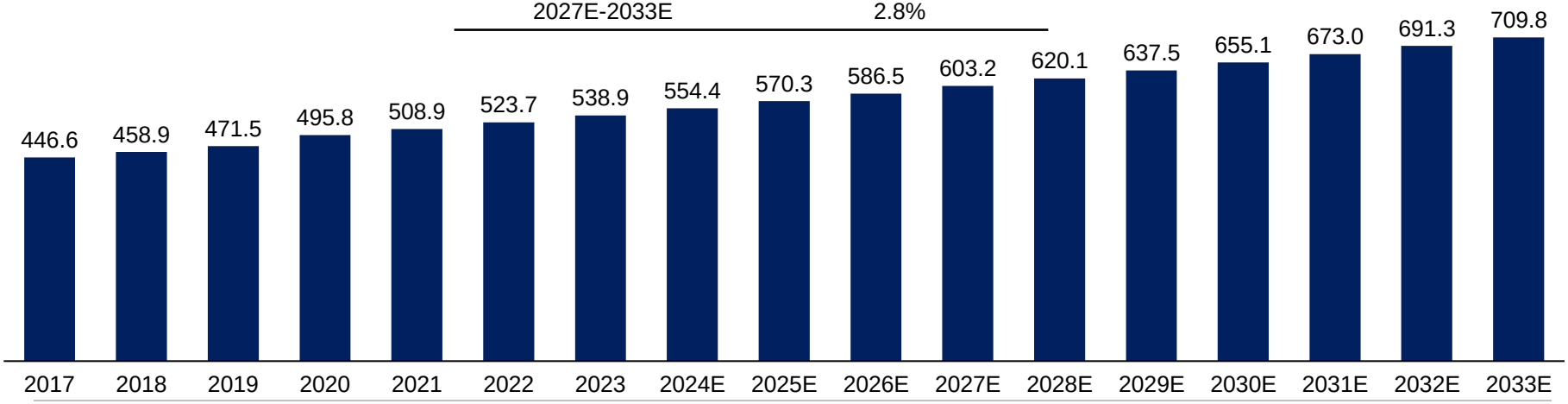
Source: NCCR,IARC,Frost & Sullivan Analysis

Global incidence of Pancreatic cancer，2017-2033E

- Pancreatic cancer is a highly malignant tumor and remains one of the deadliest types of cancer at this stage. Because of its relatively insidious clinical symptoms and its ability to invade peripheral tissues more rapidly, pancreatic cancer patients have poor 5-year survival rates, while trends in pancreatic cancer incidence and mortality vary widely around the world. The extremely high mortality rates and very low 5-year survival rates reflect a shortage of effective therapeutic agents, as well as a call for new treatment options or therapeutic agents.
- The number of pancreatic cancer cases globally increased from 446.6 thousand in 2017 to 538.9 thousand in 2023, with a compound annual growth rate of 3.2%. The number is expected to continue to grow and reach 603.2 thousand in 2027 and 709.8 thousand in 2033, with a CAGR of 2.9% and 2.8% between 2023-2027 and 2027-2033, respectively.

Global incidence of Pancreatic cancer，2017-2033E

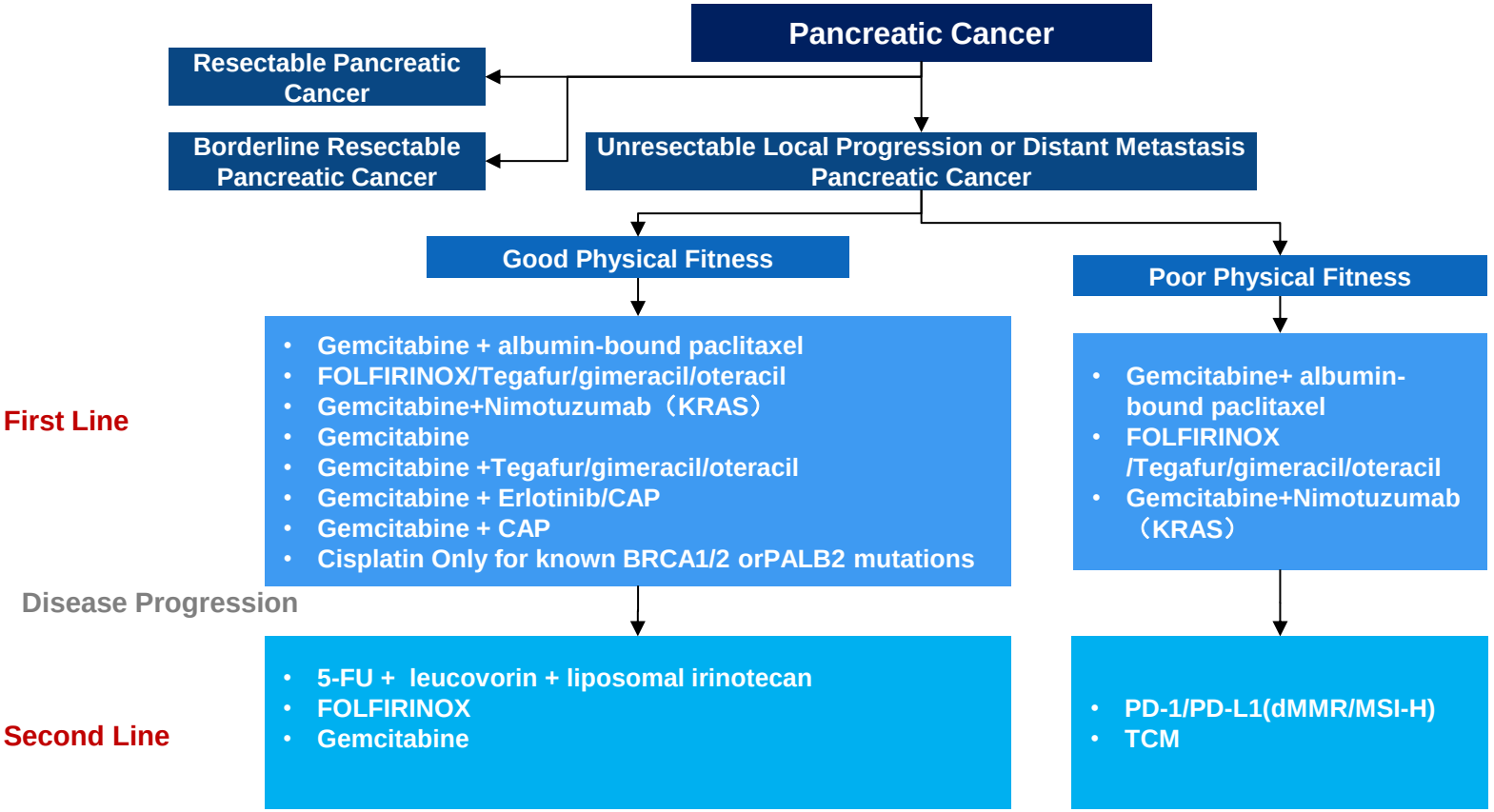
Period	CAGR
2017-2023	3.2%
2022-2027E	2.9%
2027E-2033E	2.8%



Source: NCCR,IARC,Frost & Sullivan Analysis

Treatment Paradigm of Pancreatic Cancer in China

- The treatment of pancreatic cancer mainly includes surgical treatment, radiotherapy, chemotherapy, interventional therapy, ERCP related treatment and TCM treatment. Currently, the option of targeted therapies is quite limited. Several targeted therapies have been shown to significantly impact outcomes.



Source: Diagnosis and treatment of pancreatic cancer (2022), Frost & Sullivan analysis

Overview of Small Cell Lung Cancer

Characteristics of Small Cell Lung Cancer

- Occurs mainly in the main and lobar bronchi
- Periportal masses common (~70%)Highly malignant
- Median survival after first-line chemotherapy relapse ~10 months
- SCLC remains one of the most lethal lung malignancies. There are currently few therapeutic options for patients with SCLC. Moreover, all seer stages combined SCLC five-year survival rate is less than 7%, the distant SCLC five-year survival rate is less than 3%.

Overview

1 Brief Introduction

- SCLC is a heterogeneous neuroendocrine tumor originating from Kulchitsky cells of the bronchial mucosal epithelium, and is the most aggressive subtype of lung cancer.
- SCLC accounts for 15% of all lung cancer patient.

2 Symptom

- Early symptoms are not too obvious and as the disease progresses gradually, the patient will develop a cough.
- If the condition is further aggravated, the patient may have symptoms of loss of appetite, fatigue and even anemia.

3 Diagnosis

- Enhanced CT of the chest,
- Enhanced CT of the abdomen and pelvis,
- Enhanced MRI or enhanced CT of the head
- Whole-body bone imaging.

4 Risk Factors

- Smoking
- Environmental factors (secondhand smoking), occupational exposures, hormones, etc.

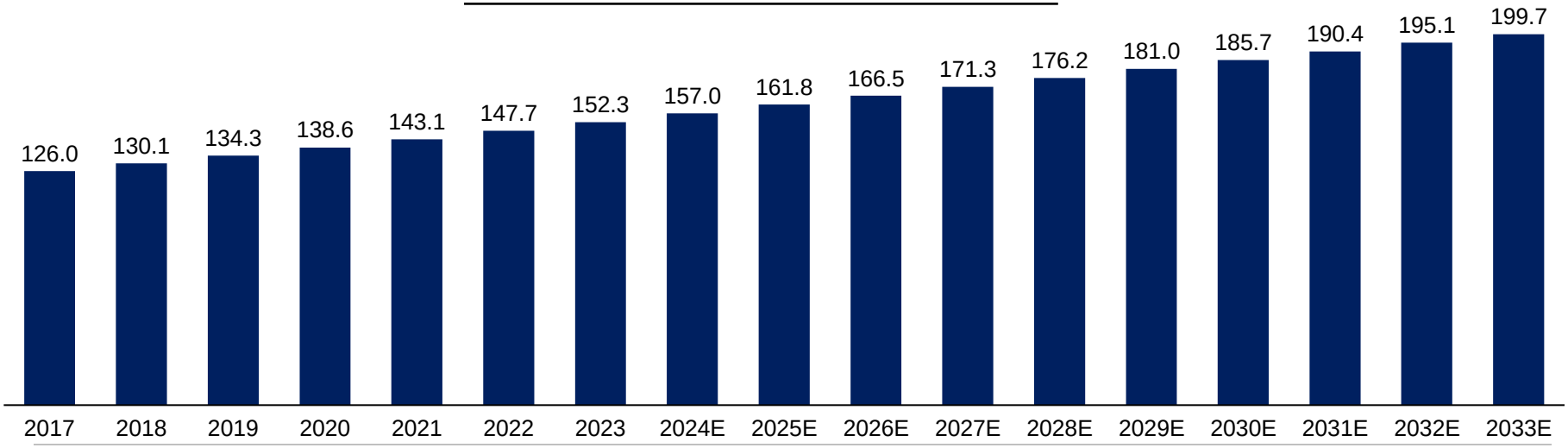
Source: Literature Review, Frost & Sullivan Analysis

Incidence of small cell lung cancer(SCLC) in China，2017-2033E

- In China, lung cancer is a malignant tumor with the highest incidence and mortality rates, and most patients are diagnosed at an advanced stage, often with a poor prognosis. The number of non-small cell lung cancer patients in China has continued to grow in recent years from 126.0 thousand in 2017 to 152.3 thousand in 2023, with a compound annual growth rate of 3.2% from 2017 to 2023. The number of people in the country is expected to continue to grow and reach 171.3 thousand in 2027 and 199.7 thousand in 2033 with CAGRs of 3.0% and 2.6% between 2023-2027 and 2027-2033, respectively.

Incidence of small cell lung cancer in China，2017-2033E

Period	CAGR
2017-2023	3.2%
2023-2027E	3.0%
2027E-2033E	2.6%



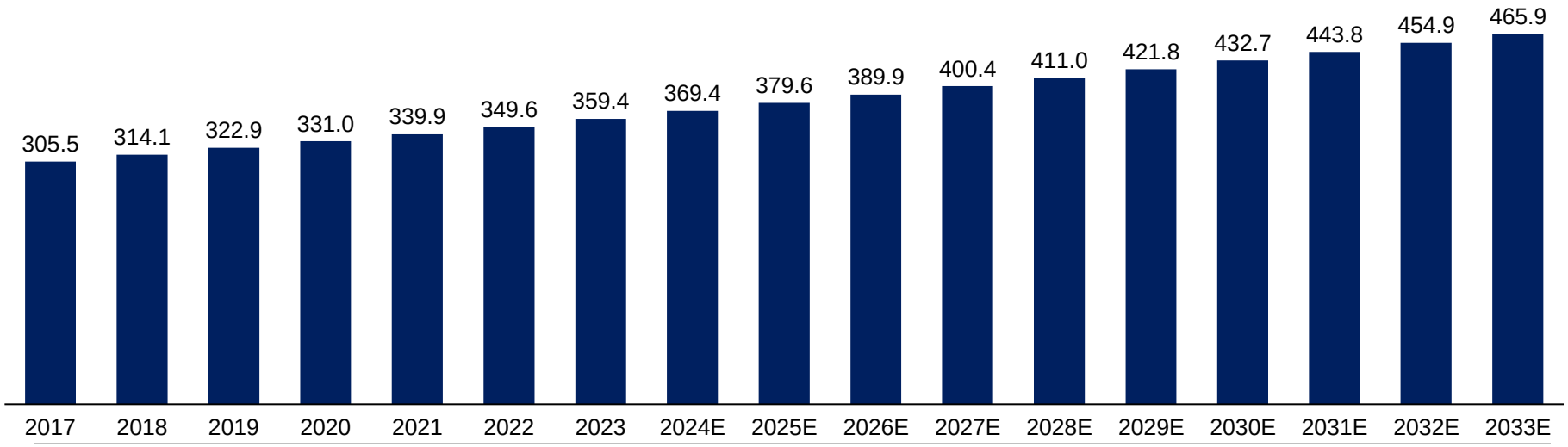
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of small cell lung cancer(SCLC)，2017-2033E

- The number SCLC cases globally increased from 305.5 thousand in 2017 to 359.4 thousand in 2023, with a compound annual growth rate of 2.8%. The number is expected to continue to grow and reach 400.4 thousand in 2027 and 465.9 thousand in 2033, with a CAGR of 2.7% from 2023-2027 and 2.6% from 2027-2033, respectively.

Global incidence of small cell lung cancer，2017-2033E

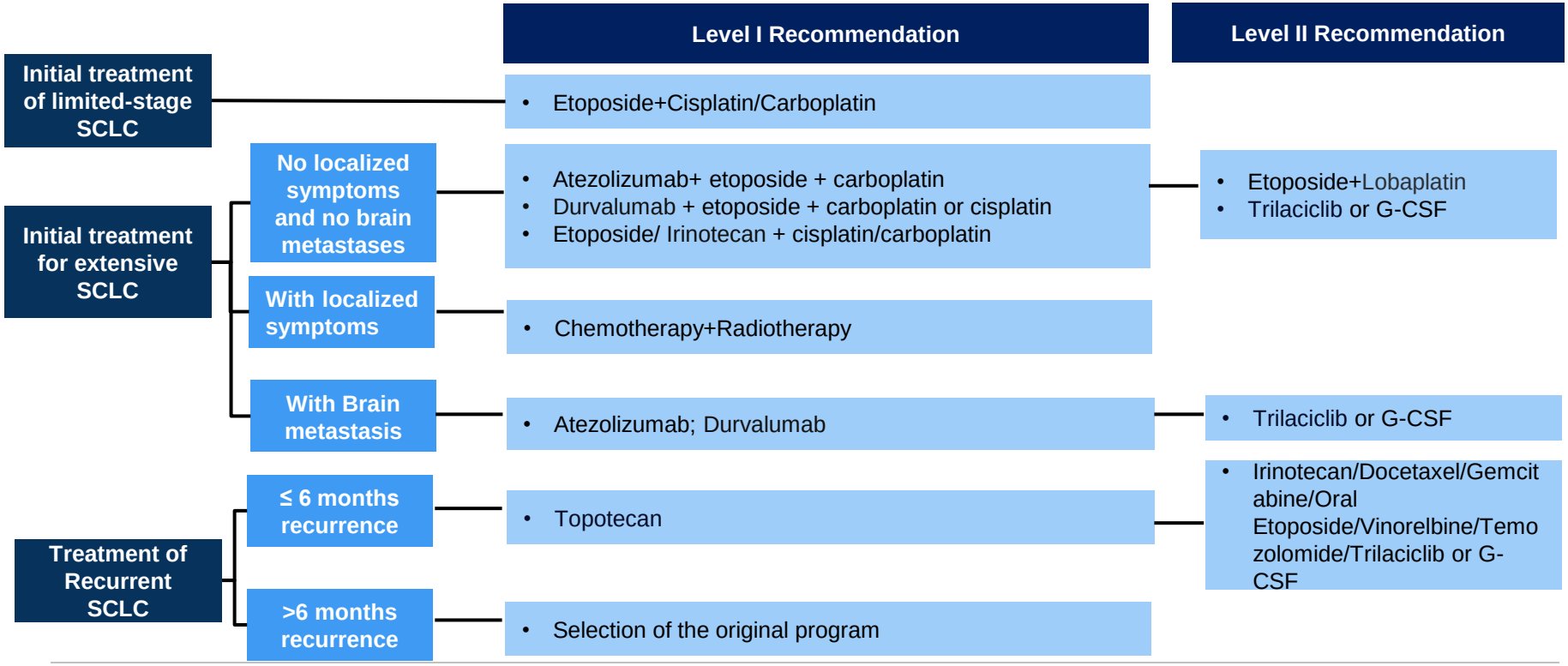
Period	CAGR
2017-2023	2.8%
2023-2027E	2.7%
2027E-2033E	2.6%



Source: Literature Review, Frost & Sullivan Analysis

Treatment Paradigm of small cell lung cancer(SCLC) in China

- For the majority of patients, diagnosis of extensive-stage small cell lung cancer (SCLC) often occurs at an advanced stage. Chemotherapy is the primary treatment modality for extensive-stage SCLC patients, but resistance to chemotherapy drugs is common during the treatment process, leading to inevitable tumor recurrence. Therefore, the development of novel drugs is crucial. In recent years, targeted therapy has gained popularity in the treatment of non-small cell lung cancer (NSCLC) patients. However, the treatment for small cell lung cancer patients is still in the experimental stage, and targeted therapy drugs applicable to SCLC patients have not been identified yet. CDK7 is unique in that it is involved in both transcriptional and cell cycle regulation, is aberrantly overexpressed in many types of cancer, and is associated with aggressive clinicopathologic features and poor prognosis. Several selective CDK7 inhibitors have shown promising anticancer activity in many preclinical models and have entered clinical trials.



Source: Literature Review, Frost & Sullivan analysis

Overview of CDK

Early development efforts focused on the development of unselective CDK inhibitors, with activities against multiple CDKs. For example, alvocidib, which inhibits CDK 1, 2, 4, 6,7 and 9, and seliciclib, which inhibits DK1, 2, 5, 7, and 9 have entered clinical trials and been assessed for various types of tumors. However, these drugs showed limited clinical activities. It is because many CDK proteins are critical for the function of normal tissues, and the promiscuity 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. 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 will eventually develop progressive disease due to intrinsic or acquired drug resistance. It has been found that when CDK 4/6 activity is inhibited, tumor cells can leverage CDK 2-CDK 2 Cyclin E activation as a complementary compensatory pathway to facilitate the proliferation of tumor cells. To combat resistance stemming from CDK4/6 inhibitors, one of the ongoing development efforts focuses on the CDK2/4/6 inhibitor to address this challenge. In addition, efforts are also made to explore CDK's role in regulating DNA transcription. The recently developed, highly specific inhibitors of CDK7 have been instrumental in revealing the potential of CDK7 as a cancer drug target. Xenograft studies in mice showed that CDK7 inhibitors are well tolerated and effective at reducing tumor growth in vivo, making CDK7 inhibitors promising candidates for cancer treatment.

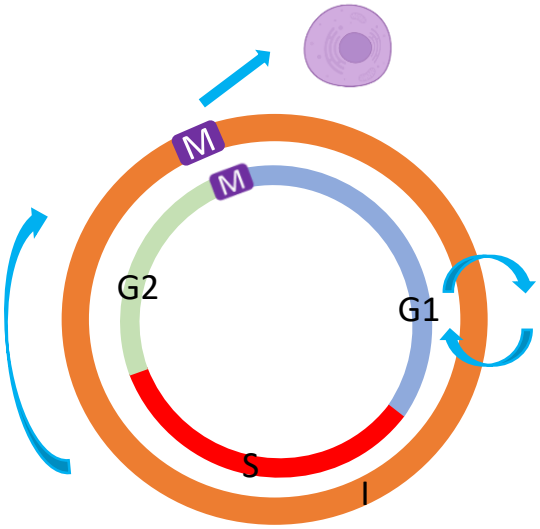
- Cell cycle regulation is complex and comprises two major phases:The former can be subdivided into three phases: G1 phase for preparing for DNA synthesis, S phase for DNA synthesis, and finally, G2 phase for preparing for cell division. The M phase includes prophase, metaphase, anaphase, and telophase. After M phase, one cell will be divided into two daughter cells. During interphase, the G1-S transition is a critical restriction point, resulting in one of three fates for the cell: continue cycling, exit active proliferation, or enter a quiescent (G0) state. Many growth factors and inhibitors interact to coordinate cell cycle progression, and the CDK4/6-Rb pathway plays a central role in regulating the G1 to S phase transition.
- Since activity of CDKs is associated with induction of stem cell properties, drugs targeting these proteins might be used for effective elimination of cancer stem cells and reduction of tumor metastases. This implicates that CDKs are involved in the pathogenesis of a high spectrum of cancers, including different types of carcinomas as well as non-epithelial malignancies. Coming from this point of view, CDKs will come more and more in the focusas therapeutical targets.

- CDKs require the presence of cyclins to become active. Cyclins are a family of proteins that have no enzymatic activity of their own but activate CDKs by binding to them. CDKs must also be in a particular phosphorylation state — with some sites phosphorylated and others dephosphorylated — in order for activation to occur. Correct phosphorylation depends on the action of other kinases and a second class of enzymes called phosphatases that are responsible for removing phosphate groups from proteins.

Source: Literature Review, Frost & Sullivan analysis

CDK landscape and functions

- Cell cycle protein-dependent kinases (CDKs), a family of protein kinases discovered for their regulatory role in the cell cycle, are also involved in transcriptional regulation, mRNA processing, and neuronal differentiation. This family of enzymes is present in all known eukaryotes, and its regulatory role in the cell cycle is fairly well conserved in evolution. Indeed, yeast cells can still grow and divide normally after the CDK gene has been replaced by its human homologue. Cell cycle protein-dependent kinases (CDKs) are a group of serine/threonine kinases whose catalytic activity can be regulated by cell cycle proteins and CDK inhibitors. CDKs have roles in regulating cell cycle checkpoints and DNA transcription, and are thought to be a key class of regulators in cell division and proliferation.



The role of CDK in cancer therapy

Classification according to function

CDK is catalytically active only after binding to the regulatory subunit, cyclin, to form a heterodimer.

Currently, cell cycle protein-dependent kinases are divided into two main types:

- One type is cell cycle-associated kinases, which mainly regulate various stages of the cell cycle, including CDK1, CDK2, CDK3, CDK4 and CDK6;
- The other types are transcription-related kinases, which mainly regulate the process of gene transcription, including CDK7, CDK8, CDK9, CDK11, CDK12 and CDK13.

CDK, belonging to the serine/threonine protein kinase family, has been reported to have 20 different family isoforms, all of which contain a homologous sequence of PSTAIRE, which binds to the corresponding regulatory subunit, cyclin, to form active heterodimers involved in physiological processes, such as transcription, metabolism, neural differentiation and development. In clinical studies, CDK inhibitors have been used not only for the treatment of various types of cancers, but also for the treatment of various non-cancer diseases, such as inflammatory diseases, central nervous system diseases and infectious diseases. This suggests that CDK plays an important role in the pathology of many cancer and non-cancer diseases.

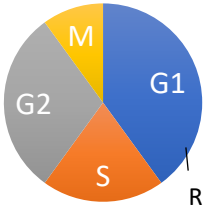
Source: Literature Review, Frost & Sullivan analysis

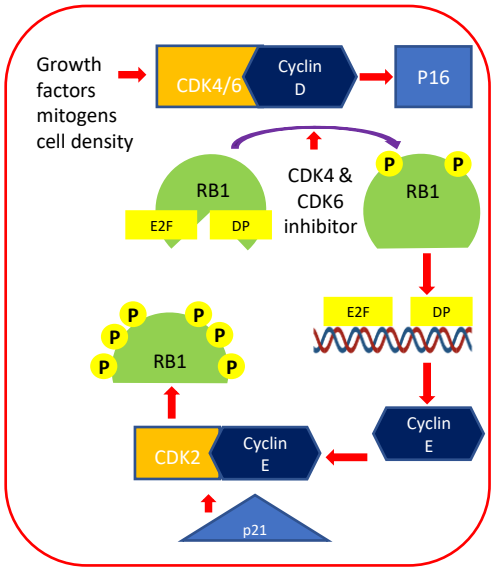
Mechanism of action of cell cycle protein-dependent kinases

- The cell cycle is a fundamental process of cellular life activity, which controls the shift from the quiescent phase to the growth and proliferation phase. Fine cell cycle protein-dependent kinases (CDKs) and cell cycle proteins (Cyclins) are the core molecules in the whole cell cycle regulatory mechanism. Cell cycle dysregulation is a common feature of human cancers, and inhibitors of cell cycle protein-dependent kinases (CDKs) play a crucial role in cell cycle control and represent one of the most promising areas of cancer therapy. Cell cycle protein-dependent kinases are members of the serine/threonine kinase family, a dimeric complex of cell cycle-catalyzed kinase subunits and regulatory subunits, and eleven CDK members have been identified.The mechanism of CDK regulation relies on both positive phosphorylation (CDK agonist kinase, CAK) and negative phosphorylation (Weel, Myt1), as well as related functions with the ability to drive the highly interconnected regulatory mechanisms assembled by the CDK-cell cycle protein complexes that drive the cell cycle.

Antitumor mechanisms of cell cycle protein-dependent kinases

- **Regulates transcription levels.** Studies have shown that cellular transcription remains at a low level during mitosis and is reactivated only when mitosis ends.CDK9 and CDK12 regulate cellular transcription. Research in the field of cell cycle therapeutics is focused on finding inhibitors of transcription CDKs.
- **Activation of anti-tumor immunity.** Studies have confirmed that CDK4/6 inhibitors not only induce tumor cell cycle arrest, but also promote anti-tumor immunity: first, CDK4/6 inhibitors activate the expression of endogenous retroviral components in tumor cells and increase intracellular double-stranded RNA levels, which in turn stimulate the production of type III interferon and increase the delivery of tumor antigens; second, CDK4/6 inhibitors markedly inhibit the proliferation of regulatory T cells, promote cytotoxic T cell clearance of tumor cells. This is the theoretical basis of CDK4/6 inhibitors combined with tumor immunotherapy.
- **Control of cellular metabolic functions.** Cell division requires cyclin and CDKs, key cell cycle regulatory proteins, and the cyclin-CDKs complex can regulate cell metabolism and thus cause tumor regression. Studies have shown that cyclin D3-CDK6 kinase phosphorylates and inhibits the metabolic activity of two key enzymes in the glucose metabolism pathway (fructose 6-phosphate kinase and pyruvate kinase M2), which directly activates the pentose phosphate pathway and the serine pathway of glucose metabolism.



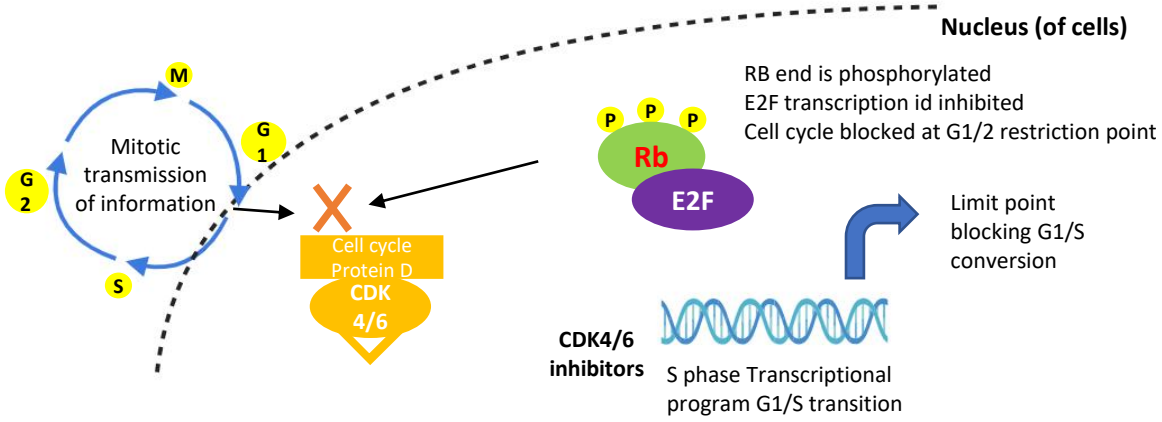


Source: Literature Review, Frost & Sullivan analysis

Overview of CDK4/6 Inhibitor Drugs

- CDK4/6, cell cycle protein-dependent kinases 4 and 6, are key regulatory proteins in the cell division and proliferation cycle of human cells, triggering the transition of the cell cycle from G1 phase to S phase. The cell cycle refers to the entire process that a cell undergoes from the completion of one division to the end of the next division, including the three processes of cell growth, replication and division. Each phase of the cell cycle has checkpoints that are tightly controlled by CDK, including cyclin and cyclin-dependent kinase (CDK). These checkpoints prevent cells with abnormalities from continuing to activate the cell cycle. The transition from the G1 phase of cell growth to the S phase, where deoxyribonucleic acid (DNA) replication occurs, is a key checkpoint in the cell cycle that is regulated by CDK4/6, and thus the CDK4/6 complex may serve as a therapeutic target for cancer. Under pathological conditions, the activity of CKD4/6 is abnormally high, and when combined with Cyclin D, it phosphorylates retinoblastoma protein and leads to the release of transcription factor E2F, which regulates the transcription of genes related to DNA replication.CDK4/6 inhibitors can effectively block the activity of CDK4/6, restoring the control of the cell cycle, blocking the proliferation of tumor cells, and thus inhibiting the growth of cancer cells Inhibitors of CDK4/6
- The cyclin-dependent kinase CDK4/6 is a key regulator of the cell cycle and, by forming a complex with cyclin D, phosphorylates Rb and then releases the transcription factor E2F, which facilitates the transcription of cell-cycle-related genes and allows cells to enter the Sphase. CDK4/6 inhibitors efficiently block the progression of tumor cells from the G1 phase to the S-phase.

Mechanism of action of CDK4/6 inhibitors

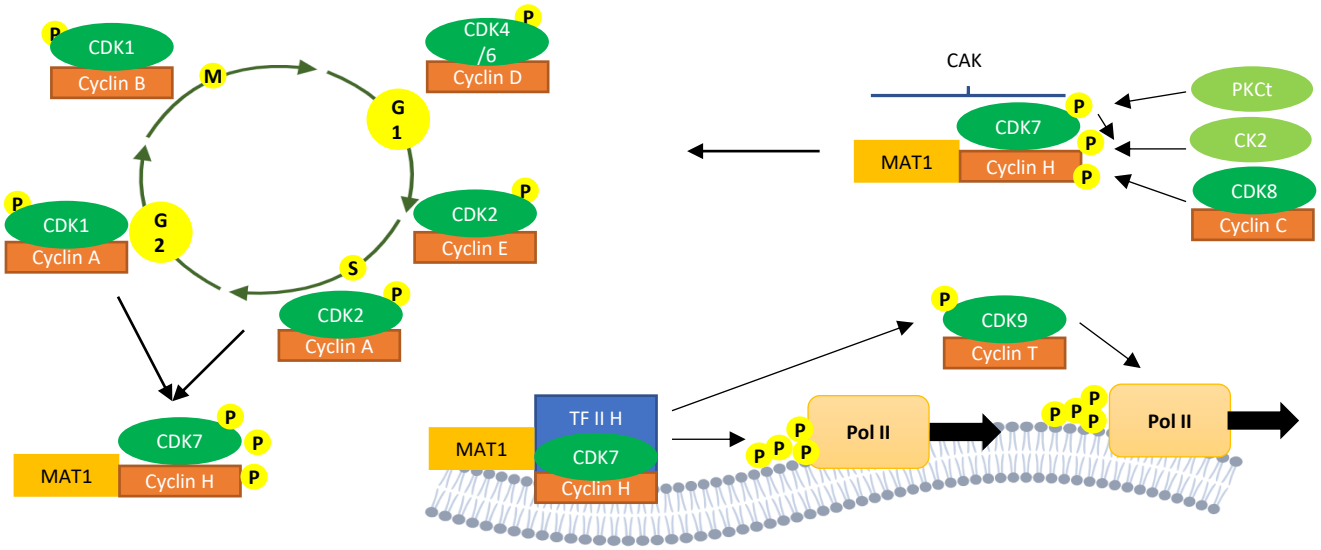


Source: Otto T. et al. Nal RevCancer. 2017:17:93.115, Frost & Sullivan analysis

Overview of CDK 7 Inhibitor

- CDK7, a member of the cyclin-dependent kinases (CDK) family and a subunit of the multiprotein basic transcription factor TFIIH, is a major regulator of cell cycle progression and gene transcription. During the cell cycle, CDK7 binds to the cell cycle protein H to form a cell cycle kinase and controls the cell cycle, especially in cancer cells, by activating other kinases in the family. CDK7 is also involved in the formation of the multiprotein-based transcription factor TFIIH, which plays a key role in cell cycle transcription and regulation, and interacts with other kinases regulated by the multiprotein-based transcription factor TFIIH. Researches have shown that the growth and proliferation of multiple tumor cells are highly dependent on CDK7, including triple-negative breast cancer (TNBC), relapsed or refractory ovarian cancer (OC), pancreatic ductal adenocarcinoma (PDAC), and hematological tumors.

Mechanism of action of CDK 7 inhibitors

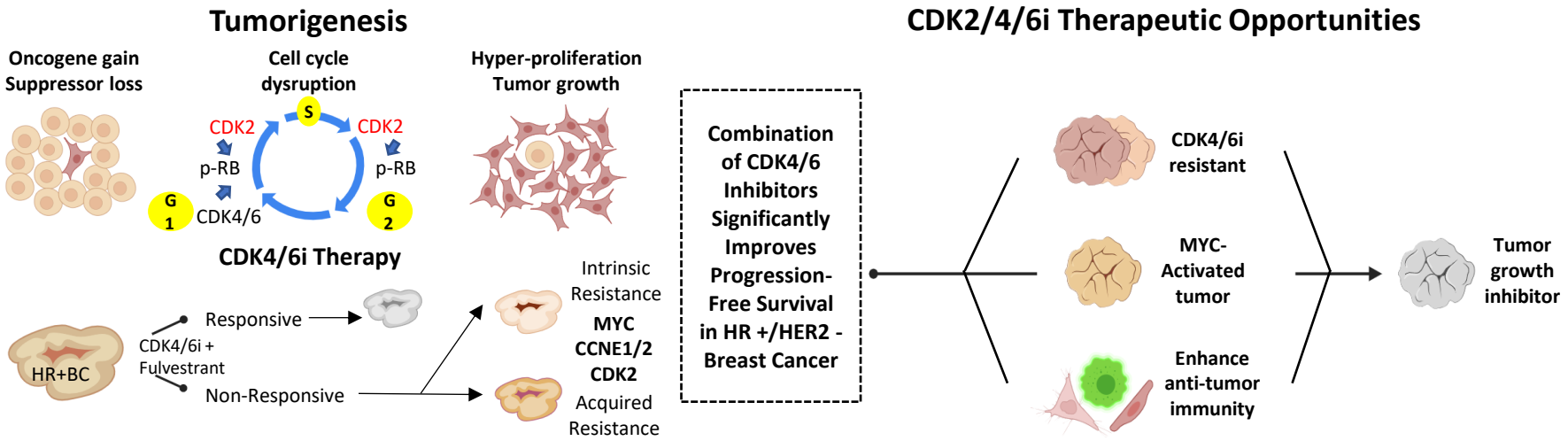


Source: Literature Review, Frost & Sullivan Analysis

Overview of CDK 2/4/6 Inhibitor

- With the application of CDK4/6 inhibitors in breast cancer treatment, overcoming drug resistance has become an important and yet to be urgently solved challenge, and the mechanism of drug resistance has been better understood. It has been found that when CDK4/6 activity is inhibited, with the amplification of Cyclin E and the activation of MYC, MYC up-regulation activates CDK2, and CDK2-Cyclin E can be used as a complementary compensatory pathway to phosphorylate Rb, release E2F, and contribute to the proliferation of tumor cells, which is the main mechanism of the acquired resistance to CDK4/6 inhibitors at present. Some clinical studies have shown that patients with high Cyclin E expression are insensitive to CDK4/6 inhibitors, and their progression-free survival is significantly shorter than that of patients with low Cyclin E expression. Inhibition of CDK2-Cyclin E avoids resistance caused by Cyclin E expansion, and this mechanism has been confirmed in CDK4/6 resistant cell lines. To achieve long-term efficacy, both CDK4 and CDK2 need to be inhibited, a novel therapeutic approach to inhibit breast cancer cells.CDK2/4/6 inhibitors were found to be effective in inhibiting the proliferation of human breast cancer cells with acquired resistance to CDK4/6 inhibitors in preclinical studies.

Mechanism of action of CDK 2/4/6 inhibitors



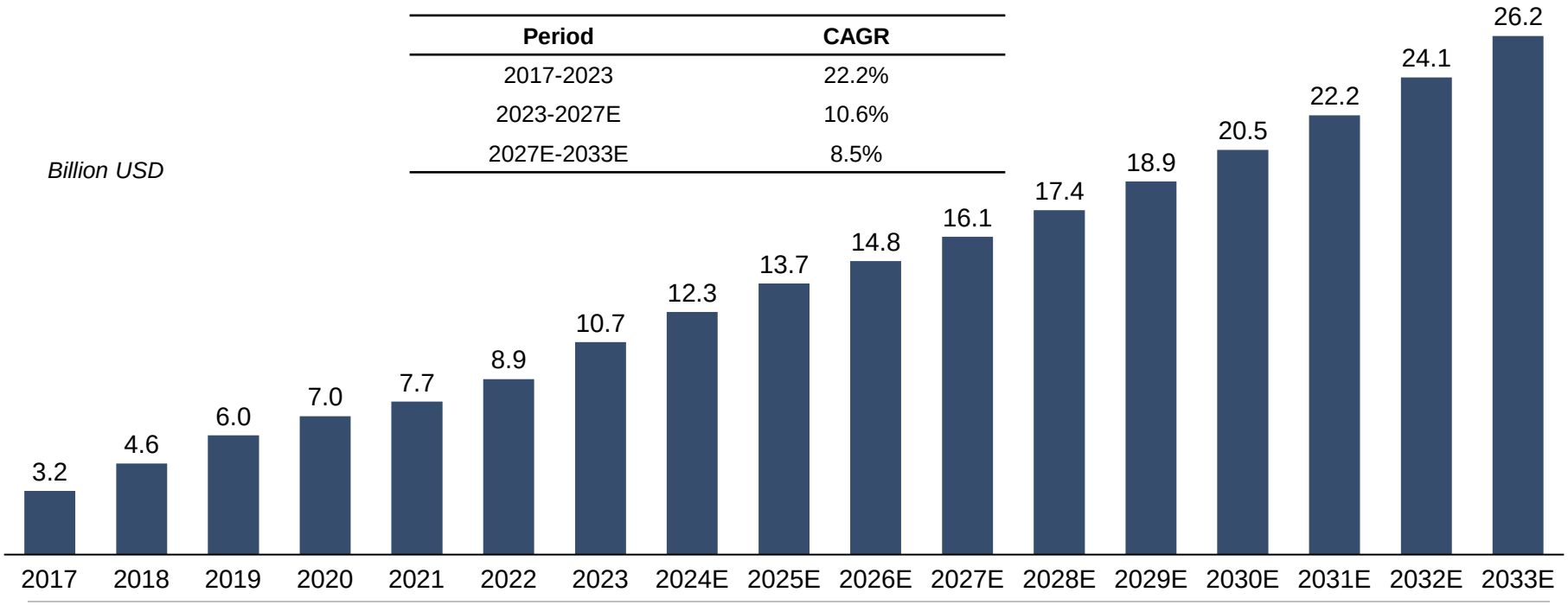
Source: Literature Review, Frost & Sullivan Analysis

Market Size of Global CDK4/6 Inhibitors

- CDK4/6 is overactive in many malignant tumors, prompting cancer cells to proliferate and spread, while CDK4/6 inhibitors can block the cell cycle in the growth phase, thus exerting the effect of inhibiting tumor cell proliferation. Currently, there are five CDK4/6 inhibitors approved and marketed globally, with the main therapeutic areas focusing on solid tumors such as breast cancer. Currently, the global CDK4/6 inhibitors market size is expanding and has grown from USD 3.2 billion in 2017 to USD 10.7 billion by 2023, at a CAGR of 22.2%. With an increasing number of CDK4/6 inhibitors coming to market, the market size will continue to expand in the future, and the global CDK4/6 inhibitors market size is expected to reach approximately USD 16.1 billion and USD 26.2 billion by 2027 and 2033, respectively, with a CAGR of 10.6% from 2023 to 2027 and at a CAGR of 8.5% from 2027 to 2033.

Market Size of Global CDK4/6 Inhibitors,2017-2033E

Period	CAGR
2017-2023	22.2%
2023-2027E	10.6%
2027E-2033E	8.5%



Source: Literature Review, Frost & Sullivan Analysis

Analysis of market drivers of CDK Inhibitor Drugs Market

Growing number of breast cancer cases leads to high demand for treatment	• The increase in the number of breast cancer cases drives the demand for CDK4/6 inhibitor anti-tumor treatment. Breast cancer is the first high incidence tumor among women in China, and the number of breast cancer incidence in China has increased from 315,200 new cases in 2017 to 341,000 cases in 2022, with a compound growth rate of 1.6%. And due to the long survival period of breast cancer, patients have a stronger demand for targeted drugs.
The continuing evolution of precision medicine	• CDK inhibitors target specific proteins associated with cell cycle regulation rather than conventional chemotherapy, which can affect both normal and cancerous cells. However, CDK inhibitors will reduce collateral damage to healthy cells, thereby minimizing the serious side effects often experienced by patients treated with conventional drugs.
Increasing clinical use of combination therapy	• The development of CDK inhibitors increasingly focuses on indications with unmet medical needs, especially those with sizeable patients or growing incidence rates, such as breast cancer. Due to a better efficacy and safety profile, CDK inhibitors are emerging as the standard of care for a number of advanced-stage cancer. Researches shown that cyclin-dependent kinase (CDK)4/6 inhibitors combined with traditional endocrine therapy can significantly improve the progression-free survival and overall survival of hormone receptor-positive and human epithelial growth factor receptor 2-negative breast cancer patients.
High efficacy of CDK4/6 targeted therapies and increased R&D investment	The advent of CDK inhibitors has dramatically changed the treatment of hormone receptor-positive metastatic breast cancer. With further research, it has now been developed that highly selective and reversible CDK inhibitors can improve efficacy. Palbociclib, Ribociclib and Abemaciclib are all highly selective and reversible inhibitors of CDK4 and CDK6. FDA has approved the combination of Palbociclib and endocrine therapy for the first- and second-line treatment of hormone receptor-positive metastatic breast cancer; it has also approved the use of Ribociclib for first-line treatment. High efficacy has brought many benefits to breast cancer patients and attracted more pharmaceutical companies to join.

Source: Literature Review, Frost & Sullivan Analysis

Future Trend of CDK Inhibitor Drugs Market(1/2)

CDK4/6 Inhibitors combined with endocrine therapy will further optimize anti-tumor regimens	Combined endocrine therapies are effective in anticancer treatment and are a trend for future clinical trials.CDK4/6 inhibitors have made great progress so far, especially for patients with hormone receptor-positive advanced breast cancer, where first-line endocrine therapy can bring longer tumor control (more than 2 years), and combined endocrine therapies have fewer and more reversible toxic side effects. It is likely that the direction of future drug development will broaden even more, combining anticancer family drugs to find even better oncological solutions. In the meantime, research is also actively seeking to identify biomarkers other than the estrogen receptor that are suggestive of the efficacy of CDK4/6 inhibitors to help achieve individualized precision. The CDK-RB1-E2F pathway targeted by CDK4/6 inhibitors is essential for progression through the cell cycle and is disrupted in the majority of cancers. In breast cancer, the activation of estrogen receptors as well as other proliferation-inducing signals stimulate 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 the 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 sequestrationof the transcription factor E2F and subsequent inhibition of cell cycle progression.
Expansion of Indications	• In the future, indications for CDK 4/6 inhibitors in cancer treatment may not be limited to breast cancer. Currently, the state of research and clinical pipeline shows significant effects of CDK 4/6 inhibitors in the treatment of other cancers, including recurrent/metastatic ovarian cancer, K-RAS mutated non-small cell lung cancer (NSCLC), prostate cancer, hematoma, and other advanced solid tumors. More progress and breakthroughs can be achieved in the field of CDK 4/6 inhibitor research by companies, benefiting more cancer patients.

Source: Literature Review, Frost & Sullivan Analysis

Future Trend of CDK Inhibitor Drugs Market(2/2)

The development of selective CDK inhibitors is promising.	• CDK has a wide range of physiological activities and has broad application prospects in the treatment of breast, pancreatic, prostate, ovarian, and small cell lung cancer. With the continuous advancement of technology, CDK inhibitor research has made some progress, but there are still major technical challenges in terms of subtype selectivity, combination therapy, and multi-target inhibition. Pan-CDK inhibitors have problems such as low specificity. Compared with pan-CDK inhibitors, selective CDK inhibitors have higher safety and specificity, and the future development prospect is more promising.
Overcoming drug resistance	• The main mechanisms of CDK4/6 inhibitors 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 the cell cycle protein E1 protein may play a key role in CDK4/6 inhibitors resistance, and direct targeting of the cell cycle protein E1 protein may be an effective way to overcome drug resistance. Meanwhile,CDK2 and CDK4 are protein kinases in cell cycle regulation and are closely related to tumorigenesis and progression. By interfering with the activities of CDK2 and CDK4, the proliferation and survival of cancer cells can be affected, which is expected to overcome certain types of drug resistance
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 dysregulation and resistance within the signaling pathway in prostate cancer after abiraterone treatment. Consequently, there is an 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 can reverse drug resistance in preclinical models, including prostate cancer. The combination of CDK inhibitors with abiraterone is believed to hold significant potential for synergistic antitumor efficacy in the context of prostate cancer. In prostate cancer, the androgen receptor serves as a pivotal driver in its progression and development. The androgen receptor is a ligand-dependent transcription factor, and in prostate cancer, ligand activation of androgen receptor 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.

Competitive Landscape of CDK Inhibitor Approved by FDA

- To date, there are 4 CDK Inhibitor approved by FDA.

Drug Name	Brand Name	Company	Indications	Target	FDA Approval Date	Global sales 2023 (billion USD)
Palbociclib	Ibrance	Pfizer	HR+/HER2- Locally Advanced or Metastatic Breast Cancer	CDK4,CDK6	2015/02	4.75
Ribociclib	Kisqali	Novartis	HR+/HER2- Locally Advanced or Metastatic Breast Cancer	CDK4,CDK6	2017/03	2.08
Abemaciclib	Verzenio	ELI LILLY	HR+/HER2- Locally Advanced or Metastatic Breast Cancer	CDK4,CDK6	2017/09	3.86
Trilaciclib	Cosela	G1 Therapeutics /Simcere	Reduction in the incidence of chemotherapy-induced myelosuppression in adult patients prior to the use of platinum/etoposide-containing regimens or topotecan-containing regimens Extensive-stage small cell lung cancer	CDK4,CDK6	2021/02	0.05

*Note: as of August 2,2024

Source: FDA, Frost & Sullivan analysis

Global CDK4/6 Inhibitor indications that are under development and the latest development status（1/2）

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Palbociclib	Pfizer	HPV-unrelated Head and Neck Squamous Cell Carcinoma	CDK4、CDK6	III	2021-07-19
		Prostate Cancer	CDK4、CDK6	II	2016-09-19
		Oligodendroglioma	CDK4、CDK6	II	2015-08-18
		Metastatic Pancreatic Ductal Adenocarcinoma	CDK4、CDK6	I	2015-07-14
		Hepatocellular Carcinoma	CDK4、CDK6	II	2011-05-19
		Refractory Multiple Myeloma	CDK4、CDK6	II	2007-11-08

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Abemaciclib	Eli Lilly and Company	Glioma	CDK4、CDK6	II	2024-05-14
		Metastatic Castration-Resistant Prostate Cancer	CDK4、CDK6	I	2023-08-21
		Meningioma	CDK4、CDK6	II	2023-07-11
		Advanced Dedifferentiated Liposarcoma	CDK4、CDK6	III	2021-07-08
		Endometrial Cancer	CDK4、CDK6	II	2020-05-19
		Advanced Digestive System Neuroendocrine Neoplasm	CDK4、CDK6	II	2019-03-27
		Bladder Cancer	CDK4、CDK6	I	2019-02-12
		Recurrent Glioblastoma	CDK4、CDK6	II	2016-12-05
		Pancreatic Ductal Adenocarcinoma	CDK4、CDK6	II	2016-12-05
		Non Small Cell Lung Cancer	CDK4、CDK6	III	2014-06-02

*Note: First posted date: 首次公示日期; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Global CDK4/6 Inhibitor indications that are under development and the latest development status（2/2）

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Ribociclib	Novartis	Diffuse Intrinsic Pontine Glioma	CDK4、CDK6	II	2023-05-06
		(Castration-Resistant Prostate Cancer)CRPC	CDK4、CDK6	I/II	2015-07-10
		Neuroendocrine Neoplasm	CDK4、CDK6	II	2015-04-15

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Trilaciclib	G1 Therapeutics, Inc.	Triple Negative Breast Cancer	CDK4、CDK6	II	2021-11-09
		Extensive-Stage Small Cell Lung Cancer	CDK4、CDK6	III	2021-05-26
		Locally Advanced or Metastatic Urothelial Carcinoma	CDK4、CDK6	II	2021-05-14

*Note: First posted date: 首次公示日期; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive landscape CDK inhibitors Approved by NMPA(1/2)

- With the approval of Ribociclib, the domestic CDK inhibitors have formed a competitive landscape of three imported drugs and several domestic drugs. In addition to Novartis' Ribociclib, Pfizer's Palbociclib and Eli Lilly's Abemaciclib were approved domestically in 2018 and 2020, respectively; and Hengrui Medicine's Dalpiciclib was also approved in December 2021 as a Class 1 new drug. In addition to this, Trilaciclib, a CDK4/6 inhibitor introduced by Simcere Pharmaceuticals, was approved in 2022 for patients with extensive-stage small-cell lung cancer to be used before chemotherapy to reduce the incidence of chemotherapy-induced myelosuppression.

CDK4/6 inhibitors Approved by NMPA (Innovative Drugs)

Drug Name/Code	Brand Name	Company	Indications	Target	Approval Date	Whether is covered by the NRDL	End User Price(RMB/box)	Treatment cost (RMB/month)
Palbociclib	IBRANCE	Pfizer	HR+/HER2- Breast Cancer	CDK4, CDK6	2018/07	Yes	4275.6	5700.8
Abemaciclib	Verzenios	ELI LILLY	HR+/HER2- Breast Cancer	CDK4, CDK6	2020/12	Yes	977.06	3910.4
Dalpiciclib	AiRuiKang	Hengrui Pharmaceuticals	HR+/HER2- Breast Cancer	CDK4, CDK6	2021/12	Yes	4305	5749.0
Trilaciclib	Cosela	Simcere/G1 Therapeutics	Prevention of chemotherapy-induced myelosuppression in patients with small cell lung cancer	CDK4, CDK6	2022/07	No	5980	8542.9
Ribociclib	Kisqali	Novartis	HR+/HER2- Breast Cancer	CDK4, CDK6	2023/01	Yes	4466.7	5955.6

*Note: as of August 2,2024

Source: NMPA, Frost & Sullivan analysis

Competitive landscape CDK inhibitors Approved by NMPA(2/2)

- To date, there are 14 generics CDK4/6 Inhibitor approved by NMPA, and all of them are generics drugs of Palbociclib

CDK4/6 inhibitors Approved by NMPA (Generics Drugs)

Drug Name/Code	Company	Approval Date
Palbociclib Capsules	QILU PHARMACEUTICAL CO.,LTD	2020-12-15
Palbociclib Capsules	Hansoh Pharmaceutical Group Company Limited	2022-06-28
Palbociclib Capsules	Jiangxi Shanxiang Pharmaceutical Co., Ltd	2022-08-30
Palbociclib Capsules	Jiangsu Aosaikang Pharmaceutical Co., Ltd	2022-12-30
Palbociclib Capsules	Hunan Kelun Pharmaceutical Co.,Ltd	2022-12-30
Palbociclib Capsules	Beijing Tide Pharmaceutical Co.,Ltd	2023-02-14
Palbociclib Capsules	Chongqing Yaoyou Pharmaceutical Co., Ltd	2023-06-21
Palbociclib Capsules	Shanghai CD Pharmaceutical Co.,Ltd	2023-08-08
Palbociclib Capsules	Jiangxi Aishite Pharmaceutical Co., Ltd	2023-11-21
Palbociclib Capsules	Jiangsu Chia Tai-tianqing Pharmaceutical Co., Ltd.	2023-12-05
Palbociclib Capsules	Hebei Dao'en Pharmaceutical Co., Ltd	2023-12-05
Palbociclib Capsules	Jilin Aodong Taonan Pharmaceutical Co.,Ltd.	2024-02-23
Palbociclib Capsules	Simcere Pharmaceutical Co.Ltd.	2024-03-05
Palbociclib Tablets	CSPC Ouyi Pharmaceutical Co.,Ltd.	2024-06-25

*Note: as of August 2,2024

Source: NMPA, Frost & Sullivan analysis

CDK4/6 Inhibitor indications that are under development and the latest development status in China

- To date, CDE shows that there are no expanded Indications for Palbociclib and Ribociclib

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Abemaciclib	Eli Lilly	Castration-Resistant Prostate Cancer(CRPC)	CDK4、CDK6	III	2022-07-11
		Non Small Cell Lung Cancer(NSCLC)	CDK4、CDK6	III	2016-06-12

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Dalpiciclib	Jiangsu Hengrui Medicine Co.,Ltd.	(metastatic hormone-sensitive prostate cancer) mHSPC	CDK4、CDK6	III	2023-09-18
		melanoma	CDK4、CDK6	I	2016-02-29

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
Trilaciclib	G1 Therapeutics/Patheon Inc	Triple Negative Breast Cancer	CDK4、CDK6	III	2021-09-28

*Note: First posted date: 首次公示日期; as of August 2, 2024

Source: CDE, Frost & Sullivan analysis

Competitive Landscape of Global CDK4/6 Inhibitor Pipeline

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date	Location
SPH6516	Shanghai Pharmaceuticals Holding	Advanced Solid Tumor	CDK4/6	I	2024-02-20	China
TQB3616	Chia Tai Tianqing Pharmaceutical	Breast Cancer	CDK4/6	III	2023-03-22	China
Lerociclib	Genor Biopharma	HR+/HER2- Breast Cancer	CDK4/6	III	2023-05-09	China
SPH4336	Shanghai Pharmaceuticals	HR+/HER2- Breast Cancer	CDK4/6	II	2023-05-24	China
BEBT-209	BeBetter Med	HR+/HER2- Breast Cancer	CDK4/6	I	2023-09-07	China
XZP-3287	Xuanzhu Biopharmaceutical	HR+/HER2- Recurrent/Metastatic Breast Cancer	CDK4/6	III	2022-02-16	China
BPI-16350	Betta Pharmaceuticals	HR+/HER2- Advanced / Metastatic Breast Cancer	CDK4/6	III	2022-06-27	China
PRT3645	Prelude Therapeutics	Breast Cancer	CDK4/6	I	2022-09-14	USA/Singapore
UCT-03-008	1200 Pharma	Advanced Solid Tumor	CDK4/6	I	2021-11-02	USA
BPI-1178	Beta Pharma, Inc.	Advanced Solid Tumor, HR+/HER2- Breast Cancer	CDK4/6	I/II	2020-02-24	China
TY-302	TYK Medicines,Inc	Breast Cancer, Prostate Cancer,Solid Tumor	CDK4/6	I	2020-06-09	China
GLR2007	Gan & Lee Pharmaceuticals	NSCLC，Glioblastoma Multiforme	CDK4/6	I/II	2020-06-19	USA

*Note: First posted date: 首次公示日期; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global CDK7 Inhibitor Pipeline

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date	Location
TY-2699a	TYK Medicines,Inc	Solid Tumor	CDK7	I	2023-05-19	China
EOC237	Shanghai Yiteng Jingang Bio-pharmaceutical Technology	Advanced Solid Tumor	CDK7	I	2023-06-09	China
GTAEXS-617	GT Apeiron Therapeutics	Advanced Solid Tumor	CDK7	I/II	2023-08-14	Belgium/UK
Samuraciclib	Carrick Therapeutics/Pfizer	HR+/HER2- Breast Cancer	CDK7	II	2023-07-27	USA/Spain/Turkey
Q901	Qurient /Merck Sharp & Dohme	Solid Tumors	CDK7	I	2022-05-27	USA/South Korea
XL102	Exelixis	Neoplasm Malignant, Epithelial Ovarian Cancer, HR+ Breast Cancer, TNBC, Metastatic Castration-resistant Prostate Cancer	CDK7	I	2021-01-27	USA
SY 5609	Syros Pharmaceuticals	Advanced Solid Tumor, Breast Cancer,SCLC, Pancreatic Cancer	CDK7	I	2020-01-22	USA

*Note: First posted date: 首次公示日期; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of Global CDK2/4/6 Inhibitor Pipeline

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date	Location
TY-0540	TYK Medicines,Inc	Advanced solid tumors	CDK2/4/6	I	2024-02-07	China
SYH2043	CSPC Ouyi Pharmaceutical	Advanced Malignant Tumors	CDK2/4/6	I	2023-01-27	China
RGT-419B	Regor Therapeutics	HR+/HER2- Breast Cancer	CDK2/4/6	I	2022-03-31	USA

*Note: First posted date: 首次公示日期; as of August 2,2024

Source: clinicaltrials.gov, Frost & Sullivan Analysis

Competitive Landscape of China CDK Inhibitor Pipeline(1/3)

- To date, there are 26 CDK Inhibitors pipeline under development in China. TY-302 is a potential best-in-class, selective oral CDK4/6 dual inhibitor developed for the treatment of advanced solid tumors. It is developed through H/D exchange with pacl a potential best-in-class CDK4/6 inhibitor due to its superior PK than its TY-302 acts as an inhibitor of CDK4/6, a key regulator of the cell cycle. TY-1210 is a potential first-in-class, small molecule, selective CDK2 inhibitor developedfor cancer treatment. TY-0609 is a potential first-in-class selective CDK4 inhibitor with significant sparing of CDK6 for cancer treatment.

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
TY-302	TYK Medicines,Inc	ER+/HER2- breast cancer that has recurred or metastasized after second-line treatment	CDK4,CDK6	**I**	2022-09
		HR+/ HER2- Locally advanced or metastatic Breast Cancer, Prostate Cancer	CDK4, CDK6	I	2020/06
TY-2699a	TYK Medicines,Inc	TNBC, ER+/HER2-Breast Cancer, Pancreatic Ductal Adenocarcinoma	CDK7	I	2023/05
TYK-00540	TYK Medicines,Inc	Advanced Solid Tumor	CDK2/4/6	I	2023/11
XZP-3287	Xzenith/Sihuan Pharmaceutical	HR+/HER2- Breast Cancer	CDK4, CDK6	III	2021/09
BPI-1178	Beta Pharma, Inc.	HR+/HER2- Breast Cancer	CDK4,CDK6	I/II	2020/02
WXWH0240	Cisen Pharmaceutical	HR+HER2-Breast Cancer, Recurrent/Refractory Ovarian Cancer	CDK2,CDK4,CDK6	I	2021/10
BPI-16350	Betta Pharmaceuticals	HR+/HER2- Breast Cancer	CDK4, CDK6	III	2022/05
BEBT-209	BeBetter Med	HR+/HER2- Breast Cancer	CDK4, CDK6	III	2022/02
TQB3616	Chia Tai Tian Qing Pharmaceutical	HR+/HER2- Breast Cancer	CDK4, CDK6	III	2022/01
FCN-437c	Fosun Pharma	HR+/HER2- Breast Cancer	CDK4, CDK6	III	2021/12
SPH4336	Shanghai Pharmaceuticals	HR+/HER2- Breast Cancer	CDK4, CDK6	II	2023/05
PF-07220060	Pfizer	HR+/HER2- Breast Cancer	CDK4	I	2023/03
PF-07104091	Pfizer	HR+HER2-Breast Cancer, NSCLC, SCLC, Ovarian Cancer	CDK2	I	2023/03
YZJ-2440	Yangtze River Pharmaceutical	HR+HER2-Breast Cancer, Solid Tumor	CDK4, CDK6	I	2020/12

*Note: First posted date: 首次公示日期; as of August.2 2024

Source: CDE, Frost & Sullivan analysis

Competitive Landscape of China CDK Inhibitor Pipeline(2/3)

- To date, there are 26 CDK Inhibitors pipeline under development in China.

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
XH-30002	JinRui Foundation Biotechnology	HR+/HER2 Breast Cancer, Advanced Colorectal Cancer, Advanced Esophageal Cancer, Advanced Gastric Cancer	CDK4,CDK6	I	2020/12
EOC237	EOC Biopharma (Shanghai)	Solid tumor	CDK7	I	2023/05
SDT-101	Suzhou Splendustx Pharmaceutical	Advanced Malignant Solid Tumor	CDK4,CDK6	I	2020/03
HRS-6209	Hengrui Pharmaceuticals	Solid tumor	CDK4	I	2023/02
HS-10342	Hansoh Pharma	Breast cancer, Solid Tumor	CDK4,CDK6	I	2021/09
QHRD110	Changzhou Qianhong Biopharma	Malignant Tumors of the Central Nervous System	CDK4,CDK6	I	2023/11
QHRD107		AML	CDK9	II	2023/08

*Note: First posted date: 首次公示日期; as of August.2 2024

Source: CDE, Frost & Sullivan analysis

Competitive Landscape of China CDK Inhibitor Pipeline(3/3)

- To date, there are 26 CDK Inhibitors pipeline under development in China.

Drug Name/Code	Company	Indications	Target	Clinical Stage	First Posted Date
ETH-155008	Shengke Pharmaceutics	AML,NHL	CDK4,CDK6, PIM3	I	2022/08
GLR2007	Gan&Lee Pharmaceuticals	Glioblastoma	CDK4,CDK6	I/II	2021/10
YK-2168	Nanjing YOKO Pharmaceutical	NHL	CDK9	I/II	2021/11
SYH2043	CSPC Pharmaceutical	Breast cancer	CDK2,CDK4, CDK6	I	2023/02
GFH009	Zhejiang GenFleet Therapeutics	Hematologic Tumors, Lymphoma	CDK9	I/II	2023/05

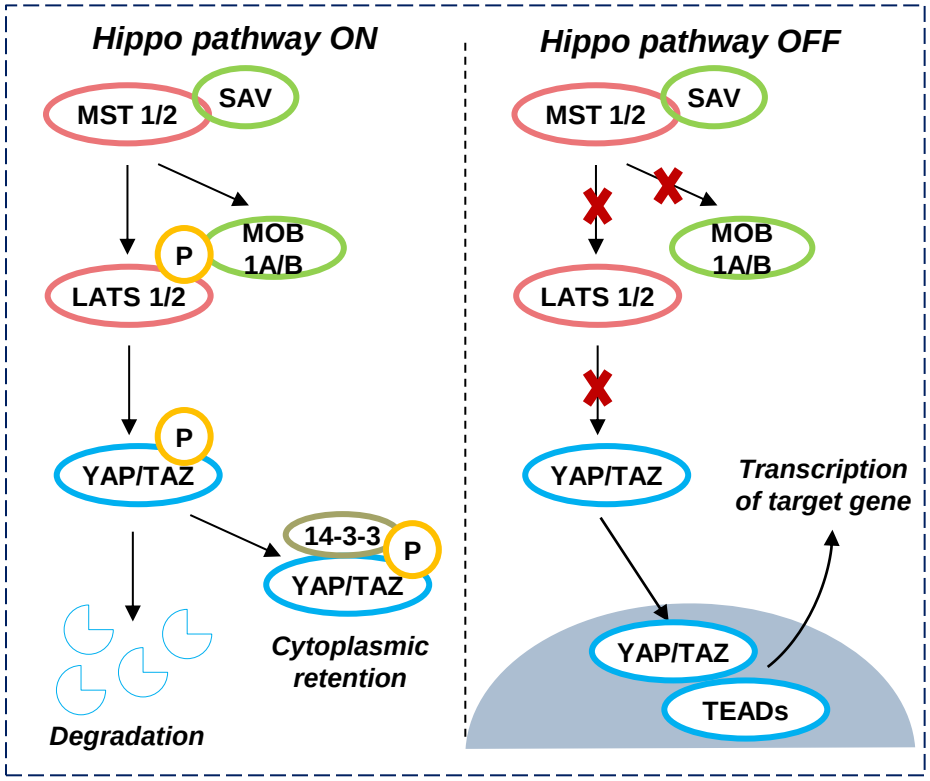
*Note: First posted date: 首次公示日期; as of August.2 2024

Source: CDE, Frost & Sullivan analysis

Overview and Mechanism of YAP

- The YAP (Yes-associated protein), also known as YAP1 or YAP65, is a transcription coregulator protein as a component in the Hippo signaling pathway. The Hippo pathway is an important organ size control signaling network and the major regulatory mechanism of cell-contact inhibition. YAP and TAZ are its targets and terminal effectors: inhibition of the pathway promotes YAP/TAZ translocation to the nucleus, where they interact with TEAD transcription factors and coactivate the expression of target genes, promoting cell proliferation.

Mechanism of the Hippo pathway



Mechanism of the Hippo pathway

- When the Hippo signaling pathway is "OFF", MSAT1/2 and LATS1/2 are inactivated, YAP/TAZ freely translocate to nucleus and bind to TEAD transcription factors, promoting the expression of downstream target genes.
- When the Hippo signaling pathway is "OFF", MSAT1/2 and LATS1/2 are inactivated, YAP/TAZ freely translocate to nucleus and bind to TEAD transcription factors, promoting the expression of downstream target genes.

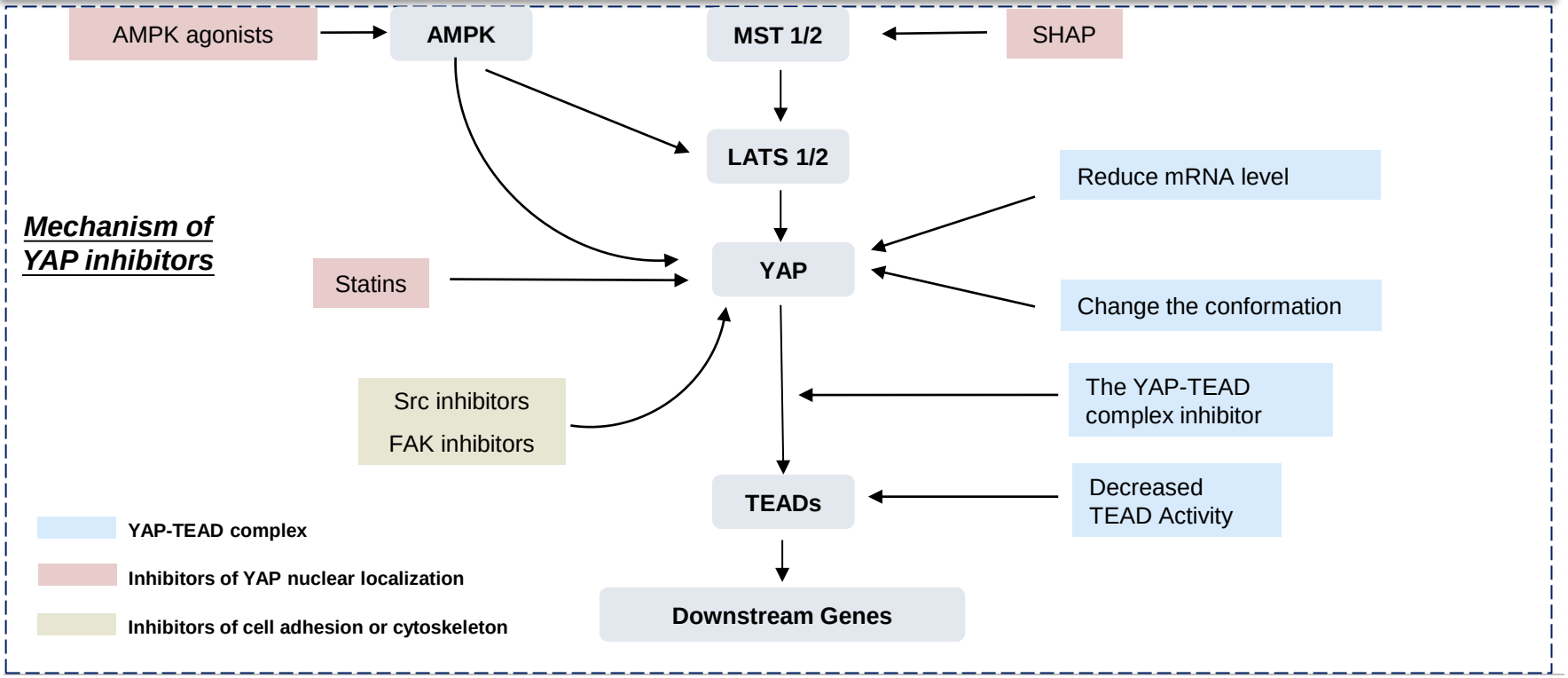
YAP in Carcinogenesis

- As key effectors on the Hippo pathway, YAP molecules control cell growth and the size of the organs. The YAP/TAZ-TEAD complex cooperate and participate in the growth and proliferation of tumor cells in breast cancer (18.23 (8.2–40.52)), liver cancer ,uveal melanoma and mesothelioma. It was also revealed that the expression of YAP/TAZ is a critical determinant in the early stages of base cell carcinoma (BCC) and squamous cell carcinoma (SCC).

Source: Literature Review, Frost & Sullivan Analysis

Overview and Mechanism of YAP inhibitor

- Currently, the main mechanisms of YAP inhibitors include inhibitors of YAP-TEAD complex, inhibitors of YAP nuclear localization or inhibitors of cell adhesion or cytoskeleton. The YAP-TEAD complex, the last step of the Hippo pathway, emerges as the better candidate target for modulating the Hippo/YAP signaling due to the less possible potential side effects compares with upstream protein inhibitors. The Hippo pathway plays an essential role in cell proliferation, tissue regeneration, and tumorigenesis, the hyperactivation of which induces metastasis, chemoresistance, and the attribute of cancer stem cells. Its dysregulation contributes to 10% of all cancers, including lung, gastric, colon, cervical, ovarian, breast, melanoma, hepatocellular and squamous cell carcinoma. The pathway is activated through binding of the YAP/TAZ complex to palmitoylated TEAD. Despite the urgent need to develop a therapeutic strategy to curb the dysregulated pathway, YAP/TAZ is difficult to be directly targeted 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.



Source: Literature Review, Frost & Sullivan Analysis

Competitive Landscape of YAP inhibitor Pipeline in China and Global

- To date, there is no YAP-TEAD inhibitor in the oncology field that received FDA approval and NMPA,and there are 4 YAP inhibitor under development globally. TY-01054 is a potential first-in-class, small molecule, oral YAP/TEAD inhibitor developed for cancer treatment.

Drug Name/Code	Target	Company	Clinical Stage	Indications	First Posted Date
CBL0137	FACT complex, YAP	Statera BioPharma, Inc.	I/II	Solid Tumor, Lymphoma , Melanoma, Hematological Cancers	2013-07-23
ION537	YAP	Ionis Pharmaceuticals	I	Solid Tumor	2020-12-09
IAG933	YAP, TEAD	Novartis	I	Mesothelioma	2021-04-23
Verteporfin	YAP、TEAD	SpectraMab	I/II	Recurrent Prostate Cancer	2017-03-01

*Note: Approval date: First approval date;
As of August.2 2024

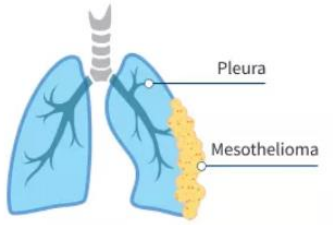
Source: clinicaltrials.gov ,FDA, Frost & Sullivan Analysis

Overview of Mesothelioma

- Mesothelioma is a rare cancer affecting the thin tissue lining the lungs, stomach, heart and other organs. Pleural mesothelioma is the most common type that affects the lungs. Mesothelioma is primarily caused by asbestos exposure. The average life expectancy for mesothelioma patients is 12 to 21 months. About 12% of people with pleural mesothelioma and 65% with peritoneal mesothelioma live for five years or longer. Operable malignant mesothelioma should receive trimodal therapy with chemotherapy, surgery, and hemithoracic radiation therapy. Inoperable malignant cases should receive combination chemotherapy orimmune checkpoint inhibitor therapy.

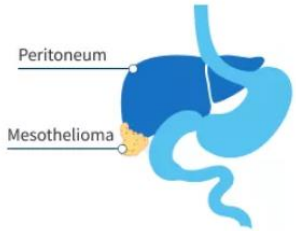
Types of Mesothelioma

Pleural mesothelioma



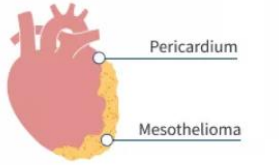
Forms in the lining of the lungs.

Peritoneal mesothelioma



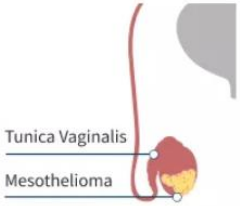
Develops in the lining around the abdomen.

Pericardial mesothelioma



Grows on the tissue around the heart.

Testicular mesothelioma



Forms on the membrane that covers the testes.

Types of Mesothelioma

- Pleural mesothelioma:, most common type
- Peritoneal mesothelioma
- Pericardial mesothelioma
- Testicular mesothelioma

Risk factors

- More than 80% of mesothelioma cases are caused by exposure to asbestos
- Genetic factors
- Infection with the simian virus 40
- Exposure to erionite

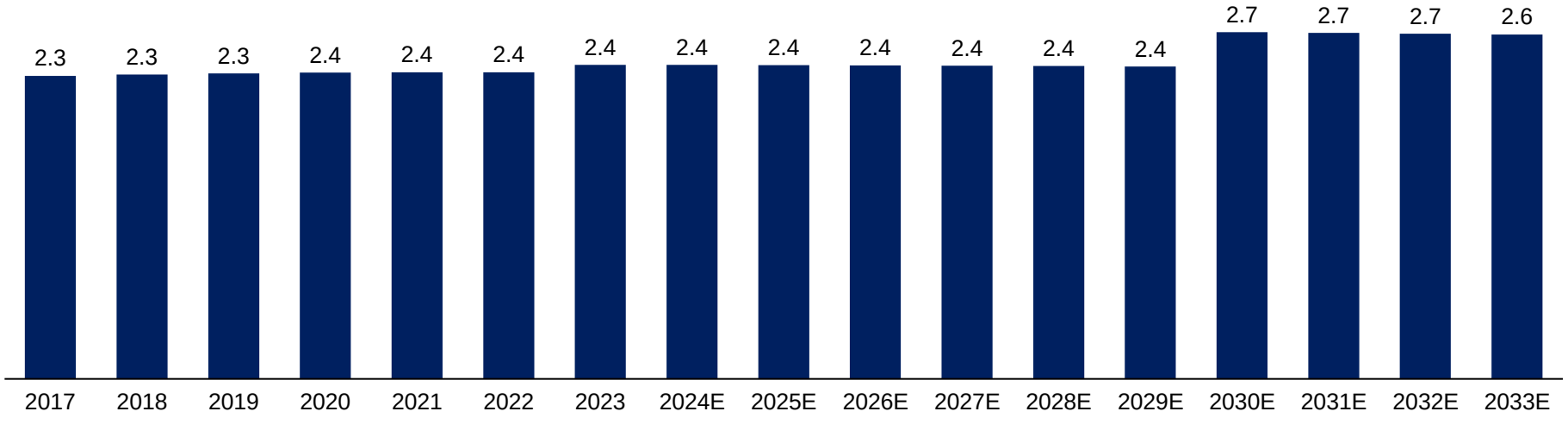
Source: Literature Review, Frost & Sullivan Analysis

Incidence of Mesothelioma cancer in China， 2017-2033E

- With the rapid development of industrialization and the extensive use of asbestos products over the past decades, posing a great threat to people's lives and health. The number of Mesothelioma cancer patients in China has continued to grow in recent years from 2.3 thousand in 2017 to 2.4 thousand in 2023, with a compound annual growth rate of 0.2%% from 2017 to 2022. The number of people in the country is expected to continue to grow and reach 2.4 thousand in 2027 and 2.6 thousand in 2033 with CAGRs of 0.4% and1.6% between 2022-2027 and 2027-2033, respectively.

Incidence of Mesothelioma cancer in China， 2017-2033E

Period	CAGR
2017-2023	0.2%
2023-2027E	0.4%
2027E-2033E	1.6%



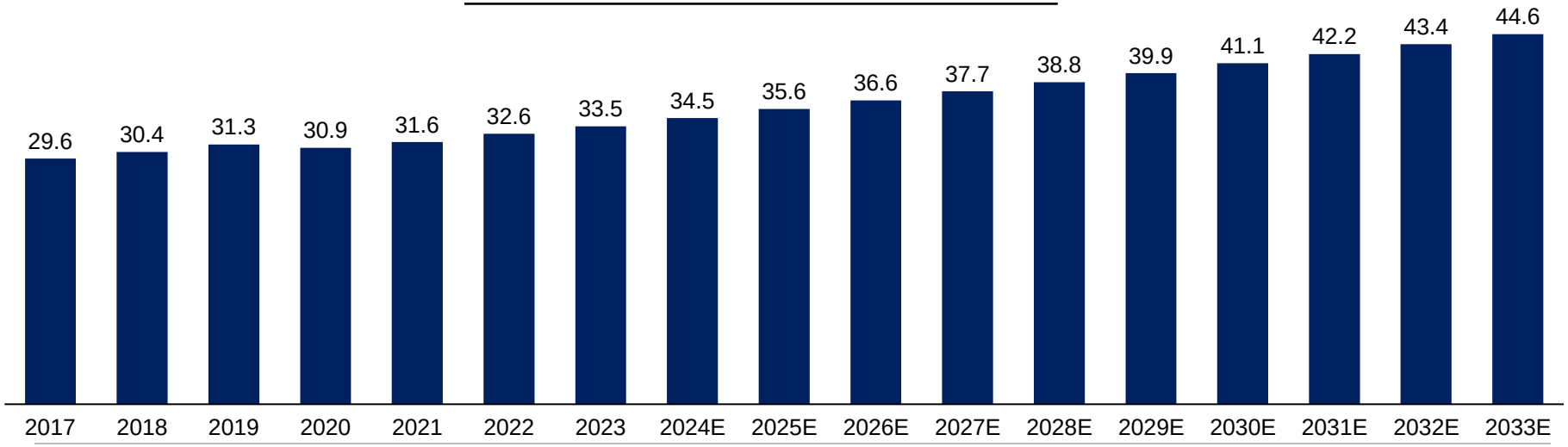
Source: Literature Review, Frost & Sullivan Analysis

Global incidence of Mesothelioma cancer， 2017-2033E

- Mesothelioma is a type of cancer that develops from the thin layer of tissue that covers many of the internal organs. The global number of Mesothelioma cancer patients has continued to grow in recent years from 29.6 thousand in 2017 to 33.5 thousand in 2023, with a compound annual growth rate of 2.0 % from 2017 to 2022. The number of people in the country is expected to continue to grow and reach 37.7 thousand in 2027 and 44.6 thousand in 2033 with CAGRs of 3.0% and 2.8% between 2022-2027 and 2027-2033, respectively.

Global incidence of Mesothelioma cancer ， 2017-2033E

Period	CAGR
2017-2023	2.0%
2023-2027E	3.0%
2027E-2033E	2.8%



Source: Literature Review, Frost & Sullivan Analysis

Appendix 1/7

- In addition to traditional chemotherapy, kinase inhibitors have been developing rapidly in the past 20 years. Although kinase inhibitors are very effective in cancer therapy, patients often develop drug resistance and disease recurrence, consequently. PROTACs showed greater advantages in drug resistant cancers through degrading the whole target protein.
- As a CDK4/6 inhibitor, TY-302 can inhibit CDK4/6 activity and 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. TY-302 is a compound modified by H/D exchange at palbociclib. Palbociclib in combination with aromatase inhibitor has been approved for the treatment of advanced breast cancer in the U.S.. 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 of20.2 months in HR+/HER2- untreated advanced breast cancer. In PALOMA-2, treatment-naïve 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+/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 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 in the palbociclib and fulvestrant group of 9.5 months, compared with 4.6 months in the placebo and fulvestrant group.
- CDK4/6 inhibitors may retard cancer progression through diverse mechanisms in addition to cell-cycle regulation. The in vivo functions ofCDK4/6 inhibition are likely to extend beyond simply enforcing reversible cryostasis. 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.
- Clinically, for androgen-sensitive prostate cancer, endocrine therapy represented by androgen receptor-androgens is one of the standard treatments, in which abiraterone treatment to hinder androgen synthesis is 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 limit of detection. Although abiraterone significantly prolongs patient survival, many patients remain resistant to it after a period of treatment.
- ER+/HER2– indicates specific molecular characteristics of breast cancer cells. “ER+”means the breast cancer cells express estrogen receptors (Estrogen Receptor), indicating sensitivity to estrogen . “HER2–” signifies that these breast cancer cells do not overexpress Human Epidermal Growth Factor Receptor 2 (HER2), distinguishing them from other breast cancer types where HER2 is overexpressed. ER+/HER2– breast cancer is a relatively common subtype. HR+ (Hormone Receptor Positive) includes both ER+ (Estrogen Receptor Positive) and PR+ (Progesterone Receptor Positive). 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+.

Appendix 2/7

- Immunohistochemical analysis on a range of tumor types indicated that CDK7 expression is elevated in tumor cells compared with their normal counterparts, and subsequently numerous studies have provided support for this finding. In oestrogen receptor-positive (ER+) Breas cancer, CDK7, cyclin H and MATi are overexpressed and are co-regulated at the mRNA level.Expression of the CAK components positively correlates with ER expression and Ser118bhosphorylation, as well as with improved patient outcomes. Conversely, in triple-negative breast cancer (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 (OSCC), hepatocellular carcinoma and glioblastoma. For OSCC, 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, ER+, 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 (SE), that control the expression of genes integral for cell identity and function have been defined. Deregulation of the SE 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.
- 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 initial 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 mammalian target of rapamycin inhibitors.
- 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. Our 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.

Appendix 3/7

- Among them, exon 19 deletion and exon 21 L858R mutation account for 85% of EGFR mutations, with exon 19 deletion contributing 44.8% and exon 21 L858R contributing 39.8% to the overall EGFR mutation profile
- Unfortunately, despite initial benefit, most patients develop acquired resistance to them within one year, which is 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 a first-generation EGFR-TKI gefitinib (according to LUX-Lung 7 study, the OS of afatinib vs. gefitinib was 27.9 vs 24.5 months)
- The T790M mutation increases the competition between ATP and the 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. The third-generation EGFR-TKIs, including osimertinib, befotertinib, furmonertinib and almonertinib, have satisfactory efficacy in overcoming acquired resistance to the first- and second-generation EGFR-TKIs mediated by T790M mutation. These mutant-selective EGFRTKIs could represent a promising approach to overcome 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, the third-generation EGFR-TKIs exhibited selectivity against EGFR mutations over wild-type EGFR. This favorable property resulted in improved safety profile
- 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 NSCLC can be nearly 25% at diagnosis, approximately 30% to 55% of NSCLC patients develop brain metastases during treatment, the incidence of brain metastases in NSCLC patients with EGFR mutation is higher than those without EGFR mutation, and the incidence of brain metastases increases year by year during the survival period. The natural average survival of NSCLC patients with brain metastases is only 1 to 2 months, and the prognosis is poor, which seriously jeopardizes 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
- To select the best first-line treatment for each patient with newly diagnosed advanced NSCLC, the tumor must be evaluated for predictive biomarkers, and activating genetic alterations amenable to targeted therapy by next-generation sequencing, colloquially referred to as driver alterations or driver mutations. Targetable genetic alterations include numerous EGFR mutations (exon 19 deletion, exon 21 L858R, T790M), ALK fusion, NTRK fusion, RET fusion, and ROS1 fusion. Patients with a targetable genetic alteration often benefit from oral TKI therapy.
- The five-year age-standardized overall survival rate for prostate cancer patients in China is 69.2%, compared to 97.4% in the US.
- Only drug candidates for indications without approved drugs, with a superior safety and efficacy profile, and potentially addressing unmet clinical needs, can be approved for marketing by conducting a pivotal Phase II trial, which is much faster than conducting a Phase III registrational clinical trial. Currently, there are no approved drugs for the treatment of BM from NSCLC; therefore, TY-9591 could be approved for marketing more quickly through a pivotal Phase II trial.

Appendix 4/7

- The global pharmaceutical industry is constantly evolving.
- The pharmaceutical industry is subject to fierce competition and rapid and significant technological advancements. Company faces competition with respect to our current drug candidates from existing products and product candidates under development in the entire oncology market, in addition to approved oncology therapy options including surgery, radiotherapy and chemotherapy.
- Company's competitors include major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Company is developing our drug candidates in competition with a number of companies that have commercialized, are in the process of commercializing, or are pursuing the development of drugs for the same target indications. Some of these competitive drugs and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.
- Many of company's competitors against which company is competing or against which we may compete may have substantially greater financial, technical and human resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved drugs than company does. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in competitors. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, company's programs. A number of companies in the pharmaceutical and biopharmaceutical industries have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, not with standing promising results in earlier trials. As drug candidates are developed through preclinical to early- to late-stage clinical trials towards approval and commercialization, it is customary that various aspects of the development programs, such as manufacturing and formulation, are altered along the way in an effort to optimize processes and results.
- Data in the healthcare industry is fragmented in origin, inconsistent in format, and often incomplete, the overall quality of data collected or accessed in the healthcare industry is often subject to challenge, the degree or amount of data which is knowingly or unknowingly absent or omitted can be material.
- A primary trend in the global healthcare industry is cost containment. Government authorities and these third-party payers have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications.
- Investment in the development of pharmaceutical products is highly speculative as it entails substantial upfront expenditures and significant risks that a drug candidate may fail to demonstrate efficacy and safety to gain regulatory or marketing approvals or become commercially viable.
- Company faces significant competition in seeking appropriate strategic partners and the negotiation process can be time-consuming and complex.
- Osimertinib stands out as the first third-generation EGFR-TKI to demonstrate superior efficacy compared to previously approved EGFR-TKIs. None of the subsequently approved third-generation EGFR-TKI opted for head-to-head trials with Osimertinib. Osimertinib is currently the sole third-generation EGFR-TKI to have undergone a real-world Phase IV study, the results of which were largely consistent with its pivotal trial outcomes. Given that pivotal trial often yield more favorable clinical data than real-world studies, Osimertinib's sustained effectiveness underscores its status as the most effective third-generation EGFR-TKI currently available.

Appendix 5/7

- The proportion of T790M mutations in NSCLC patients treated with EGFR-TKIs, both globally and in China, is approximately 50%. EGFR exon 20 insertions are heterogeneous at the molecular level but can be characterized as in-frame insertions or duplications of between 3 and 21 bp (corresponding to 1 to 7 amino acids) clustered between amino acid positions 762 and 774 of the EGFR protein.

- In the absence of an approved fourth-generation EGFR-TKI, patients who develop resistance to third-generation EGFR-TKIs are typically transitioned to chemotherapy or alternative therapies other than EGFR-TKIs. In addition, the cumulative incidence of the EGFR C797S mutation in NSCLC patients who are likely to experience disease progression after initial treatment with osimertinib is only 12.5%, indicating a relatively small subset of patients eligible for fourth-generation EGFR-TKI treatment. Consequently, the impact of fourth-generation EGFR-TKIs on overall EGFR-TKI market share dilution is anticipated to be minimal.

- As of the Latest Practicable Date, five fourth-generation EGFR-TKIs are undergoing clinical development, all of which were in Phase I/II stages and among which the most clinically advanced one entered clinical stage in 2022, with expectation of potential approval and market availability in China by 2033.

- Second-generation EGFR-TKIs have more targets and irreversibly inhibit HER2 in addition to EGFR, potentially leading to cardiac-related toxicity issues that do not occur during treatment with first generation EGFR-TKIs. Furthermore, the recommended clinical dosage of second-generation EGFR-TKIs is higher than that of the first-generation EGFR-TKIs, which approach the dosage that causes DLTs, resulting in increased toxicity compared to first-generation EGFR-TKIs.

- CDK2 and CDK4 are both involved in initiating DNA replication and mitosis during the G1 and S phases of the cell cycle. CDK2, in particular, is considered an attractive target because it plays diverse roles in cell cycle regulation and may involve different signaling pathways compared to CDK4/6.

- Although currently most of these studies have been in early development stage, more progress and breakthroughs can be achieved in the field of CDK4/6 inhibitor research by companies, benefiting more cancer patients in the future. Specifically, CDK4 and CDK6 are critical mediators of cellular transition into S phase and are important for the initiation, growth and survival of many cancer types. The effects of CDK4/6 inhibition are far more wide-reaching. New insights into their mechanisms of action have triggered identification of new therapeutic opportunities, including the development of novel combination regimens, expanded application to a broader range of cancers and use as supportive care to ameliorate the toxic effects of other therapies.

- As of the Latest Practicable Date, Twelve companies were approved to manufacture abiraterone in China, and three companies were authorized to manufacture toremifene citrate in China.
- According to Frost & Sullivan, if the safety data and efficacy data collected in Phase I clinical trials meet the requirements for conducting a Phase III clinical trial, such a trial can proceed after communication with the CDE and obtaining regulatory clearance from the NMPA.
- It is common for Phase I and Phase II trials of antitumor drugs without a control group to be designed as open-label trials.

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- The mandatory mutation tests for NSCLC patients in China include EGFR, ALK rearrangement/fusion, ROS1 rearrangement/fusion, and MET exon 14 jump mutation; optional mutation teats include MET amplification, HER2 exon 20 insertion, BRAF V600E mutation, RET rearrangement/ fusion, KRAS exon 2 and 3 point mutation, NTRK rearrangement /fusion tumor mutation load, and PD-L1.All testing costs are self-paid by the patients or otherwise covered by insurance in the private-pay market. Globally, American Society of Clinical Oncology ("ASCO"), European Society for Medical Oncology ("ESMO"), Chinese Society of Clinical Oncology ("CSCO") and other authorities and international organizations consider EGFR, ALK rearrangement, ROS1 rearrangement, BRAF V600E mutation and PD-L1 immunohistochemistry as mandatory mutation tests, and other recommended mutation tests include RET, MET exon 14, HER2, KRAS and NTRK. The cost of testing are self-paid by patients or otherwise covered by insurance in the private-pay market.

- Approximately 20% of NSCLC patients are in stage I or II at the time of initial diagnosis, 30% in stage III, and the remaining approximately 50% are stage IV patients.
- The average life expectancy of patients with NSCLC at the time of brain metastases diagnosis is approximately one year.

- If the lesions cannot be removed by surgery, patients with driver genes will be treated with targeted drugs combined with chemotherapy and other therapeutic approaches. For patients with brain metastases detected in the course of treatment, the dosage of the original targeted drug will be increased or the original targeted drug will be combined with chemotherapy, or chemotherapy or radiotherapy will be used alone as monotherapy.

- PS refers to the ECOG Performance Status Scale, a standard criteria for measuring how the disease impacts a patient's daily living abilities. It describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (such as walking and working). PS=0 means fully active, able to carry on all pre-disease performance without restriction; PS=1 means restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; PS=2 means ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours; PS=3 means capable of only limited self-care; confined to bed or chair more than 50% of waking hours; PS=4 means completely disabled; cannot carry on any self-care; totally confined to bed or chair; and PS=5 means dead.

- Additionally, the proportion of Chinese prostate cancer patients with distant metastasis at the time of initial diagnosis is approximately 30.5%, significantly higher than the 6.8% observed in North America.
- As the treatments for NSCLC patients with brain metastases include chemotherapy, radiotherapy, targeted agents, and immune checkpoint inhibitors. Most NSCLC patients are treated with targeted therapies in combination with other treatment approaches such as chemotherapy, radiotherapy (uses external beams of intense energy to kill cancer cells, not drugs), following the diagnosis of brain metastases. The choice of treatment options varies from doctors in different countries.

- The Pivotal Phase II BM Clinical Trial and Phase II BM Clinical Trial were initiated when TY-9591 reached the primary endpoint of the Phase I NSCLC Clinical Trial, which, according to Frost & Sullivan, is a common indication of the preliminary conclusion of a clinical trial.

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- AstraZeneca submitted the supplemental application of osimertinib in combination with chemotherapy for the treatment of adults with locally advanced or metastatic EGFR-mutated NSCLC to the NMPA in January 2024. Approval for this combination therapy is anticipated to be obtained during the second half of 2024. However, due to the poor physical condition of the targeted patients, the number eligible for this combination therapy may be relatively small. Consequently, the approval of osimertinib combined with chemotherapy is expected to have a limited impact on TY-9591 monotherapy, which is currently in pivotal/registrational clinical trials.

- According to Frost & Sullivan, it is in line with common practice for Livzon to have the option to terminate the Livzon Agreement within a reasonable notice period. In addition, due to the significant investment of time and resources made by licensees in drug development, it is not common for licensees to terminate license agreements, unless it becomes commercially unfeasible to continue.

- However, only approximately 25% of NSCLC patients with brain metastases in China are qualified to receive surgical treatment. Among these qualified patients, even fewer choose to receive surgical operations. This is likely because brain tumor surgery is an invasive procedure on the skull, which deters patients from choosing this type of treatment. For example, according to Frost & Sullivan, the most common type of surgery to remove a brain tumor is a craniotomy. This procedure involves making an incision in the scalp and removing a piece of bone from the skull to give the neurosurgeon access to the tumor.

- As of January 22, 2024, there were four third-generation EGFR-TKIs for the treatment of NSCLC approved for marketing in China. The average natural survival time for NSCLC with BM, rather than advanced stage III and stage IV NSCLC with BM, is one to two months, as recorded in the China Treatment Guidelines for Lung Cancer with Brain Metastases (2021 edition) (the latest treatment guidelines for lung cancer with brain metastases in China). There is no survival data for stage III and stage IV NSCLC with brain metastases. Zorifertinib by Alpha Biopharma is a first-generation EGFR-TKI, which does not constitute a competitor of TY-9591 because first-generation EGFR-TKIs have weaker efficacy compared to third-generation EGFR-TKIs, making it challenging for them to compete effectively.

- According to Frost & Sullivan, it is a common industry practice for biopharmaceutical companies to engage in similar CDMO transactions with external technology service providers during the process of pharmaceutical pilot scale-up, which is crucial in the drug development cycle allowing pharmaceutical companies to assess the scalability of the manufacturing process and identify any potential problems that may arise during full-scale production.
- According to Frost & Sullivan, the contract term of TY-9591 CCT Agreements are in line with the industry practice and therefore and imposing a restriction on the term of the TY-9591 CCT Agreements for a period of not more than three years would deviate from the market prevailing practice.