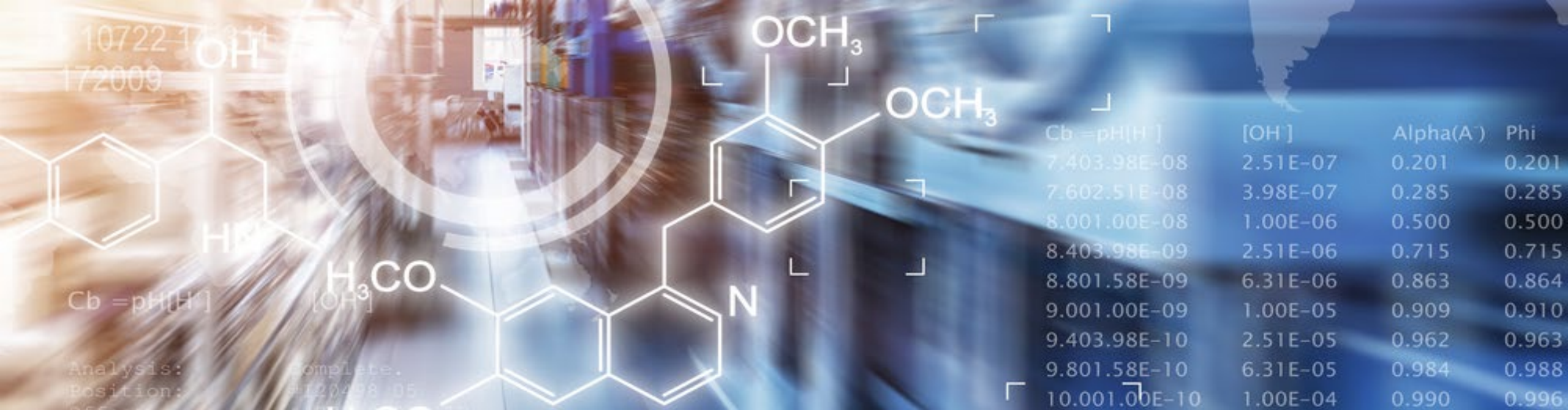

Project Audi

Industry Report on China's Innovative Drug Market

Sept. 2025

Terms and abbreviations (1/5)

Terms and abbreviations

Abb	Terms	Abb	Terms
ABL	Abelson	ATM	Ataxia Telangiectasia Mutated
AD	Auto-modification Domain	ATP	Adenosine Triphosphate
ADC	Antibody-drug Conjugate	AXL	AXL Receptor Tyrosine Kinase
ADCC	Antibody-dependent Cell-mediated Cytotoxicity	BC	Breast Cancer
ADR	Adverse Drug Reaction	BER	Base Excision Repair
AF1	Activation Function Domain-1	BL	Marginal Zone Lymphoma
AF2	Activation Function Domain-2	BRAF	B-Raf Proto-Oncogene
AI	Aromatase Inhibitor	BRCA1	Breast Cancer Susceptibility Gene 1
ALK	Anaplastic Lymphoma Kinase	BRCA2	Breast Cancer Susceptibility Gene 2
ALL	Acute Lymphoblastic Leukemia	BsAb	Bispecific Antibody
ALP	Alkaline Phosphatase	CCL	C–C motif Chemokine
AMA	Anti-mitochondrial Antibody	CD	Cluster of Differentiation
AML	Acute Myeloid Leukemia	CDC	Cell Division Cycle
APC	Antigen-presenting Cell	CDE	Center for Drug Evaluation
API	Active Pharmaceutical Ingredient	CDK	Cyclin-dependent Kinases

Source: China Insights Consultancy

Terms and abbreviations (2/5)

Terms and abbreviations

Abb	Terms	Abb	Terms
CEL	Chronic Eosinophilic Leukemia	DU	Duodenal Ulcer
CFDA	China Food and Drug Administration	EGFR	Epidermal Growth Factor Receptor
CIS	Carcinoma *in situ*	ER	Estrogen Recepto
CLL	Chronic Lymphocytic Leukemia	ER-stress	Endoplasmic Reticulum-Stress
CMA	Chinese Medical Association	ET	Essential Thrombocythemia
CML	Chronic Myelogenous Leukemia	FANCD2	Fanconi Anemia Group D2 Protein
CMML	Chronic Myelomonocytic Leukemia	FDA	Food and Drug Administration
CNL	Chronic Neutrophilic Leukemia	FISH	Fluorescence *in situ* Hybridization
COPD	Chronic Obstructive Pulmonary Disease	FL	Follicular Lymphoma
CSCO	Chinese Society of Clinical Oncology	FLT3	Fms-like Tyrosine Kinase-3
CTLA	Cytotoxic T-lymphocyte-associated Protein	FXR	Farnesoid X Receptor
DC	Dendritic Cell	GBD	Global Burden of Disease
DDR	DNA Damage Response	GC	Gastric Carcinoma
DLBCL	Diffuse Large B-cell Lymphoma	G-CSF	Granulocyte Colony-stimulating Factor
DNA-PK	DNA-dependent Protein Kinase	GERD	Gastroesophageal Reflux Disease

Source: China Insights Consultancy

Terms and abbreviations (3/5)

Terms and abbreviations

Abb	Terms	Abb	Terms
GGT	Gamma-glutamyltransferase	IND	Investigational New Drug
GU	Gastric Ulcer	KHK	Ketohexo Kinase
H_2RA	Histamine Type-2 Receptor Antagonist	KRAS	Kristen Rat Sarcoma Viral Oncogene Homolog
HCL	Hairy Cell Leukemia	LBL	Lymphoblastic Lymphoma
HER2	Human Epidermal Growth Factor Receptor 2	LPL	Lymphoplasmacytic Lymphoma
HL	Hodgkin Lymphoma	mAb	Monoclonal Antibody
HLA	Human Leukocyte Antigen-DR	MAH	Marketing Authorization Holder
HP	*Helicobacter pylori*	McAb	Monoclonal Antibody
HR	Hormone Receptor	MCL	Mantle Cell Lymphoma
HSCT	Hematopoietic Stem Cell Transplantation	MDS	Myelodysplastic Syndromes
IARC	International Agency for Research on Cancer	MET	Mesenchymal-epithelial Transition Factor
ID	Inhibitior of Differentiation	MHC	Major Histocompatibility Complex
IFN-γ	Interferon Gamma	MIIT	Ministry of Industry and Information Technology
IHC	Immunohistochemistry	MoA	Mecchanism of Action
IL	Interleukin	MPN	Myeloproliferative Neoplasms

Source: China Insights Consultancy

Terms and abbreviations (4/5)

Terms and abbreviations

Abb	Terms	Abb	Terms
MZL	Marginal Zone Lymphoma	NSCLC	Non-small Cell Lung Cancer
NAFL	Nonalcoholic Fatty Liver	NTRK	Neurotrophic Tyrosine Receptor Kinase
NAFLD	Nonalcoholic Fatty Liver Disease	OCA	Obeticholic acid
NASH	Non-alcoholic Steatohepatitis	ORR	Objective Response Rate
NDA	New Drug Application	PARP1	Poly ADP-ribose Polymerase-1
NDRC	National Development and Reform Commission	PBC	Primary Biliary Cholangitis
NERD	Non-erosive reflux disease	P-CAB	Potassium-Competitive Acid Blocker
NGS	Next Generation Sequencing	PCNA	Proliferating Cell Nuclear Antigen
NHEJ	Non-homologous End Joining	PD-1	Programmed Death Protein-1
NK	Natural Killer	PD-L1	Programmed Death-ligand 1
NLPHL	Nodular Lymphocyte-predominant Hodgkin Lymphoma	PFS	Progression-free Survival
NME	New Molecular Entity	PI3KCA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
NMPA	National Medical Products Administration	PMF	Primary Myelofibrosis
NPC	National People's Congress	PPI	Proton Pump Inhibitor
NRDL	National Reimbursement Drug List	PR	Progesterone Receptor

Source: China Insights Consultancy

Terms and abbreviations (5/5)

Terms and abbreviations

Abb	Terms	Abb	Terms
PROTAC	Proteolysis Targeting Chimeras	TAM	Tamoxifen
PU	Peptic Ulcer	TCM	Traditional Chinese Medicine
PV	Polycythemia Vera	T-DMI	Trastuzumab Emtansine
R&D	Research and Development	T-Dxd	Trastuzumab Deruxtecan
r/r	Relapsed/Refractory	TG	Triglyceride
RE	Reflux Esophagitis	TGFβ	Transforming Growth Factor-β
RET	Rearranged During Transfection	TKI	Tyrosine Kinase Inhibitor
ROS1	ROS Proto-oncogene 1	TNBC	Triple-negative Breast Cancer
SCLC	Small Cell Lung Cancer	TNFα	Tumor Nerosis Factor Alpha
SERD	Selective Estrogen Receptor Degrader	TP53	Tumor Protein P53
SERM	Selective Estrogen Receptor Modulator	TRAE	Treatment-related Adverse Event
SF3B1	Splicing Factor 3b Subunit 1	UDCA	Ursodeoxycholic Acid
SLL	Small Lymphocytic Lymphoma	USP1	Ubiquitin-specific Protease-1
STAT3	Signal Transducers and Activators of Transcription-3	VBP	Volume-Based Procurement
T2DM	Type 2 Diabetes Mellitus	ZES	Zollinger-Ellison Syndrome

Source: China Insights Consultancy

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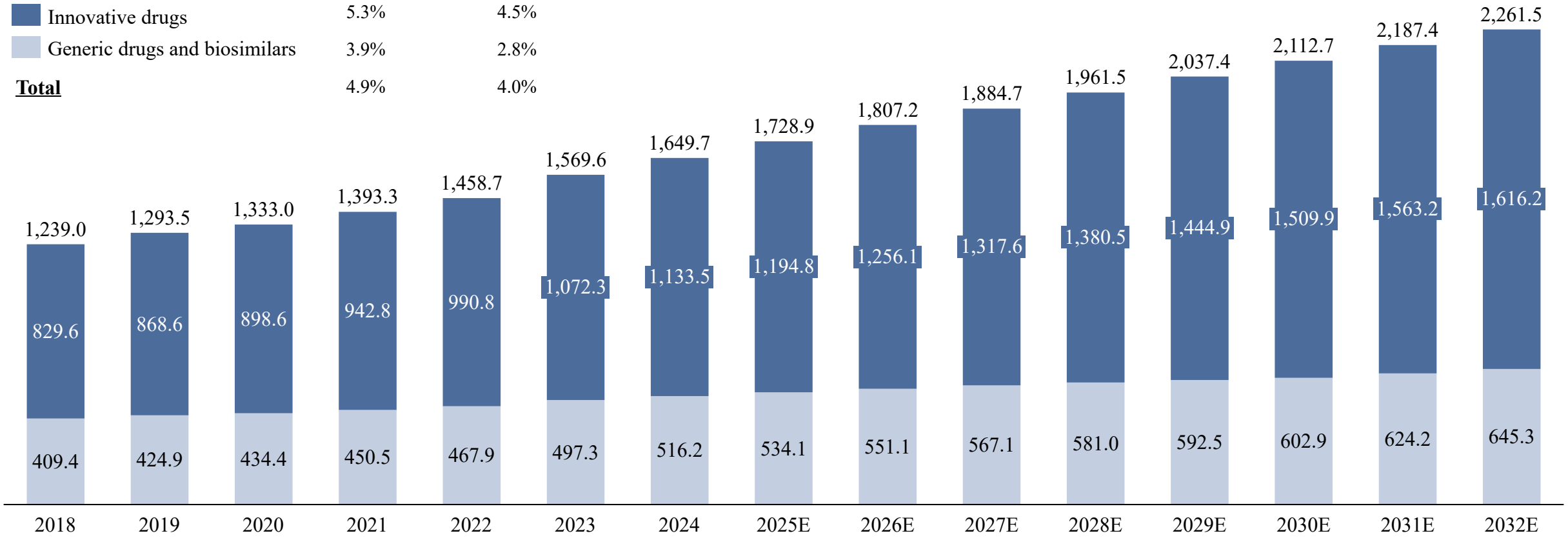
Global pharmaceutical market size, 2018-2032E

Global pharmaceutical market size, 2018-2032E

billion USD

CAGR	2018-2024	2024-2032E
Innovative drugs	5.3%	4.5%
Generic drugs and biosimilars	3.9%	2.8%
Total	4.9%	4.0%



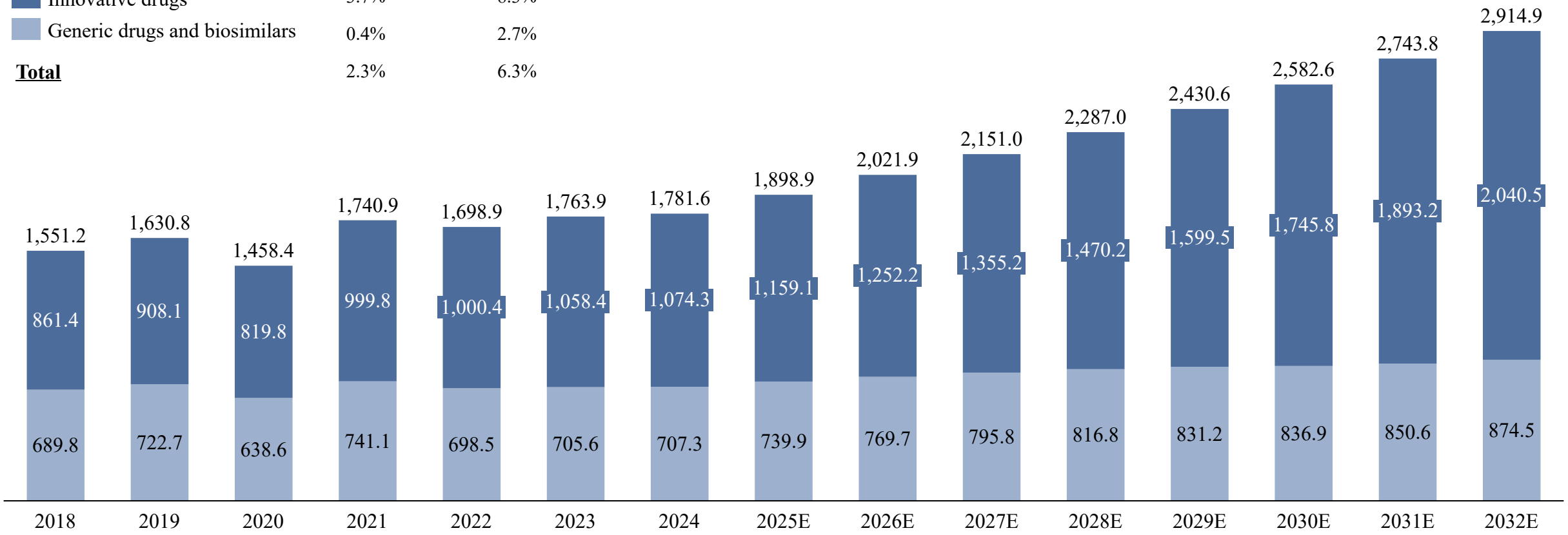
Source: China Insights Consultancy

China’s pharmaceutical market size, 2018-2032E

China’s pharmaceutical market size, 2018-2032E

CAGR	2018-2024	2024-2032E
Innovative drugs	3.7%	8.3%
Generic drugs and biosimilars	0.4%	2.7%
Total	2.3%	6.3%

billion RMB

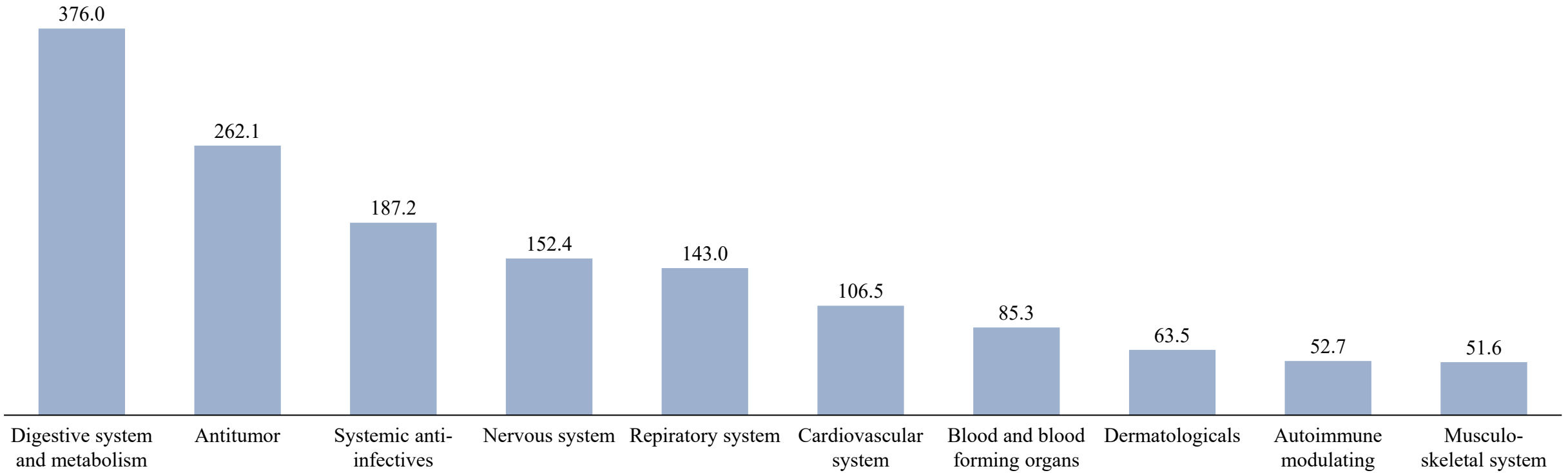


Note: the market size in 2020 and 2022 decreased due to the influence of COVID-19.

Source: China Insights Consultancy

Top 10 therapeutic areas in terms of revenue globally, 2024

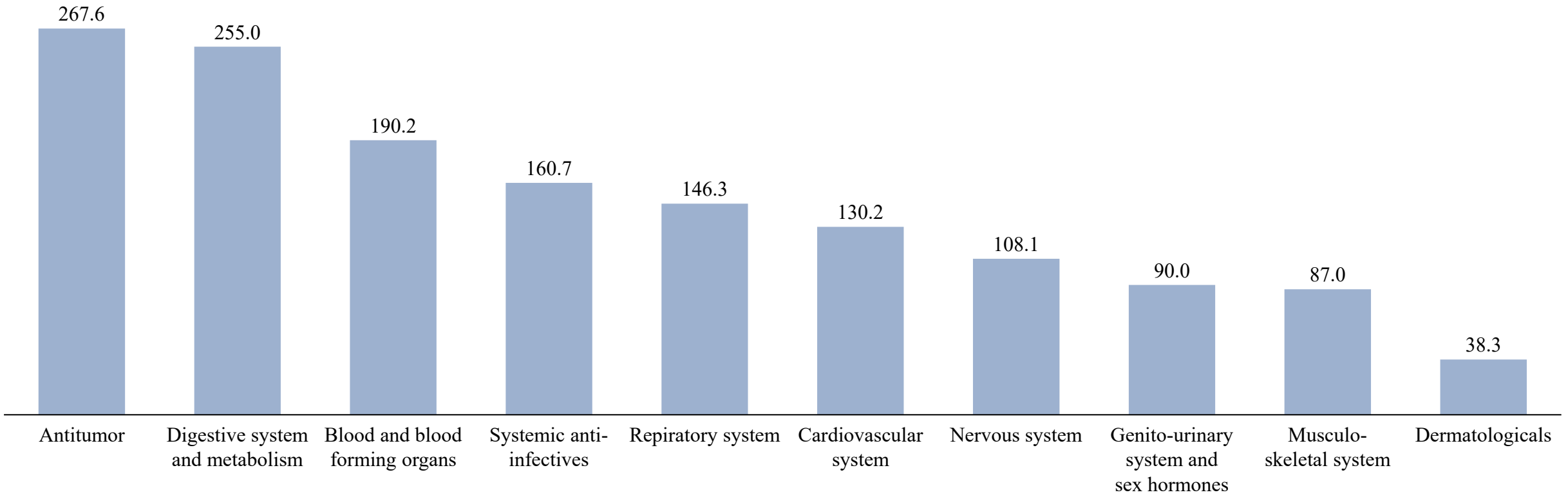
billion USD



Source: China Insights Consultancy

Top 10 therapeutic areas in terms of revenue in China, 2024

billion RMB



Source: China Insights Consultancy

Introduction to innovative drugs

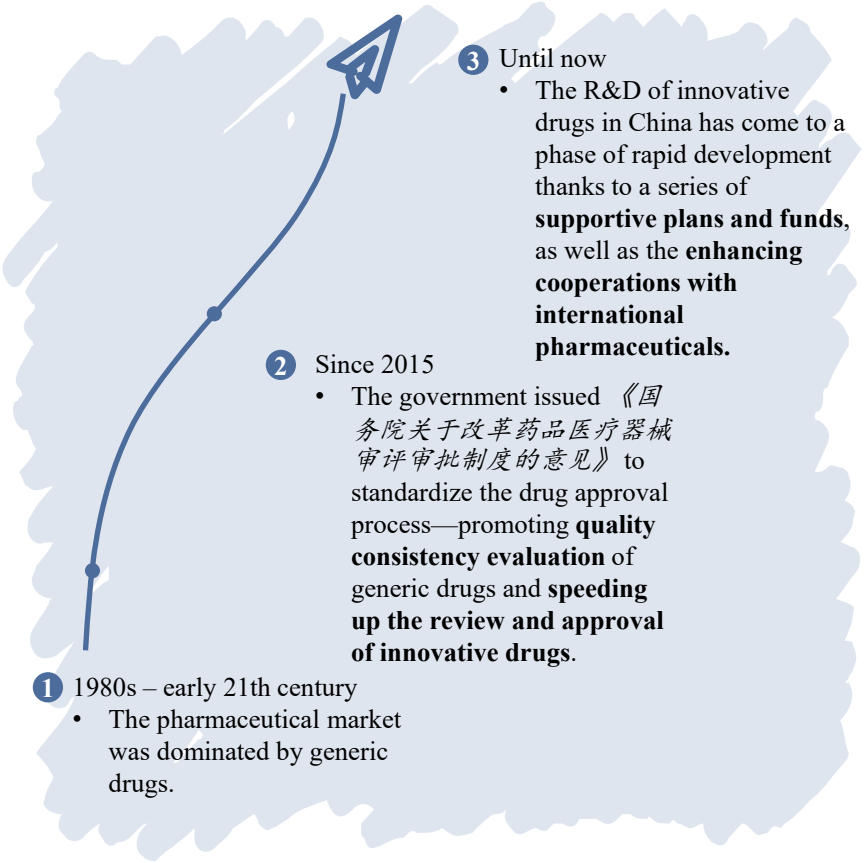
Introduction and classification:

- According to *Drug Registration Management Measure* issued by NMPA in 2020, innovative drugs(excluding TCM) refers to large- or small molecules that have not been marketed anywhere around the world.

Small-molecule drugs (化学药品)	Description
Category I	• Innovative drugs that **have not been marketed in China or abroad**, referring to drugs that contain **NMEs with clear structures, pharmacological effects and clinical value.**
Category II	• Improved new drugs that have been optimized in structure, dosage form, prescription process, route of administration, indications, etc. based on known active ingredients.
Category III	• Domestic MAHs have a generic version over the original drug that is marketed abroad but not in China.
Category IV	• Domestic MAHs have a generic version over the original drug that is marketed in China.
Category IV	• Drugs that have been marketed abroad apply for a market authorization in China(including original drugs, improved new drugs and generic drugs).
Therapeutic biologic products (治疗用生物制品)	**Description**
Category I	• Innovative biological products **that have not been marketed in China or abroad.**
Category II	• Improved biological products.
Category III	• Biological products that have been marketed in China or abroad.

Development history:

- The innovative drugs market in China has gone through a period of exploration, standardization and rapid development.



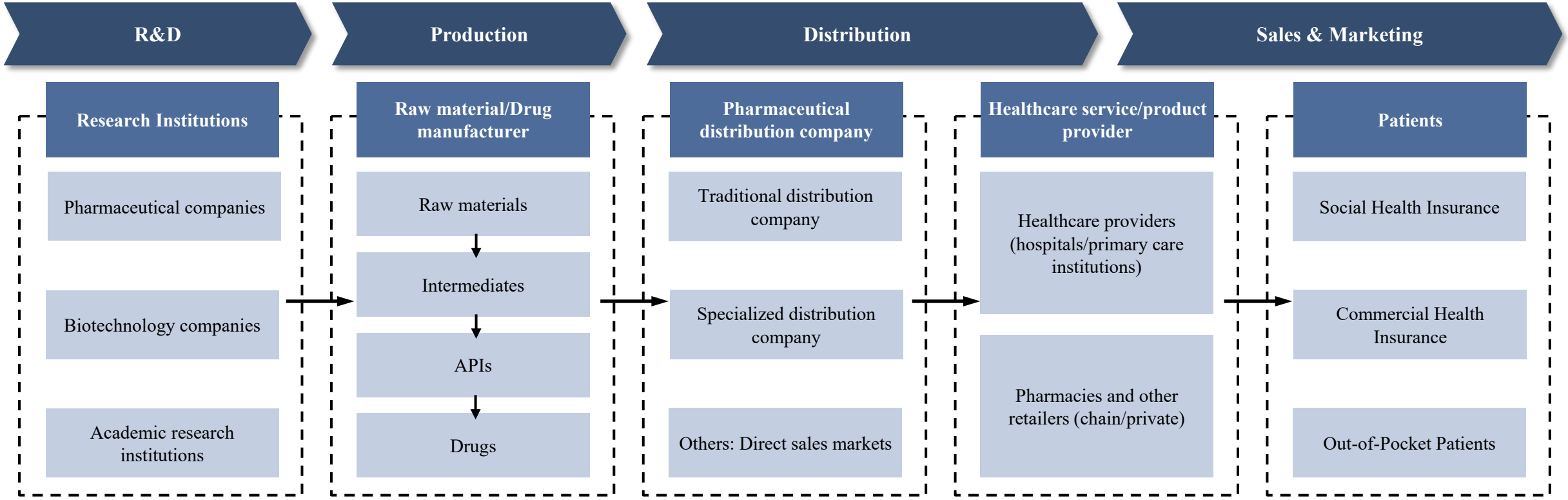
Note: NMEs stand for new molecular entities, referring to active ingredients that contain no active moiety that has been previously approved by the Agency in an application according to FDA.

Source: NMPA; China Insights Consultancy

The pharmaceutical industry value chain spans from upstream raw material producers and drug manufacturers to downstream sales terminals like hospitals, pharmacies, and patients

Pharmaceutical market value chain analysis

- The pharmaceutical industry is a crucial component of the national economy.
- Within the pharmaceutical industry, **raw material producers and drug manufacturers** are positioned at the upstream end of the value chain, providing production services. **Commercial companies** offer distribution and logistics services for the pharmaceutical industry. The downstream end of the value chain includes sales terminals such as **hospitals, pharmacies, and patients**.



Source: China Insights Consultancy

Analysis and comparisons of R&D models of innovative drugs in China

China's innovative drugs market → R&D models

R&D models	Revenue allocation	Cost allocation	Risk bearing	Resource	Requirement for R&D capability
Independent R&D model • A company **initiates and conducts R&D projects** independently by self-established teams.	• Revenue from successfully marketed products exclusively goes to the company.	• The R&D cost is undertook entirely by the company.	• The company to bear total risks all around the value chain.	• The resources are internally derived.	• The company is required to have robust experience and technical accumulations.
License-in model • A company(licensee) **acquires the rights** to a product, technology, or intellectual property from another organization(licensor).	• The licensee pays royalties, upfront, milestone fees and even sales milestones to the licensor.	• The licensee is not necessarily obliged to take cost of R&D.	• The licensee to bear risks in clinical development.	• The resources are internally derived.	• It depends on the pipeline screening and clinical translation of the licensee.
Co-development model • To develop a new drug together with one or more other organizations.	• The allocation is up to the co-development contract to meet expectations from all parties.	• The cost is shared by all parties according to the contract.	• Risks to be shared.	• Resources are shared among all parties.	• It sets high standards for all parties in terms of personnels, funds, channels.

Source: China Insights Consultancy

China continues to deepen reforms in pharmaceutical review and approval, gradually transitioning the drug market towards a landscape led by innovative drugs (1/2)

Overview of China's policy encouraging innovation in innovative drugs

Department	Policy Name	Key Contents	Issuance Time
The State Council	《全链条支持创新药发展实施方案》	Strengthen policy support across the entire chain-coordinating price management, insurance, drug allocation, investment, and optimizing review and assessment mechanisms-to drive breakthroughs in innovative drugs. Mobilize innovation resources and reinforce basic research to lay a solid foundation for China's innovative pharmaceutical development	2024-07
National Health Commission	《深化医药卫生体制改革 2023年下半年重点工作任务》	Promoting medical and pharmaceutical reform and innovation. Supporting drug R&D innovation, standardizing centralized procurement to ensure quality and availability of medications	2023-07
CDE	《药审中心加快创新药上市许可申请审评工作规范(试行)》	This accelerated review and approval process targets three categories of innovative drugs: breakthrough therapy drugs, innovative drugs for children, and innovative drugs for rare diseases, expediting their market entry to meet the medication needs of relevant patients	2023-04
The State Council	《"十四五"市场监管现代化规划》	Steadily enhance the safety, efficacy, and accessibility of drugs. Optimize management methods to accelerate the market entry of new and high-quality drugs. Improve rapid review and approval mechanisms for innovative drugs and vaccines, speeding up access to urgently needed drugs for clinical use and rare disease treatments. Strengthen guidance for the development of major innovative drugs. Encourage simultaneous domestic and international research and application for new drugs	2023-04
The State Council	《"十四五"国民健康规划》	Deepen the reform of the drug and medical device review and approval system. Accelerate the review and approval of qualifying innovative drugs, urgently needed drugs in short supply, medical devices, and treatments for rare diseases	2022-05
NMPA	《中华人民共和国药品管理法实施条例(修订草案征求意见稿)》	In the event of a patent dispute during a drug registration application, the parties may file a lawsuit in the people's court or apply for an administrative ruling from the State Council's patent administration department. During this period, the technical review of the drug will not be suspended	2022-05
CDE	《单臂临床试验用于支持抗肿瘤药上市申请的适用性技术指导原则》	The development strategy of single-arm clinical trials has significantly shortened the time to market for new drugs. In recent years, many new drugs have demonstrated highly promising efficacy data in the early stages of clinical research. As a result, an increasing number of development companies are opting to use single-arm clinical trials to support the marketing applications for anti-tumor drugs	2022-03
CDE	《药审中心加快创新药上市申请审评工作程序(试行)(征求意见稿)》	The main focus is to encourage the research and development of new drugs to meet clinical needs, promptly summarize and apply experiences from emergency reviews during the pandemic, and accelerate the review process for innovative drugs	2022-02

Source: CDE; NMPA; China Insights Consultancy

China continues to deepen reforms in pharmaceutical review and approval, gradually transitioning the drug market towards a landscape led by innovative drugs (2/2)

Overview of China's policy encouraging innovation in innovative drugs

Department	Policy Name	Key Contents	Issuance Time
MIIT and others	《"十四五"医药工业发展规划》	Promoting the industrialization and application of innovative drugs and high-end medical devices, and improving the support system for pharmaceutical innovation	2022-01
The State Council	《"十四五"市场监管现代化规划》	Improving the rapid review and approval mechanisms for innovative drugs, vaccines, and medical devices to accelerate the review and approval process for urgently needed drugs for clinical use, treatments for rare diseases, and medical devices	2022-01
NDRC	《"十四五"生物经济发展规划》	Developing synthetic biology technologies and promoting innovation in synthetic biology. Systematically advancing applications in areas such as new drug development, disease treatment, agricultural production material synthesis, environmental protection, energy supply, and new material development	2021-12
NMPA	《"十四五"国家药品安全及促进高质量发展规划》	The regulatory environment supporting high-quality industrial development is further optimized. The reform of the review and approval system continues to deepen, approving a batch of urgently needed innovative drugs for clinical use, accelerating the market entry of innovative drugs with clinical value to promote public health. The evaluation capability of innovative products has significantly improved, enabling globally innovative drugs and medical devices applied for in China to be quickly launched in the domestic market	2021-12
The State Council	《"十四五"全民医疗保障规划》	Improving the evaluation mechanism for drugs covered by medical insurance, strengthening the monitoring of the implementation of the medical insurance drug list and the evaluation of innovative drugs, supporting pharmaceutical innovation, and enhancing the accessibility of negotiated drugs	2021-09
NPC	《中华人民共和国国民经济和社会发展第十四个五年规划和2035年远景目标纲要》	Improving the rapid review and approval mechanisms for innovative drugs, vaccines, and medical devices, accelerating the review and approval of urgently needed drugs and medical devices for clinical use and rare disease treatments, and facilitating the prompt domestic launch of urgently needed new drugs and medical devices already approved abroad	2021-03
NDRC and others	《关于扩大战略性新兴产业投资培育壮大新增长点增长极的指导意见》	Implement a biotechnology benefit project to create a market for domestically innovated drugs and other products	2020-09
NMPA	《突破性治疗药物申评工作程序(试行)》	During clinical trials, applicants can apply for the breakthrough therapy designation for innovative or improved new drugs that treat life-threatening diseases or significantly improve quality of life, typically no later than the start of phase I trials	2020-07

Source: CDE; NMPA; China Insights Consultancy

Following NDA, access to NRDL and bid for regional or centralized VBP are two major events that could potentially impose pressure of price reduction

National Drug Reimbursement list application and inclusion process

1. Product launch after regulatory approval
2. Preparation for NRDL listing
3. Pharma companies submit application
4. Expert review and vote for shortlist
5. Price negotiation and tendering
6. NRDL inclusion results

- Preliminary conditions and criteria for eligibility of NRDL released
- Pharmaceutical companies could prepare required qualifications and documents accordingly

- Experts assess clinical value, budget impact and cost-effectiveness of underlying drugs proposed to be included in NRDL

- Drug manufacturers present price quote and bid for NRDL inclusion
- If proposed price exceeds certain threshold, drug manufacturers may lose the bid

- Two drug groups in NRDL with different reimbursement level
- Class A: 100% reimbursed
- Class B: partially reimbursed, varies across municipalities and provinces

- In the new 2024 NRDL, 91 new drugs were added, and their prices were reduced by an average of 63% through negotiations and bidding.
- The catalog now contains a total of 3159 drugs, including 1,765 western medicines and 1,394 traditional Chinese medicines. The new version of the NDRL has added drugs in areas such as anti-tumor, rare diseases, and antivirals. Drugs for chronic diseases such as diabetes have also been included, such as Dorzagliatin for type 2 diabetes patients.

Evolution of centralized VBP program

2018.11 4+7 pilot | 2019.9 4+7 expansion | 2019.12 2nd round | 2020.7 3rd round | 2021.1 4th round | 2021.6 5th round | 2021.11 6th round | 2022.7 7th round | 2023.3 8th round | 2023.11 9th round | 2024.12 10th round

Scale	11 pilot cities	25 provinces	nationwide	nationwide	nationwide	nationwide	Nationwide (for Insulin)	nationwide	nationwide	nationwide	nationwide
# of drugs	25	25	32	55	45	61	16	61	39	42	62
Avg price cut	52%	59%	53%	53%	52%	56%	48%	48%	56%	58%	75%

- China's volume-based procurement (VBP) program encourages generic drug use and reduces costs for off-patent drugs. Initially covering 11 cities in 2018, it quickly expanded nationwide.
- From the second batch, the VBP threshold was set at three companies, adjusted to four or more from the seventh batch.
- Centralized procurement for drugs has yielded cost savings by creating economies of scale and improving purchasing and negotiation power over pricing by pooling procurement process for drugs across multiple buyers. Pharma companies in turn should design market access strategies to cope with expected price cut.

Source: NHSA; frontiers; China Insights Consultancy

Growth drivers and trends in innovative drugs development

Drivers and trends in innovative drugs development

Growth drivers & Future trends	
 **Rising population aging and people's awareness of health**	• **China's population is aging increasingly**, which will inevitably rise the prevalence of chronic diseases and drive the need for innovative treatment options. IARC's 2023 report shows 20 million new cancer cases and 9.7 million deaths globally. Lung cancer and female breast cancer are the most commonly occurring cancers worldwide, accounting respectively for 12.4% and 11.6% of total new cases in 2023 • In addition, the improvement of people's living standards will **increase their awareness of health**. As more patients' diseases are diagnosed at an early stage, more and more patients are willing to choose innovative drugs with better effects and fewer side effects to treat their diseases, which is bound to promote the growth of the innovative drug market
 **Ongoing advancements in technology and research**	• Ongoing advancements in technology have enabled the design and production of innovative drugs with improved efficacy and safety profiles. Novel advancement such as **wider selection of targets, antibody-drug-conjugates** are enhancing the therapeutic potential of targeted anti-cancer drugs. And the small molecule innovative drugs have been **kinase inhibitors, epigenetic inhibitors and proteasome inhibitors and others** • With the technological development, AI and computer-assisted drug development are becoming mainstream, and technological ideas such as PROTAC technology, allosteric modulator, and deuterated drugs are also highly anticipated
 **Growing investments in research and development activities**	• Growing investments in research and development activities by pharmaceutical and biotechnology companies are driving the development of innovative drugs. These investments aim to **explore new therapeutic targets and enhance the efficacy of existing treatments** • Collaborations and partnerships between pharmaceutical companies, and academic institutions are driving the development and commercialization of innovative drugs. These collaborations leverage complementary expertise and resources to accelerate drug discovery and development processes
 **Policies support new drug development**	• In recent years, the government have introduced several policies to support the development of innovative drugs, including **optimizing the review and approval process for new drugs, promoting medical insurance payment, encouraging investment and financing support, price management** and others. For example, 2022.01, MIIT and others released《"十四五"医药工业发展规划》, 2022.03, CDE published《单臂临床试验用于支持抗肿瘤药上市申请的适用性技术指导原则》and 2023.04, CDE posted《药审中心加快创新药上市许可申请审评工作规范(试行)》,etc. • The implementation of these policies is expected to greatly enhance the innovation capabilities of the pharmaceutical industry, accelerate the research and development and market launch of innovative drugs, and increase the commercialization success rate of innovative drugs, thereby promoting the high-quality development of the entire pharmaceutical industry

Source: China Insights Consultancy

Entry barriers to innovative drug industry

Entry barriers to innovative drug industry

Entry barriers	
Regulatory Hurdles: Strict Regulations and Lengthy Approval Processes	• The Chinese innovative drug market is highly regulated, with **complex frameworks** imposed by national health authorities in each step of the drug development process. Pharmaceutical/biotech companies must comply with these stringent regulations, which require significantly increased monetary and time input • After a drug is approved, it is subject to **ongoing monitoring** of adverse events and efficacy, which can add to regulatory burden. Companies must also negotiate with healthcare payers to obtain reimbursement and achieve favorable market access
Technological Expertise Required in R&D and Manufacturing	• Early-stage drug development faces challenges in **identifying suitable molecular targets and selecting a lead compound** that effectively modulates the target. Disease-causing cells often lack a uniform target, and a single disease can stem from diverse phenotypic variants. These issues complicate innovative drug discovery • Lead compounds must go through preclinical studies (in cell cultures and animals), formulation development, translation into clinical trials, and commercialization, each of which requires a different skill set
Capital Intensity: Significant Financial Investment for New Drug R&D	• Developing a new drug requires extensive preclinical and clinical trials to ensure safety and efficacy, as well as drug development and manufacturing scale-up, which in total **cost hundreds of millions to billions of dollars**. The high costs and extended development periods deter new entrants, who must gather substantial resources before generating any revenue • The **success rate of drug development is low**, and many candidates fail during clinical trials or regulatory approval, at the end of the drug discovery process. This uncertainty discourages investment, especially in high-risk innovative therapies targeting unmet medical needs
Talent Management: High Recruiting Standards and Extensive Training	• Innovative drug development involves expertise ranging from biochemistry and medicine to business development and marketing. Talents must be adept at **multidisciplinary tasks**. For example, a business development expert should also understand the mechanism and clinical performance of the drug to be promoted, and a medical expert must know regulatory requirements while designing clinical trials • Investing in talent education and training programs can accelerate innovation. However, companies must also manage the resources required for training and the risk of losing trained talent to competitors

Source: China Insights Consultancy

Summary of core and key products of Xuanzhu Biopharmaceutical 2024

Summary of core and key products of Xuanzhu Biopharmaceutical 2024

Product	Anaprazole	XZP-3287	XZP-3621	KM602	KM501	XZP-7797	XZP-6924
Approved competitors	• 6 types (PPIs)	• 6 types (CDK4/6 i)	• 8 types (ALK-TKI)	• 0 (CD80-Fc fusion protein)	• 0 (HER2/HER2-ADC)	• 6 types (PARPi)	• 0 (USP1 inhibitor)
Eligible incidence in China, 2024	• 55.8 mn ppl (DU) • 38.3 mn ppl (RE)	• 315.5 k ppl (early stage and advanced HR+/HER2- BC)	• 74.4 k ppl (1st-line ALK+ advanced NSCLC) • 16.8 k ppl (resectable ALK+ NSCLC)	• 524.0 k ppl (NSCLC, melanoma, CRC, GC with PD-L1 high expression)	• 914.2 k ppl (BC, gastric cancer, biliary cancer, and NSCLC with HER2 expression)	• 316.7 k ppl (solid tumor with HRD or BRCA mutation)	• 316.7 k ppl (solid tumor with HRD or BRCA mutation)
Alternative treatment	• Other PPI: Ilaprazole/ Omeprazole • P-CAB/H_2RA	• Other CDK4/6i: Ribociclib/ Dalpiciclib • Chemotherapy/T-Dxd/AIs/Everolimus	• Other ALK-TKI: Crizotinib/ Lorlatinib/ Brigatinib • Chemotherapy ± immunotherapy	• PD-1/PD-L1 inhibitors: Nivolumab/ Pembrolizumab/ Duvaliusumab • Clinical trials	• Clinical trials	• Other PARPi: Olaparib/ Pamiparib/ Niraparib • Chemotherapy ± immunotherapy/ Endocrine therapy	• PARPi: Olaparib/ Pamiparib/ Niraparib • Chemotherapy ± immunotherapy/ Endocrine therapy
Underlying pricing* (RMB)	• 11/20 mg[1]	• ~70/360 mg[2]	• ~170/250 mg[2]	• ~3,300/month[2]	• ~7,000/month[2]	• ~8,000/month[2]	• ~8,000/month[2]
Year of availability	• Since 1994 (Lansoprazole)	• Since 2018 (Palbociclib)	• Since 2013 (Crizotinib)	• Expected to be approved in 2033 (KM602)	• Expected to be approved in 2027 (JSKN003)	• Since 2018 (Olaparib)	• Expected to be approved in 2032 (HSK39775)

Note: 1 NRDL price; 2 Underlying pricing is obtained from a comprehensive consideration of the price upon approval and current price of approved competitors or alternative treatments

Source: CDE; Drug Instructions; China Insights Consultancy

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Introduction to peptic ulcer (PU)

Definition of PU

- **Peptic ulcer (PU)** refers to the inflammatory reaction, necrosis, and shedding of mucosa caused by various pathogenic factors, forming ulcers. PU is a common chronic disease, which can occur in the esophagus, stomach, or duodenum, with the stomach and duodenum being the most common.

Risk factors of PU

Gastric acid and pepsin: The excessive secretion of gastric acid and pepsin are considered as the most important risk factor of PU, which may destroy the barrier and damage the gastric mucosa directly.

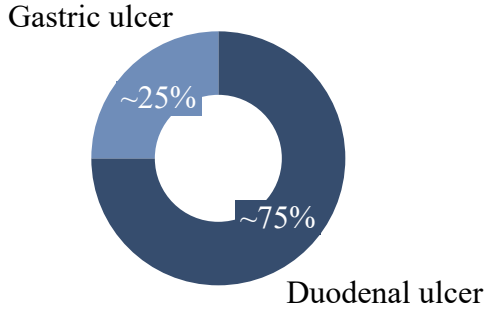
HP infection: It has been reported that HP infection is highly related to the onset of PU. More than 50% of PU patients are infected by HP, making the elimination of HP vital for the recovery of PU.

Medication: The long-term usage of a series of medication would damage the protection of gastric mucosa, leading to the onset of PU. Among which, NSAIDs are the most common ones.

Genetic factors: Some patients are with a family history of PU, indicating the genetic factors may play a role in the onset of PU.

Other factors: The addiction of alcohol and cigarettes, stress effects, and other systemic diseases showed significant coloration to the onset of PU.

Classification of PU



- According to the affected area, PU can be classified into two main types, **GU** and **DU**. The ratio of incidence rate between GU and DU is approximately 1:3.
- Very few patients may suffer from compound ulcers.

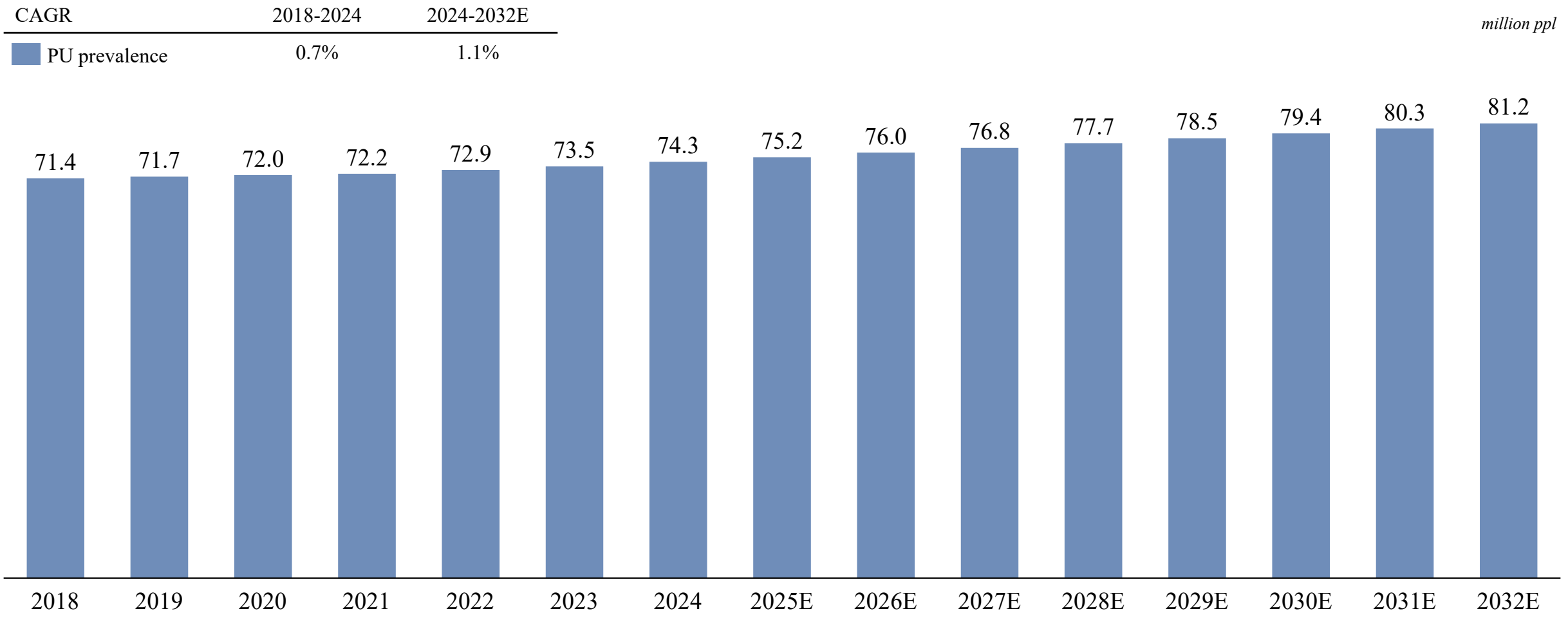
Diagnosis of PU

- Gastroscopy is the **most important** basis for diagnosing PU.
- Radiology and ^{13}C urea breath tests may be helpful in the diagnosis of PU.

Source: CNKI; Internal Medicine; China Insights Consultancy

The prevalence of PU in China, 2018-2032E

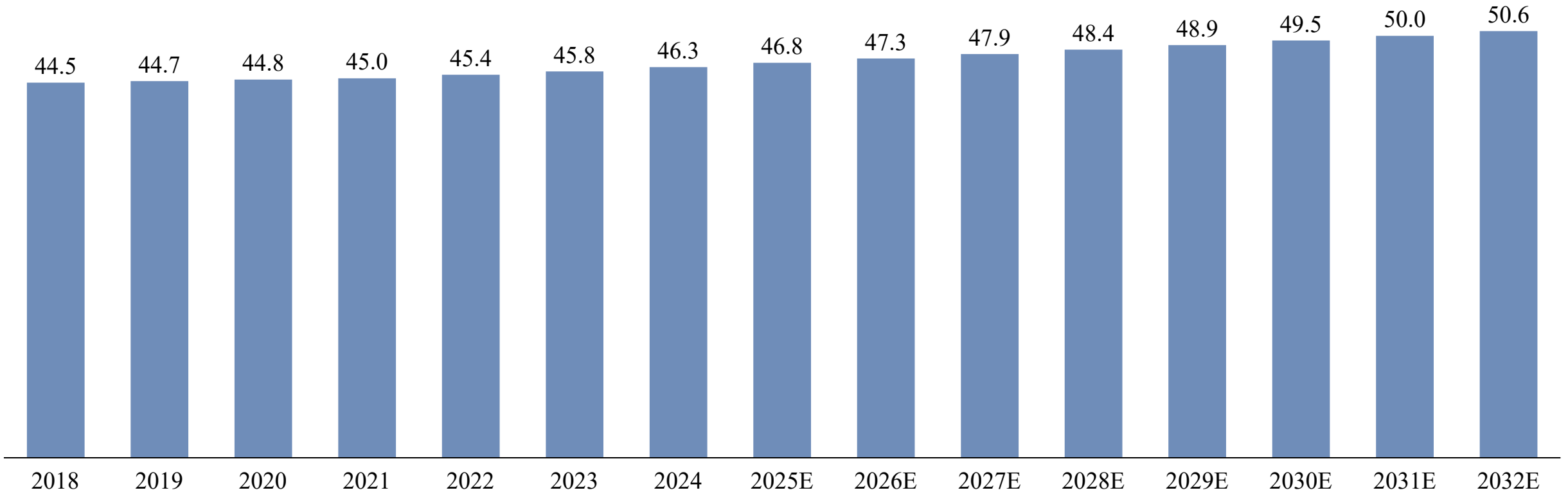
The prevalence of PU in China, 2018-2032E



Source: China Insights Consultancy

The prevalence of PU patients diagnosed with Helicobacter Pylori infections

CAGR	2018-2024	2024-2032E
PU patients diagnosed with Helicobacter Pylori infections	0.7%	1.1%



Source: China Insights Consultancy

Treatment for PU

Main Treatment

- Antisecretory treatment is the preferred therapy for PU.

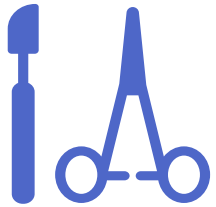
- H_2RA drugs are the firstly-developed ant-isecretory drugs. With its acceptable effect, reasonable price, and rare ADRs, it is still an option for PU patients.
- **PPI drugs are now the first choices for PU patients**. PPIs inhibits proton pumps directly, bringing strong antisecretory effect. More than 80% of GU and 90% of DU can be healed within 4 weeks by using PPI drugs.
- P-CAB drugs are the newly-developed antisecretory drugs with even stronger antisecretory effect. But due to the ambiguous mechanism, these drugs haven't been largely applied yet.

Summary of representative antisecretory drugs

Type	Drug	Size (mg/tablet)	Therapeutic dosage (mg)	Maintenance dosage (mg)
H_2RA	Famotidine	20	20, bid	20, qd
H_2RA	Ranitidine	150	150, bid	150, qd
PPI	Anaprazole	20	20, qd	-
PPI	Omeprazole	10/20	20, qd	20, qd
PPI	Pantoprazole	20	40, qd	20, qd
PPI	Rabeprazole	10	20, qd	10, qd
P-CAB	Keverprazan	10	20, qd	-

Supplementary Treatment

- More than 50% of PU patients are infected by HP. HP infection is also considered as one of the risk factors for PU. It is recommended that PU patients with HP infection should accept a 2-week antibiotic treatment.



- PU patients with active bleeding or esophageal obstruction should accept endoscopic therapy. For patients with severe active bleeding, esophageal perforation, suspect cancerization, or other symptoms that cannot be relieved under endoscope, surgery is their final option.

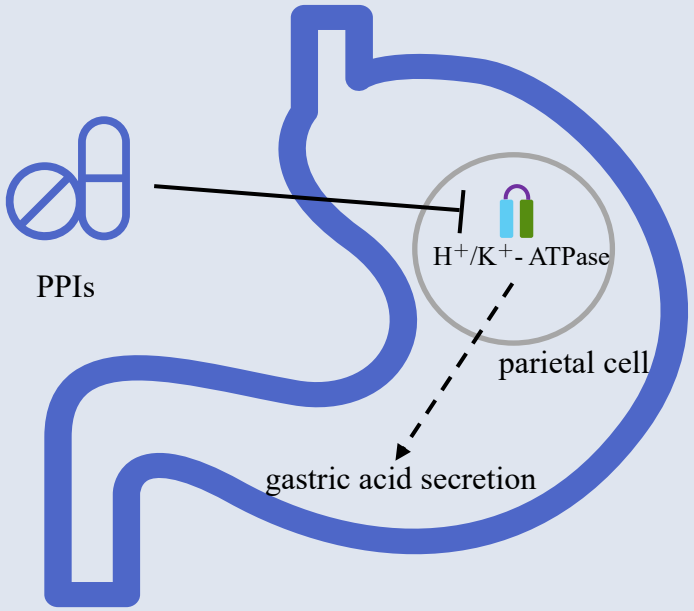
- Relieving mental stress, quitting smoking and alcohol would be of great help for PU patients. Bismuth and antiacid drugs with weak alkalinity are recommend for mild PU patients to relieve intermittent discomfort.

Source: Internal Medicine; Drug Instructions; China Insights Consultancy

With strong antisecretory effect and reasonable price, PPIs are the main drugs for PU

Summary of common antisecretory drugs

	P-CAB	H_2RA	PPI
Antisecretory effect	★★★★★	★★☆☆☆	★★★★☆
Price	★★★★☆	★☆☆☆☆	★★☆☆☆
Side effect	• Unclear • Minor	• Clear • Minor	• Clear • Minor
Mechanism	• Inhibiting K^+ from binding with the H^+/K^+ - ATPase reversibly	• Blocking the H_2 receptor on parietal cells	• Inhibiting the H^+/K^+ - ATPase irreversibly
Features	• Unnecessary to be activated, leading to a more rapid and stronger antisecretory effect	• Inhibiting the proton pumps indirectly, with mild antisecretory effect	• Inhibiting the proton pumps directly, leading to a durable and strong antisecretory effect
Representative drugs	• Vonoprazan • Tegoprazan	• Roxatidine • Cimetidine	• Omeprazole • Rabeprazole



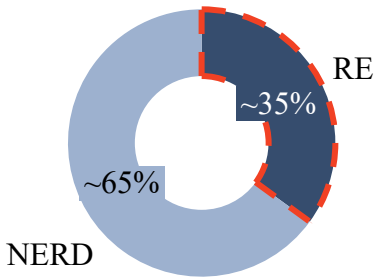
- PPIs would be sent to extracellular fluid from blood and enter the parietal cells eventually. A disulfide covalent bond would be formed between PPI and H^+/K^+- ATPase which is responsible for the gastric acid secretion, leading to the strong antisecretory effect.
- With **over 90% cure rate** and a wide range of indications, PPIs have long been considered as the main drugs for PU.

Source: CNKI; Drug Instructions; China Insights Consultancy

Introduction to reflux esophagitis (RE)

Introduction to RE

Distribution of GERD



- GERD is defined as a discomfort caused by the reflux of gastric contents. GERD can be divided into RE and NERD according to the existence of esophageal mucosal erosion. As reported in academic articles, approximately 35% of GERD can be categorized as RE.
- By gastroscopy, the degree and scope of esophageal injury can be observed, which are essential for the diagnosis and classification of RE.

Etiology of RE

- **LES dysfunction** LES is the sphincter located at the bottom of esophagus, responsible for preventing gastric contents from entering the esophagus. The dysfunction of LES may lead to the onset of RE.
- **Reduced esophageal clearance effect** Esophageal is able to clear out small amounts of refluxed gastric contents. The reduced esophageal clearance effect may cause the onset of RE.
- **Damaged esophageal mucosal barrier** Smoking, taking alcohol, and having irritation food will damage esophageal mucosal and cause RE.

Classification of RE*

Class	Gastroscopy findings
Normal	No rupture observed on esophageal mucosa
Class A	More than one rupture observed with the longest diameter ＜ 5 mm
Class B	More than one rupture observed with the longest diameter ＞ 5 mm; no fused lesion observed
Class C	The lesions are fused, but less than 75% circumference of the esophagus is damaged
Class D	The lesions are fused, more than 75% circumference of the esophagus is damaged

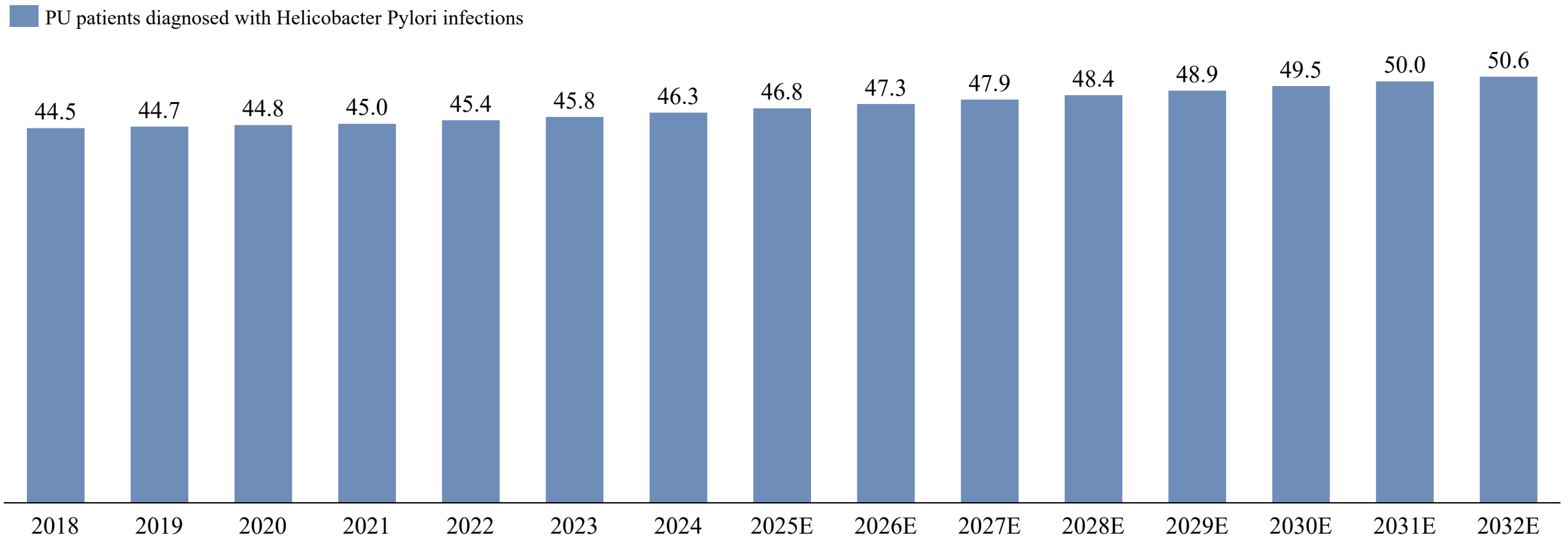
*: According to Los Angles Classification System

Complications of RE

- **UGIB:** The rupture on esophageal mucosa may damage the blood vessel nearby, leading to haematemesis or melena. Severe UGIB with massive blood lost may endanger the life of the patient.
- **Esophageal stenosis:** The scar left by the rupture on esophageal mucosa may cause esophageal stenosis afterward. Patients with severe esophageal stenosis requires surgical treatment.
- **Barrett esophagus:** The recurrent onset of RE may lead to the squamous epithelium of esophageal mucosa covered by columnar epithelium, very few of which may develop into adenocarcinoma.

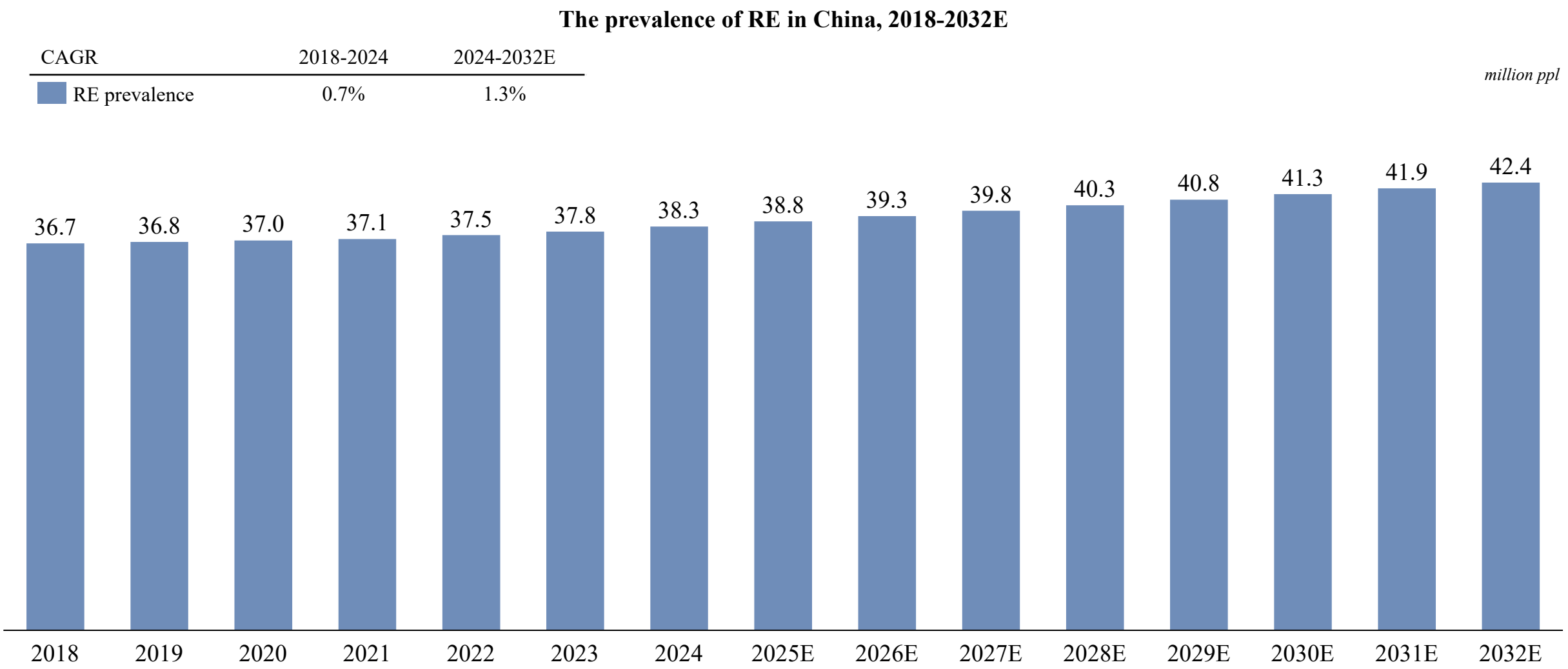
Source: CNKI; Internal Medicine; China Insights Consultancy

The prevalence of PU patients diagnosed with Helicobacter Pylori infections



Source: China Insights Consultancy

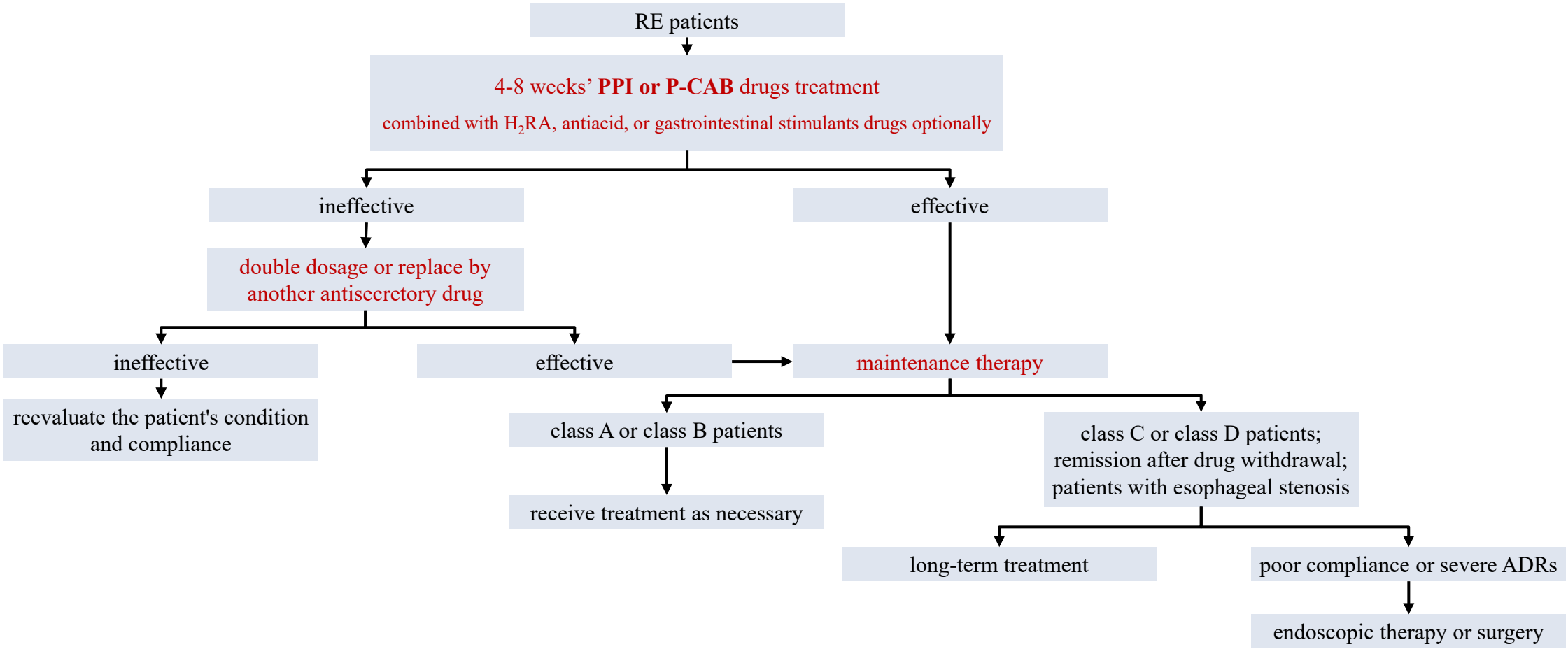
The prevalence of RE in China, 2018-2032E



Source: China Insights Consultancy

Treatment path for RE, CMA

Treatment path for RE, CMA



Source: CNKI; China Insights Consultancy

Summary of innovative clinical pipelines for PU and RE in China, as of LPD

Summary of innovative clinical pipelines for PU and RE in China, as of LPD

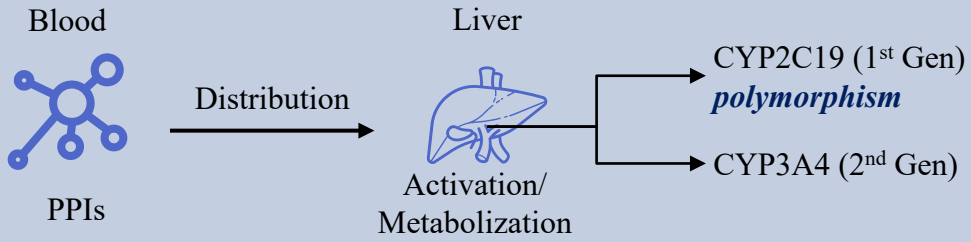
Type	Drug Name	Company	Phase	Indications	First Posted Date	Trial Number
PPI	Anaprazole	Xuanzhu Biopharma	II	RE	2022-11-03	CTR20222800
P-CAB	JP-1366	Livzon Pharma	NDA	RE	2025-08-15	CTR20243235
P-CAB	XC2309	Zhejiang Medicine	II	DU	2024-08-27	CTR20243235

Note: PU stands for peptic ulcer; GERD stands for gastroesophageal reflux disease; RE stands for reflux esophagitis.

Source: CDE; Pharmacodia; China Insights Consultancy

Classification and indications of PPI drugs

Metabolism pathways of PPI drugs



- The activation and metabolization of PPIs relies on CYP450 system in human liver, the 1st gen PPI drugs mainly rely on CYP2C19 while some of the 2nd gen rely on CYP3A4.
- Due to the polymorphism of CYP2C19 gene, the pharmacokinetic feature of the 1st gen PPI drugs vary among population, while the 2nd gen show more steady features.

Classification of PPI drugs

	PPI Drugs	Initial approval
1st generation	Lansoprazole	1994
	Pantoprazole	1997
	Omeprazole	2000
2nd generation	Anaprazole	2023
	Rabeprazole	2000
	Esomeprazole	2002
	Ilaprazole	2007

Indications of oral and injectable PPI drugs

• Mild GU and DU	• Marginal ulcer	• Mild reflux esophagitis	• Stress ulcer	• Mild ZES	• Relieve other discomforts caused by hyperchlorhydria • Assist the treatment against HP infection
• Compound ulcers • Severe GU or DU	• Marginal ulcer with bleeding	• Severe reflux esophagitis	• Stress ulcer complicated with other severe symptom	• Severe ZES	• -

Source: MENET; Pharmacodia; Drug Instructions; China Insights Consultancy

Summary of approved PPI drugs in China, as of LPD

Approved PPI drugs in China, as of LPD

Generation	Drug Name	Initial approval	Original manufacturer	Generic	NRDL inclusion	NRDL listed indications	VBP inclusion
1st Gen	Lansoprazole	1994	Takeda Pharma	Y	Category II (oral), 2004 Category II (injectable), 2009	GU; DU; marginal ulcer; HP infection; reflux esophagitis; ZES	2021 (injectable)
	Pantoprazole	1997	Takeda Pharma	Y	Category II (oral & injectable), 2004	PU; reflux esophagitis; gastrinoma; HP infection (combined with antibiotics)	2021 (oral & injectable)
	Omeprazole	2000	AstraZeneca	Y	Category II (oral & injectable), 2004 Category I (oral), 2009	GU;DU; HP infection-related PU or reflux esophagitis (combined with antibiotics); ZES; PU with acute bleeding (injectable)	2020 (oral); 2022 (injectable)
2nd Gen	Anaprazole	2023	Xuanzhu Biopharm	N	Category II (oral) 2023	DU	-
	Rabeprazole	2000	Eisai	Y	Category II (oral) 2004	GU; DU; marginal ulcer; GERD; gastrinoma; HP infection-related DU; refractory GERD; ZES	2023 (oral)
	Esomeprazole	2002	AstraZeneca	Y	Category II (oral), 2004 Category II (injectable), 2009	GERD; NSAID-related GU; HP infection-related DU (combined with antibiotics)	2021 (oral & injectable)
	Ilaprazole	2007	Livzon Pharma	N	Category II (oral), 2017 Category II (injectable), 2019	DU; GERD; stress ulcer or PU with bleeding (injectable)	-

Source: NRDL; NHSA; Drug Instructions; Pharmacodia; China Insights Consultancy

Unpredictable metabolic features, pressure to liver and kidney, and challenge to compliance raised unmet clinical needs of PPI drugs

Analysis of clinical unmet needs of PPI drugs

➢ Unpredictable metabolic features

- The metabolism of all the 1st gen PPI drugs rely on CYP2C19 enzyme. But **CYP2C19 gene shows polymorphism among individuals, which will largely impact the metabolism of PPI drugs**, leading to unpredictable plasma concentration.
- Due to the enzymatic pathways that PPI drugs are metabolized, **it is likely that PPI and other drugs may arise medication interaction.** For instance, clarithromycin and rifampicin can reduce enzymatic activity which correspondingly impact the functioning of PPI drugs.

➢ Pressure to liver and kidney

- Most PPI drugs are metabolized in hepatocytes and excreted through urine afterward. **The single metabolism pathway is likely to bring high pressure to liver and kidney**, and even cause severe hepatic damage or renal injury sometime. **This makes PPI drugs unsuitable for patients with damaged hepatic or renal function**, especially the elderly should be particularly cautious when using them.

➢ Challenge to compliance

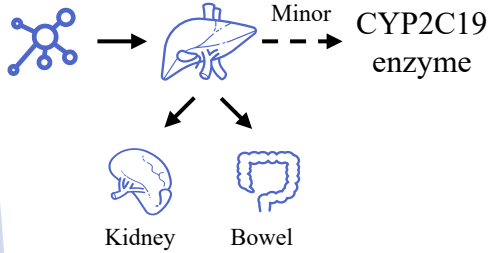
- Most GERD and PU patients **have recurrence seasonally and need to receive PPI treatment for more than two months on a daily basis**. However most patients fail to comply to prescriptions, which reversely leads to continued onset of diseases.
- PPI drugs may cause a series of ADRs, including fatigue, digestive discomfort, dizziness, and headache, most of which are mild and self-limiting. **The onset of ADRs is likely to bring more barriers to the compliance of the patients**.

Source: China Insights Consultancy

With improved metabolic pathway, better medication safety and strong antisecretory effect, anaprazole is a promising PPI drug for PU and GERD patients.

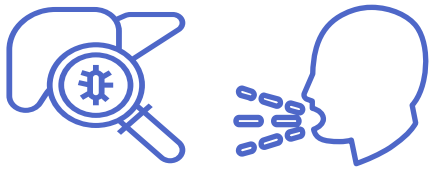
Summary of advantages of anaprazole

- Anaprazole is an innovative 2nd gen PPI drug developed by Xuanzhu Biopharm. According to the clinical trials, anaprazole showed strong antisecretory effect with better safety assurance, and improved pharmacokinetic feature, making it a promising PPI drug for PU and GERD patients. Anaprazole sodium has already been approved by NMPA in 2023.



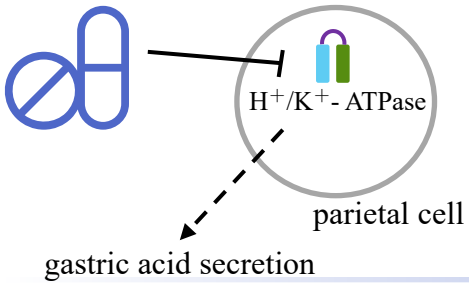
◆ Improved metabolic pathway

- Only 3.5% of the metabolism of anaprazole relies on CYP2C19 enzyme. With minor impact from the polymorphism of CYP2C19, the plasm concentration of anaprazole is predictable.
- Moreover, unlike other PPI drugs that can only be excreted through urine, **anaprazole can be excreted through urine and feces, reliving the pressure to kidneys.**



◆ Better medication safety

- As a novel 2nd gen PPI drug, anaprazole showed convincing safety assurance with a **lower ADRs rate compared to rabeprazole** (8.2% vs 11.0%) and no TRAEs observed.
- Besides, anaprazole can be metabolized through multi-enzymatic and non-enzymatic pathways, reducing impact from medication interaction and providing better safety.



◆ Fast and long-lasting antisecretory effect

- Due to its innovative configuration, anaprazole has a higher pKa, thus making it **more effective to reduce the production of acid in a short period**. In its clinical trials, 81.2% of the patients experienced significant relief of the symptoms in the first day on anaprazole.
- Meanwhile, the configuration allows anaprazole to bind with the cys822 residue of the target profoundly, leading to a **long-lasting antisecretory effect.**

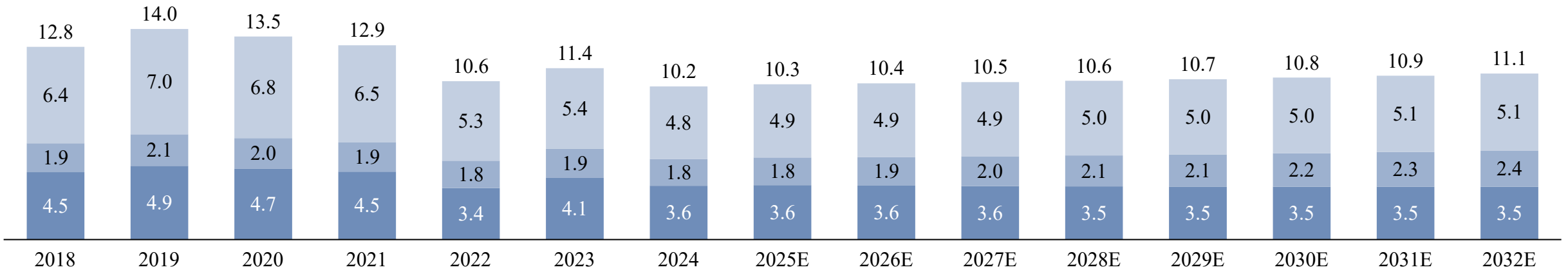
Source: Drug Instructions; Chinese Medical Journal; NHSA; CNKI; China Insights Consultancy

Market size of oral PPI drugs in China, 2018-2032E

Market size of oral PPI drugs in China, 2018-2032E

CAGR	2018-2024	2024-2032E
PU	-4.6%	0.7%
RE	-1.4%	3.9%
Other indications	-3.7%	-0.2%
Total	-3.8%	1.0%

billion RMB



Key Analysis

- As commonly-used drugs, oral PPI drugs had a market size over 10 billion RMB for years**. Mainly due to the influence of COVID-19 and VBP inclusion in recent years, the market size suffered from reductions during 2020-2022**. According to indications, oral PPI drugs applied for PU showed slight decrease and those for RE showed increase.
- As the market size of oral PPI drugs showed signs of recovery in 2023, with the growth in clinical needs, it is expected that **the market size will stabilize** at around 11.1 billion RMB in the next decade.

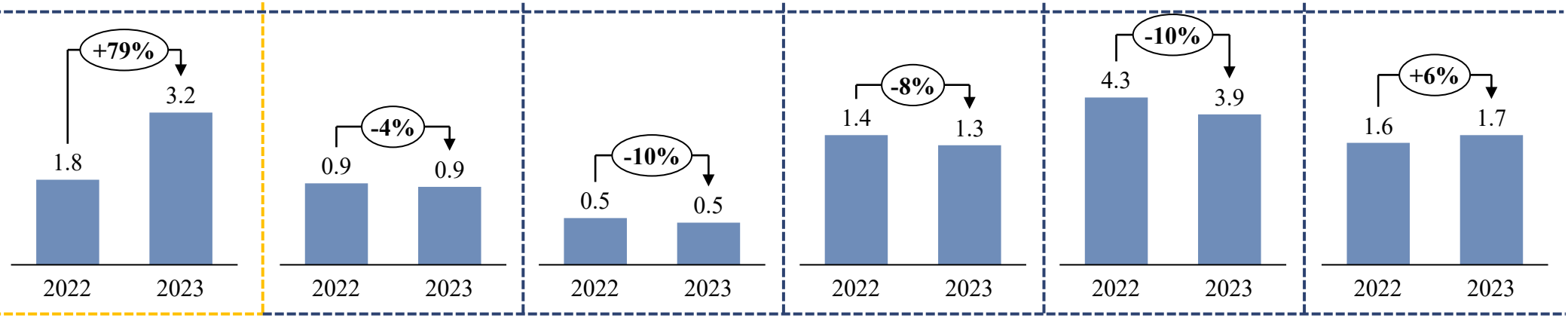
Source: China Insights Consultancy

Comparison of oral PPI drugs market size before and after the inclusion of National Key Supervision List

Comparison of oral PPI drugs market size before and after the inclusion of National Key Supervision List

billion RMB

	Ilaprazole (not included)	Lansoprazole	Pantoprazole	Omeprazole	Rabeprazole	Esomeprazole
Market size in 2022	1.8	0.9	0.5	1.4	4.3	1.6
Market size in 2023	3.2	0.9	0.5	1.3	3.9	1.7
Diff.	+79%	-4%	-10%	-8%	-10%	+6%



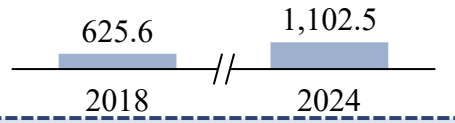
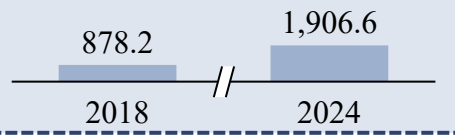
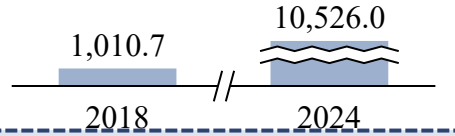
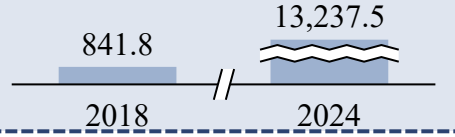
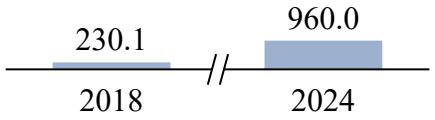
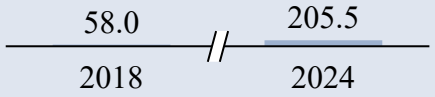
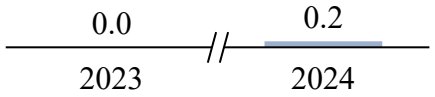
Key Analysis

- National Health Commission of China released the new version of National Key Supervision List for Drugs in January, 2023. **Apart from ilaprazole, all other PPI drugs approved were listed, indicating the prescription of these drugs would be under close supervision in order to standardize clinical medication.**
- Except from esomeprazole, all the listed PPI drugs suffered from different degrees of reduction in market size, while the un-listed ilaprazole achieved huge growth in market size. It is expected that the supervision policy will restrain the growth of classic PPI drugs and enable the innovative PPI drugs, like anaprazole, to obtain a better prospect.

Source: China Insights Consultancy

Summary of the volume and price changes of oral PPIs in China

Summary of the volume and price changes of oral PPIs in China

Drug name	Volume change: 2018-2024 CAGR	Volume change (mn pieces) (calculated by minimal specification)	Price change: 2018-2024 CAGR
Lansoprazole	9.9%		-7.9% (15 mg)
Pantoprazole	13.8%		-18.9% (20 mg)
Omeprazole	47.8%		-25.1% (20 mg)
Rabeprazole	58.3%		-33.6% (10 mg)
Esomeprazole	32.2%		-25.1% (20 mg)
Ilaprazole	23.5%		-1.2% (5 mg)
Anaprazole	23-34：4408.2%		23-24(20mg): -77.8%

Source: China Insights Consultancy

Summary of the volume and price changes of oral PPIs in China

Summary of the volume and price changes of oral PPIs in China

billion RMB

Drug name	Injectable Price change: 2018-2024 CAGR	Oral Price change: 2018-2024 CAGR	Market size change: 2018-2024 CAGR	Market share 2024
Lansoprazole	-40.4%	-7.9% (15 mg)	-6.3%	8.4%
Pantoprazole	-33.3%	-18.9% (20 mg)	-24.0%	4.2%
Omeprazole	-26.6%	-25.1% (20 mg)	-10.3%	16.9%
Rabeprazole	-14.0%	-33.6% (10 mg)	-9.4%	27.6%
Esomeprazole	-38.7%	-25.1% (20 mg)	-2.2%	19.0%
Ilaprazole	-19.3%	-1.2% (5 mg)	18.2%	23.7%
Anaprazole	/	23-24(20mg): -77.8%	23-24: 900.0%	0.2%

Source: China Insights Consultancy

Comparisons of oral PPIs in China

Drug type	Scope of indication	Unite price in 2024	4-week spending	DU Efficacy: 4-week healing rate[1]	RE efficacy: 4-week healing rate[1]	Incidence of drug-related AEs	Common AEs(≥1%)	Market share 2024
Lansoprazole	Peptic ulcer, Zollinger-Ellison syndrome, reflux esophagitis	RMB1.3/15mg	~ RMB70	~89.4%	~67.6%	~11.5%	• Diarrhea, abdominal pain, skin rash and/or itching.	8.4%
Pantoprazole	Peptic ulcer, Zollinger-Ellison syndrome, reflux esophagitis	RMB0.9/20mg	~ RMB50	~85.0%	~55.0%	~29.2%	• Diarrhea, headache, upper respiratory tract infection, and abdominal pain.	4.2%
Omeprazole	Peptic ulcer, Zollinger-Ellison syndrome, reflux esophagitis	RMB0.3/20mg	~ RMB20	~89.0%	~67.0%	~23.5%	• Headache, abdominal pain, diarrhea, nausea, vomiting, and flatulence.	16.9%
Rabeprazole	Peptic ulcer, reflux esophagitis, Helicobacter Pylori Infection	RMB0.5/10mg	~ RMB30	~96.6%	~65.0%	~12.1%	• Diarrhea, headache, rhinitis, nausea, pharyngitis and abdominal pain.	27.6%
Esomeprazole	Peptic ulcer, gastroesophageal reflux disease, Helicobacter Pylori Infection	RMB2.2/20mg	~ RMB120	~88.0%	~78.0%	~11.9%	• Headache, respiratory infection, and abdominal symptoms	19.0%
Ilaprazole	Duodenal ulcer, reflux esophagitis	RMB13.1/5mg	~ RMB360	~86.4%	76.1%	~12.5%	• Diarrhea, headache and dizziness, abnormal elevated ALT and AST.	23.7%
Anaprazole	Duodenal ulcer	RMB11/20mg	~ RMB300	~93.3%	N.A.	~8.2%	• Elevated ALT and AST[2].	0.2%

1 The efficacy and AEs data were extracted from different clinical trials and for illustrative purpose.
2 ALT stands for alanine aminotransferase, AST stands for elevated aspartate aminotransferase.

Source: drug lable, literature review, China Insights Consultancy

The increasing patients population, uprising R&D investment, and reasonable policy administration will drive the market of digestive disease drugs in China to a more prosperous future

Market drivers

An increasing number of digestive system diseases patients

- As the life pace accelerates, people are forced to adapt a more unhealth lifestyle, which would eventually lead to the onset of digestive system disease. According to GBD database, the incidence of GERD showed stable growth trend annually while the prevalence of PU has been steadily kept at a high position for over 100 cases per 10,000 population in the last few decades. With the growing patients population, the market of digestive disease drugs will experience rapid development in the next few years.

More efficiency and higher investment in R&D

- According to China Science and Technology Statistics, China's pharmaceutical research and development (R&D) expenditure grown at a CAGR of 13.6% from 2016 to 2022. Increasing funding from private and government organizations for the development of pharmaceutical manufacturing, as well as advancements in R&D activities for the formulation of new digestive diseases drugs, are propelling the growth of the market.

Improving accessibility of digestive disease drugs

- China government has released policies on hierarchical diagnosis and treatment as well as restricting the prices of basic drugs, which would give the patients more options and relieve disease burden, promoting the accessibility of digestive disease drugs. This promotion would drive the market to a more prosperous future.

Source: China Science and Technology Statistics; China Insights Consultancy

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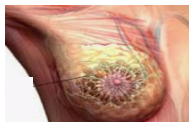
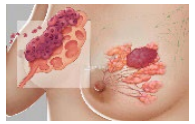
Overview of breast cancer

Introduction to breast cancer





- **Breast cancer (BC)** is a disease that abnormal breast cells grow out of control and form tumors, which the most-commonly diagnosed malignant tumor in women in the world, as well as the first cause of death from malignant tumors.
- In 2022, breast cancer caused 670 000 deaths globally. BC is the second most common type of cancer globally and the most prevalent cancer in the U.S.
- Like many other cancers, causes of breast cancer can vary, but genetic predisposition (BRCA1 or BRCA2 mutations), estrogen and progesterone exposure and lifestyle factors and a few factors that have attributed to the heightened risk of breast cancer.

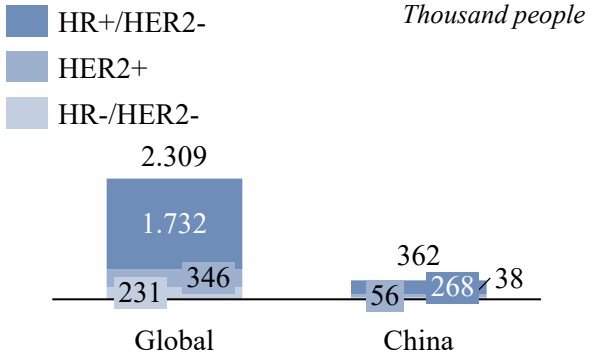
Symptoms

Early stage	Advanced stage
• No apparent symptoms at early stage	• A breast lump or thickening, often without pain • Change in size, shape or appearance of the breast • Dimpling, redness, pitting or other changes in the skin

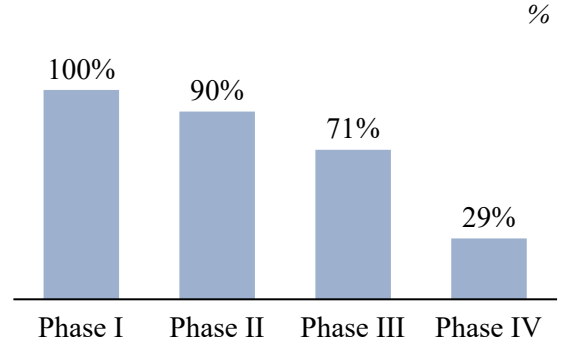
Stage of BC

Stage	Phase 0	Phase I	Phase II	Phase III	Phase IV
	← 65% →		← 27% →	← 6% →	
Feature	• CIS	• Early invasive cancer • Tumor size＜2cm	• Tumor size is 2cm-5cm	• Tumor size＞5cm	• Tumor in any size

The incidence of BC, 2022



Five-year survival rate of BC, 2022



Classification of BC*

HR+/HER2-	HER2+	TNBC
• Tumor have ER or PR, which can promote the growth of HR+ tumors, but without HER2	• Tumor have HER2, which has been shown to be associated with aggressive BC	• Tumor tested negative for ER, PR and HER2
• Low grade, slow growing, best prognosis, higher survival rate	• More aggressive and fast-growing than HR+/HER2 type	• Aggressiveness, early relapse, present in advanced stages

- Treatments for breast cancer, therefore, will depend on the stage and classification and will include surgery if at **an early stage and chemotherapy, chemotherapy, endocrine therapy and HER2 targeted therapy, etc. based on various factors**

Note: Note: *ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2

Source: China Insights Consultancy

Breast cancer incidence in China, 2018-2032E

Breast cancer incidence in China, 2018-2032E

CAGR	2018-24	2024-32E
BC	2.5%	1.9%

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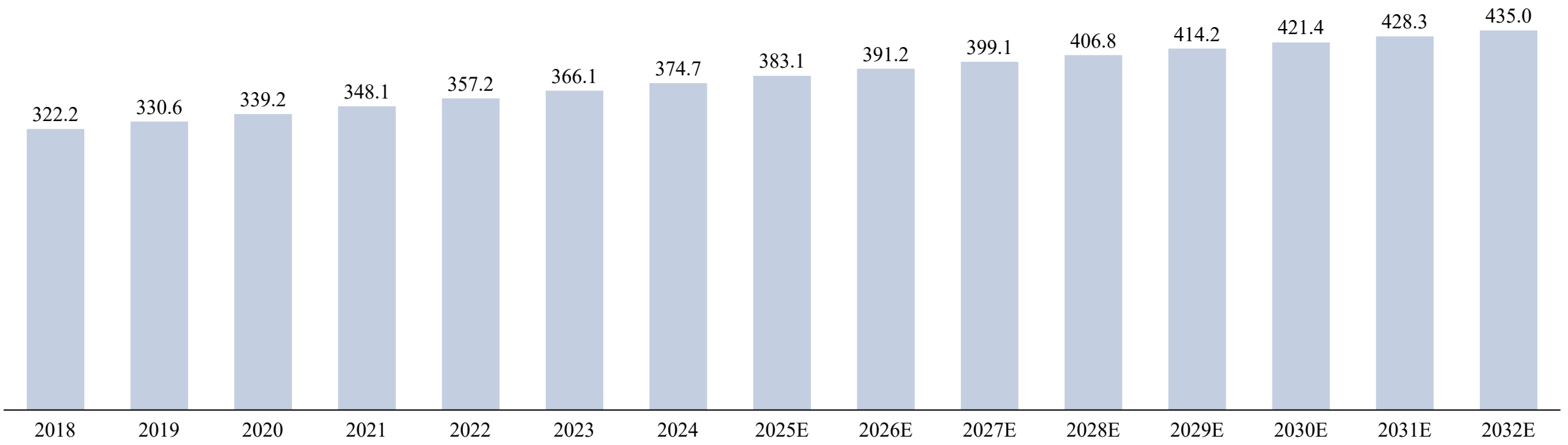

Source: China Insights Consultancy

Eligible patients for CDK4/6 inhibitor adjuvant therapy in China(early stage), 2018-2032E

Eligible patients for CDK4/6 inhibitor adjuvant therapy in China(early stage), 2018-2032E

CAGR	2018-24	2024-32E
BC	4.3%	3.4%

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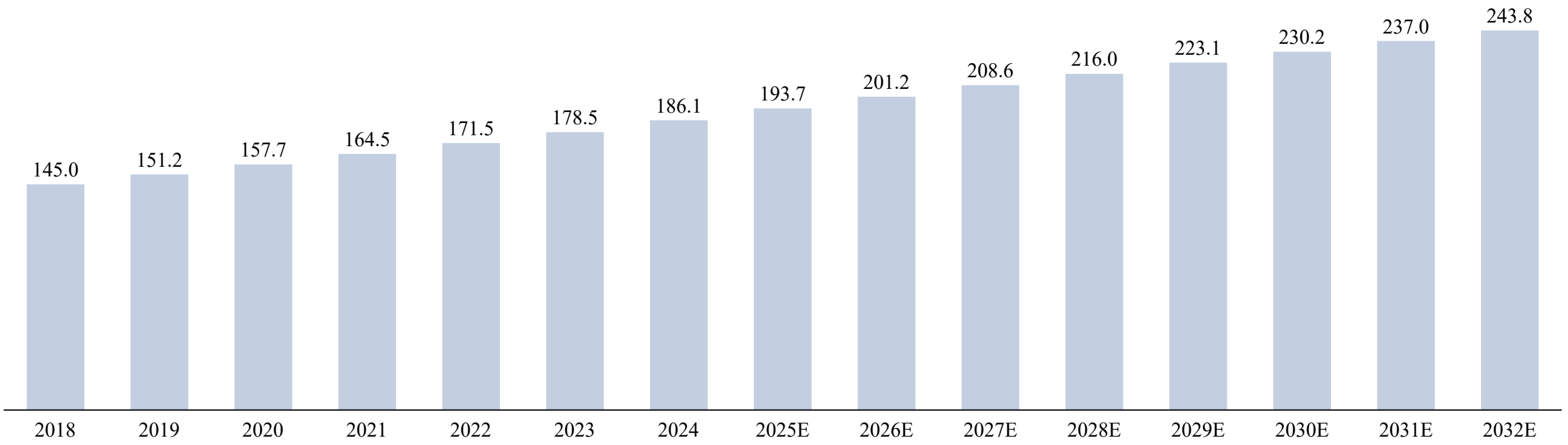


Source: China Insights Consultancy

Treatment path for breast cancer

Target patients of the Company's products

Treatment path for breast cancer (CSCO 2025)

Classification		Postoperative adjuvant treatment for early breast cancer	Salvage treatment for advanced breast cancer		
			Grade I	Grade II	Grade III
Breast cancer	HR+/ HER2-	Adjuvant chemotherapy (Grade I): • 1–3 positive lymph nodes: TC×4; AC • ≥4 positive lymph nodes: AC-T; ddAC-ddT Adjuvant endocrine treatment: • Primary therapy for post-menopausal patients (Grade I): AI + **Abemaciclib/ Ribociclib** • Primary therapy for pre-menopausal patients (Grade I): OFS + AI/TAM ± **Abemaciclib/ Ribociclib**	• ET-naïve/Failed to TAM: AI + **CDK4/6 i** • Failed to non-steroidal AIs/Failed to steroidal AI: Fulvestrant + **CDK4/6 i** • HR+/HER2-low: Endocrine therapy + **CDK4/6 i** if CDK4/6 inhibitor naïve; or T-Dxd	• ET-naïve: Fulvestrant + **CDK4/6 i**; AI • Failed to TAM: AI + chidamide/ everolimus; Fulvestrant + **CDK4/6 i** • Failed to non-steroidal AIs: Steroidal AI + chidamide/everolimus • Failed to steroidal AI: Fulvestrant + everolimus; Non-steroid AI + **CDK4/6 i** • Failed to CDK4/6 i: another **CDK4/6 i** or Targeted therapy + ET; clinical trials • HR+/HER2-low: Chemotherapy; TROP2 ADC	• ET-naïve: TAM; Toremifene • Failed to TAM: AI; Fulvestrant • Failed to non-steroidal AIs: Fulvestrant; Steroidal AI • Failed to steroidal AI: Fulvestrant; non-steroidal AIs • HR+/HER2-low: Dato-DXd; clinical trials
	HER2+	Primary treatment (Grade I): • Positive axillary lymph nodes: AC-THP; TCbHP • Negative axillary lymph nodes, tumor sized >2 cm: AC-TH; TCbH; TC + H	• Trastuzumab sensitive: THP; TH + pyrotinib • Trastuzumab-resistant: Pyrotinib + capecitabine; T-Dxd	• Trastuzumab-sensitive: TXH; HP + chemotherapy • Trastuzumab-resistant: T-DM1 • Pyrotinib-resistant: T-Dxd; HP + other chemotherapy; T-DM1	• Trastuzumab-sensitive: Pyrotinib + capecitabine • Trastuzumab-resistant: Neratinib/Lapatinib/Marget-uximab + chemotherapy
	TNBC	Primary treatment (Grade I): • Positive lymph nodes, tumor sized >2 cm: AC-T; ddAC-ddT (Olaparib for extended therapy, with BRCA mutation type, Grade II) • Tumor sized ≤2 cm and with negative lymph nodes: TC×4; AC	• Chemotherapy • Chemotherapy + PD-1 inhibitors: Albumin-bound paclitaxel/GP + PD-1 inhibitors	• Other chemotherapy • Chemotherapy + PD-1 inhibitors: Albumin-bound paclitaxel/GP + PD-1 inhibitors	• Olaparib for the presence of BRCA mutation • Other chemotherapy

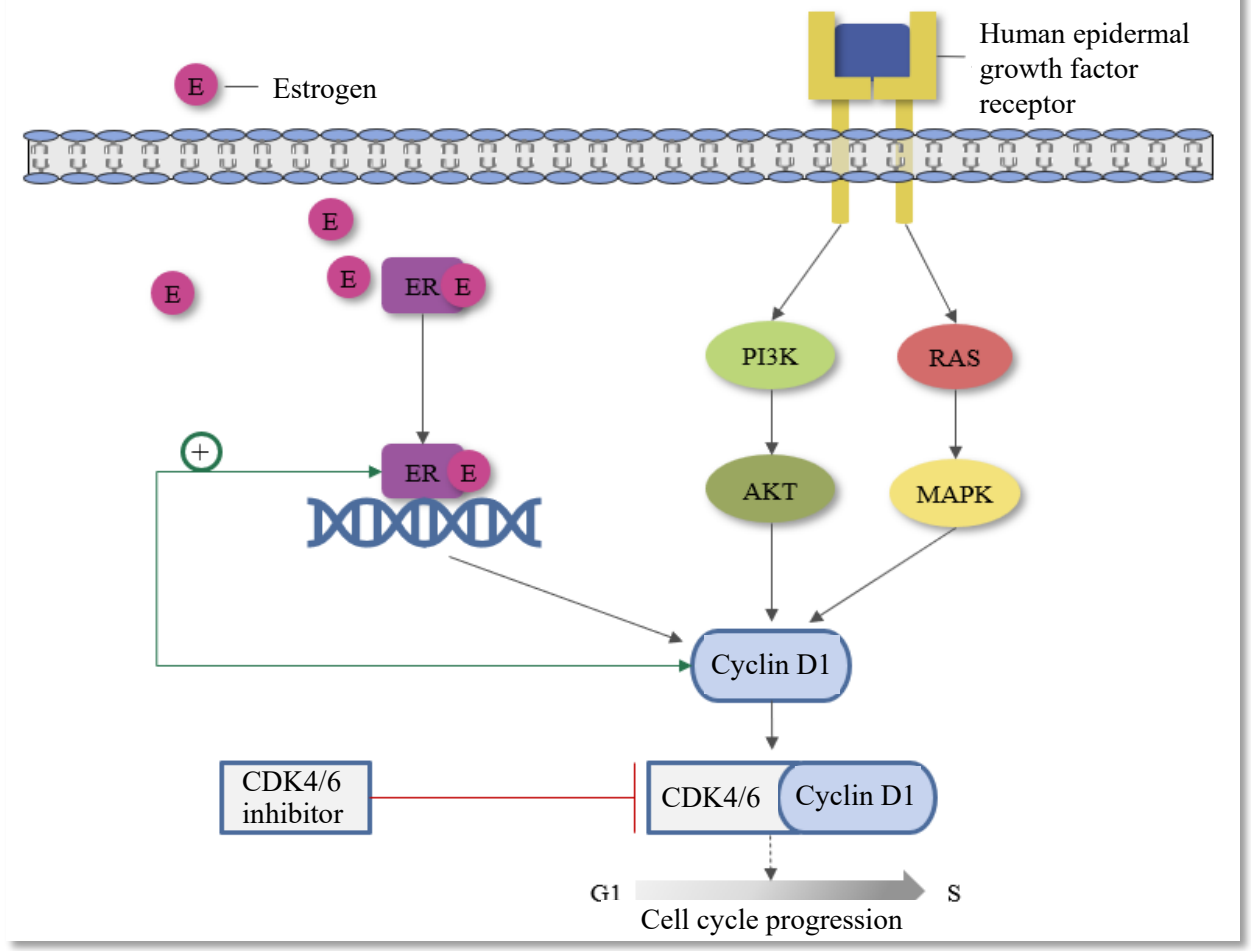
Note: ET: Endocrine therapy; TAM: Tamoxifen; AI: Aromatase inhibitor; CDK4/6 i: CDK4/6 inhibitor; T-DM1: Trastuzumab emtansine; T-Dxd: Trastuzumab deruxtecan; A, Anthracyclines; T, Taxanes; C, Cyclophosphamide; G, Gemcitabine; X, Capecitabine; Cb, Carboplatin; H/P, Trastuzumab/pertuzumab; OFS, Ovarian function suppression

Source: CSCO2025, China Insights Consultancy

Introduction of CDK4/6 inhibitor

Introduction of CDK4/6 inhibitor

MoA of CDK4/6 and CDK4/6 inhibitor



CDK4/6:

- **Cyclin-dependent kinase (CDK) is an important regulator protein of cell division cycle (CDC)**
- CDK4/6 catalyzes the phosphorylation of retinoblastoma protein (Rb), thereby initiating the transcription of downstream molecules
- They are key regulatory factors for the cell cycle to enter the S phase from the G1 phase. Studies have found that CDK4/6 is overexpressed in many cancers, including breast cancer, leading to uncontrolled cell division cycles, which is a hallmark feature of cancer

CDK4/6 inhibitor :

- **CDK4/6 inhibitors are highly selective targeted therapeutic drugs that can selectively inhibit CDK4/6, restore normal regulation of the cell cycle, and thus block DNA synthesis and proliferation of tumor cells**
- CDK4/6 inhibitors inhibit the activity of CDK4 and CDK6 kinases in breast cancer cells, block Rb protein phosphorylation, and inhibit tumor cell proliferation by blocking the progression of the cell cycle
- And CDK4/6 inhibitors repress the expression of the upstream estrogen receptor signaling pathway, and have a synergistic effect with endocrine therapy, thereby delaying and reversing endocrine resistance

Source: China Insights Consultancy

Competitive landscape of CDK4/6 inhibitor in China

Overview of NMPA approved CDK4/6 inhibitor innovative drug

Lines	Drug Name	Original manufacturer	Indications	Approval Date	NRDL year	Price (RMB)
1L	Palbociclib	Pfizer	HR+/HER2- la/mBC (combined with aromatase inhibitors, AIs)	July 2018	2023	203.6/125 mg
1L (Combo: AIs)/ 2L (Combo: fulvestrant)	Abemaciclib	Lilly	HR+/HER2- la/mBC (combined with AIs or fulvestrant)	March 2021	2022	69.8/150 mg
/			As adjuvant therapy for HR+/HER2- early BC (combined with ET)	December 2021	2024	
2L	Dalpiciclib	Hengrui	HR+/HER2- la/mBC that progressed after ET (combined with fulvestrant)	December 2021	2023	205.0/150 mg
1L			As first-line therapy for HR+/HER2- la/mBC (combined with AIs)	June 2023	2024	
1L	Ribociclib	Novartis	As first-line therapy for HR+/HER2- la/mBC (combined with AIs)	January 2023	2024	70.9/200 mg
/			As adjuvant therapy for HR+/HER2- early BC (combined with AI)	May 2025	/	
≥2L	Birociclib	Xuanzhu Bio	HR+/HER2- la/mBC (combined with fulvestrant)	May 2025	/	/
>3L			Mono use for HR+/HER2- la/mBC			
2L	Lerociclib	Genor BioPharma	HR+/HER2- a/mBC after ET (combined with fulvestrant)	May 2025	/	/
1L			HR+/HER2- a/mBC (combined with AIs)			
2L	Fovinaciclib	Avanc Pharma	HR+/HER2− mBC, 2L after ET progression in combination with fulvestrant	May 2025	/	/
2L	Tibremciclib	Betta Pharma	HR+/HER2− mBC, 2L after ET progression in combination with fulvestrant	June 2025	/	/

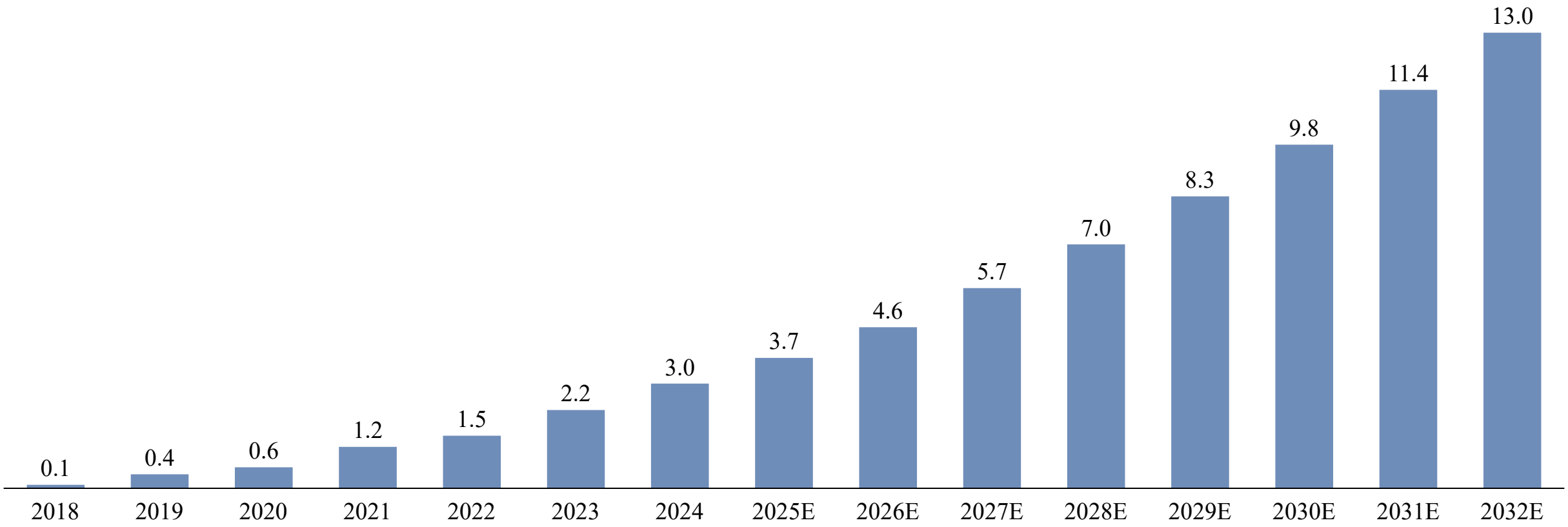
Source: China Insights Consultancy

Market size of CDK4/6 inhibitor treating breast cancer in China, 2018-2032E

Market size of CDK4/6 inhibitor treating breast cancer in China, 2018-2032E

CAGR	2018-2024	2024-2032E
CDK4/6 inhibitors	78.8%	20.2%

billion RMB



Source: China Insights Consultancy

Pipelines of CDK4/6 inhibitors for breast cancer by CDE, phase 3 and beyond

Pipelines of CDK4/6 inhibitors for breast cancer, CDE-registered, phase 3 and beyond

Lines	Drug Name	Company	Phase	Indications	First Posted Date*	Trial Number
1L	FCN-437c	Fochon Pharmaceuticals	NDA	HR+/HER2- aBC (Combo: AIs)	2025-01-09	N/A
Adjuvant	Dalpiciclib	Hengrui	NDA	As adjuvant therapy for HR+/HER2- early or advanced BC combined with ET	2025-05-09	N/A
1L	Birociclib	Xuanzhu bio	NDA	HR+/HER2- aBC (Combo: AIs)	2025-05-14	N/A
≥2L	BEBT-209	BeBetter Med	III	HR+/HER2- aBC after ET (Combo: fulvestrant)	2022-02-28	CTR20220426
Adjuvant therapy	Ribociclib	Novartis	III	Adjuvant treatment for HR+, HER2-negative BC in combination with ET	2025-04-09	CTR20251325

Notes: a/mBC stands for advanced/metastatic BC; a/r/mBC stands for advanced/recurrent/metastatic BC

Source: Pharmacodia; CDE; China Insights Consultancy

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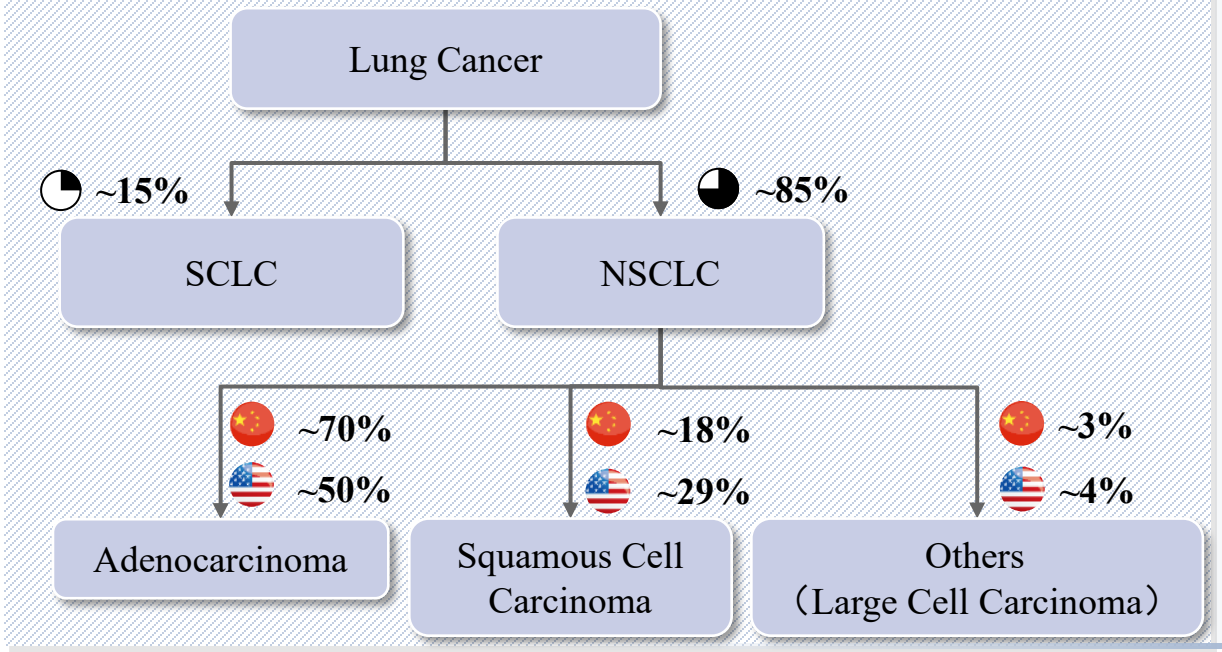
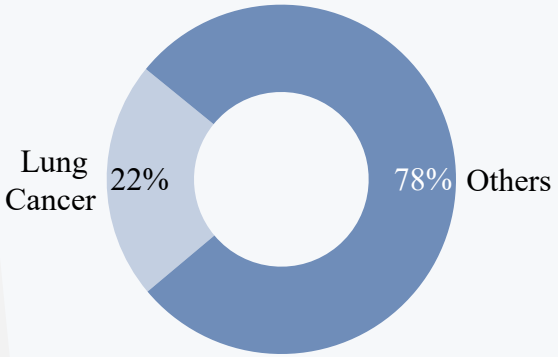
Epidemiology of lung cancer

- **Lung cancer occurs when there is genetic damage to the DNA of cells in the airways**
- **Primary Bronchogenic Carcinoma:** Commonly known as lung cancer, is a malignant tumor originating from the bronchial mucosa or glands. It is one of the most prevalent and deadly malignancies in China and worldwide
- **Ranking:** In 2022, lung cancer ranked first among all newly diagnosed cases of malignancy in China, accounting for 22% of cases

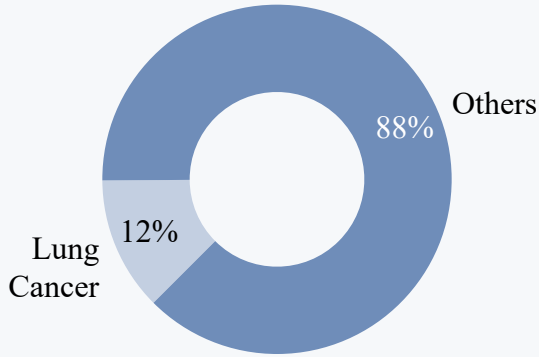
Classification of Lung Cancer Pathology, 2020*



Lung Cancer Proportion in Total Cancer Incidence in China



Lung Cancer Proportion in Global Total Cancer Incidence



Etiological Factor

- **Smoking:** >80% of lung cancer cases in the Western world attributable to cigarette smoking
- **Age:** Incidence and death rates rise significantly after 45; ~53% of cases occur in 55–74 years old in the US
- **Occupational Exposure:** Accounts for 5–10% of global lung cancer cases, such as asbestos, arsenic, and chromium
- **Air Pollution:** The combustion of fossil fuels, and particular matter suspended in the air
- **Chronic Obstructive Pulmonary Disease (COPD):** Primarily occurs due to smoking

Notes: *: Global variations in lung cancer incidence by histological subtype in 2020: a population-based study

Source: The Lancet Oncology, National Cancer Center, IARC, GLOBOCAN, Prospectus, China Insights Consultancy

Lung cancer incidence in China, 2018-2032E

Lung cancer incidence in China, 2018-2032E

CAGR	2018-24	2024-32E
NSCLC	4.1%	3.0%
SCLC	4.1%	3.0%
Total	4.1%	3.0%

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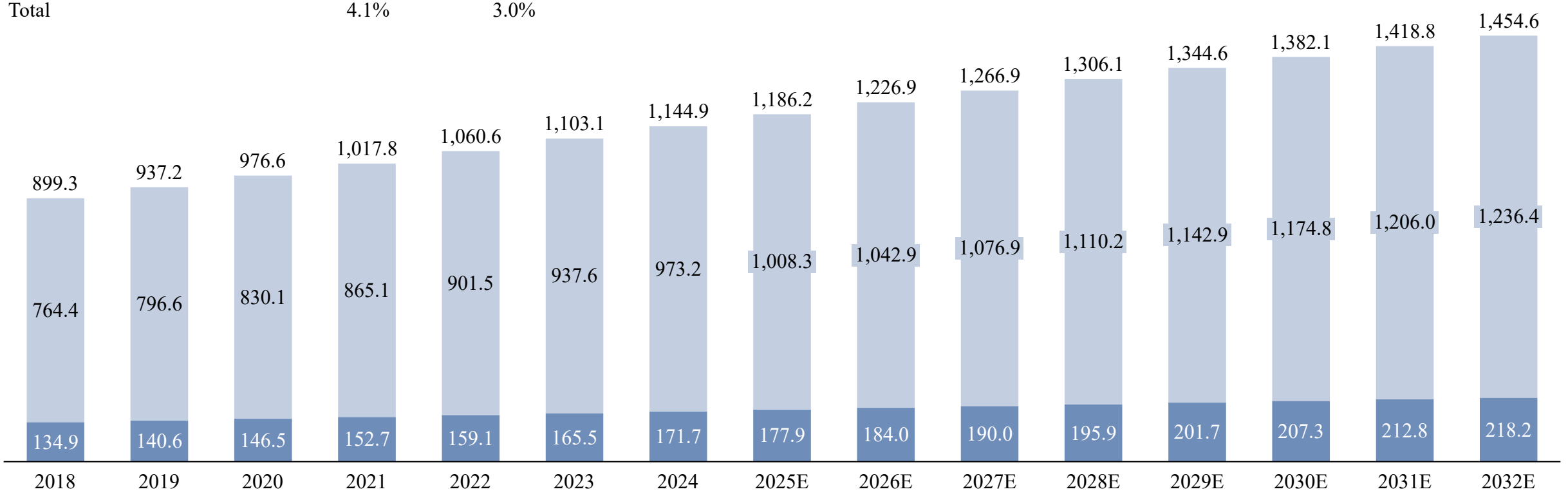
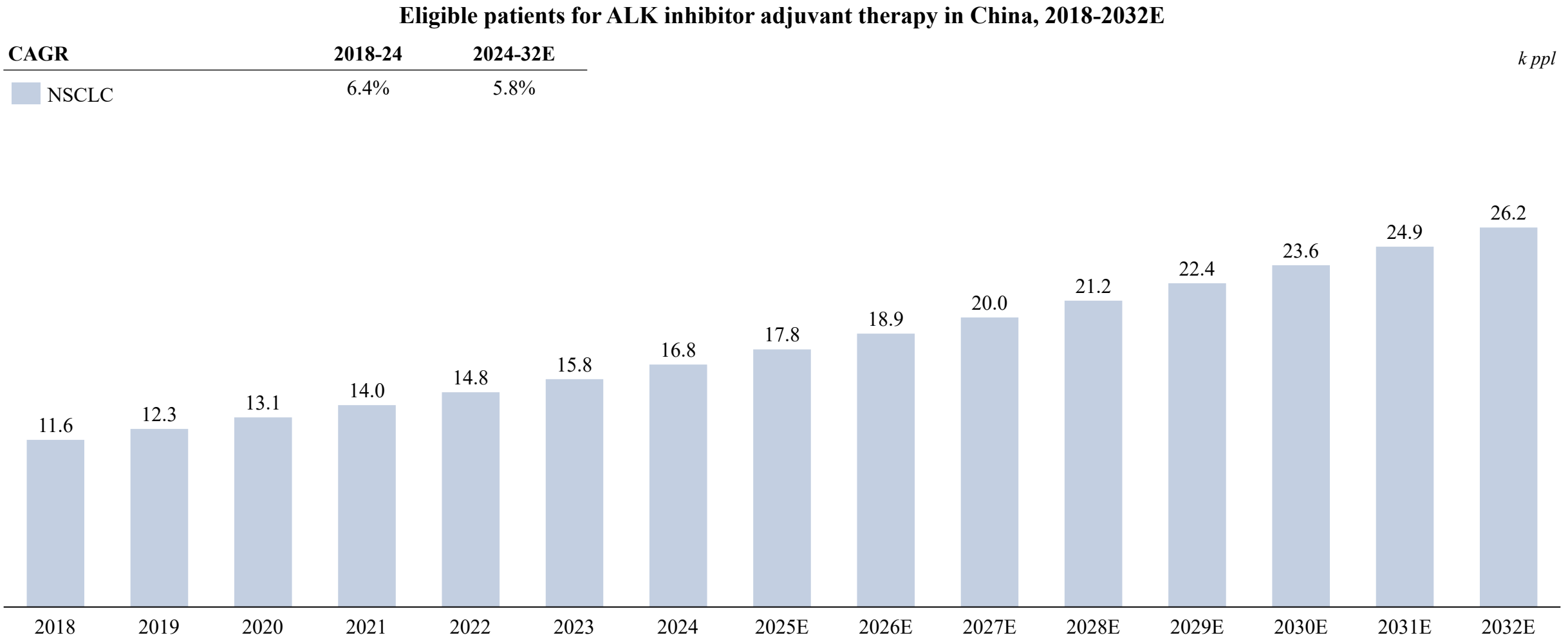


Source: China Insights Consultancy

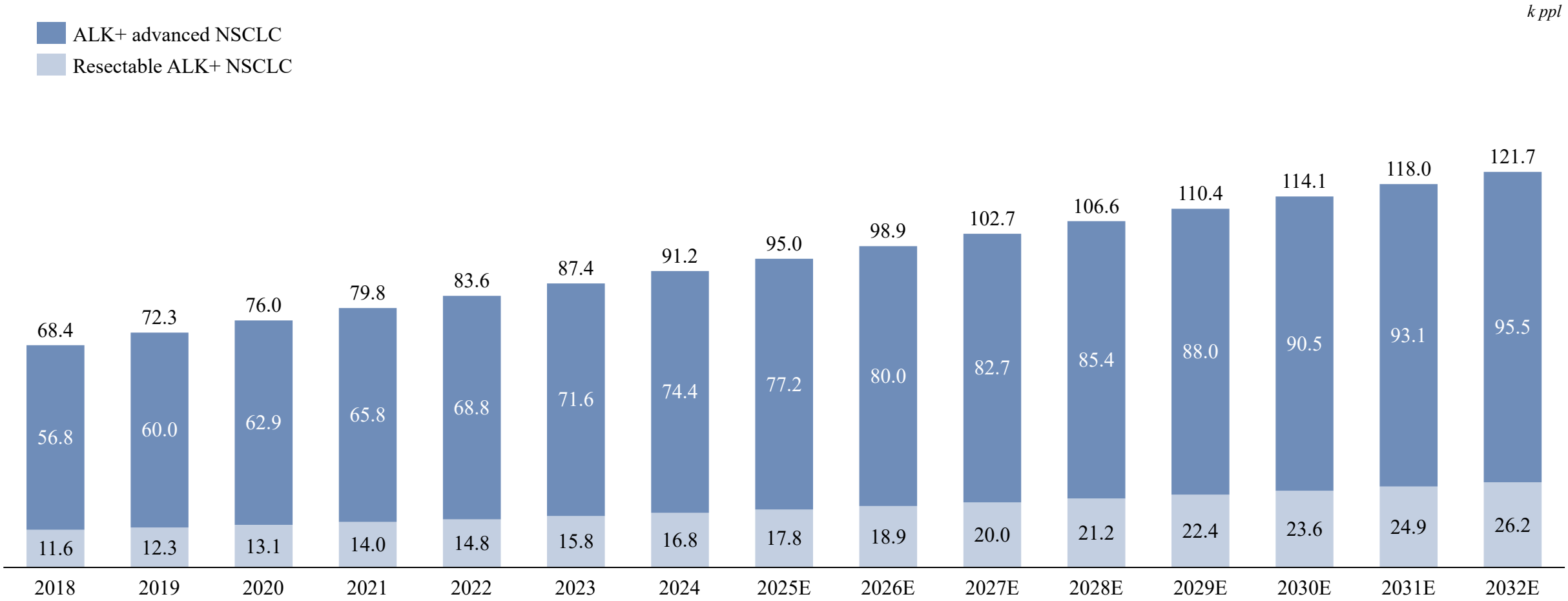
Eligible patients for ALK inhibitor adjuvant therapy in China, 2018-2032E



Source: China Insights Consultancy

Eligible patients for XZP-3621

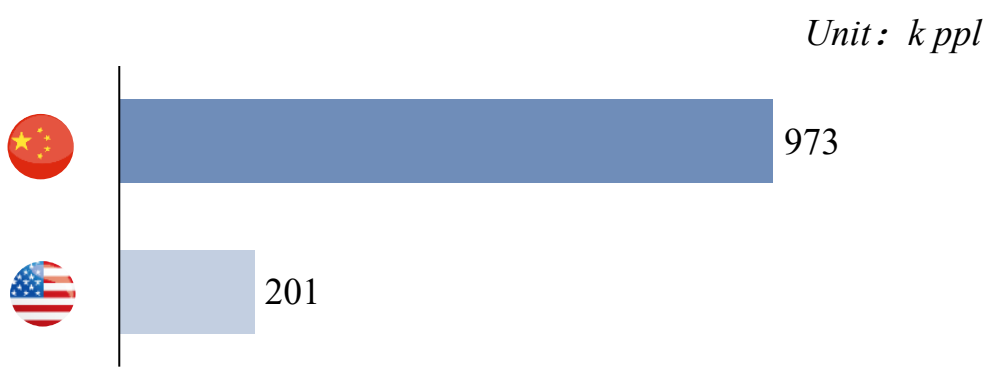
Eligible patients for XZP-3621



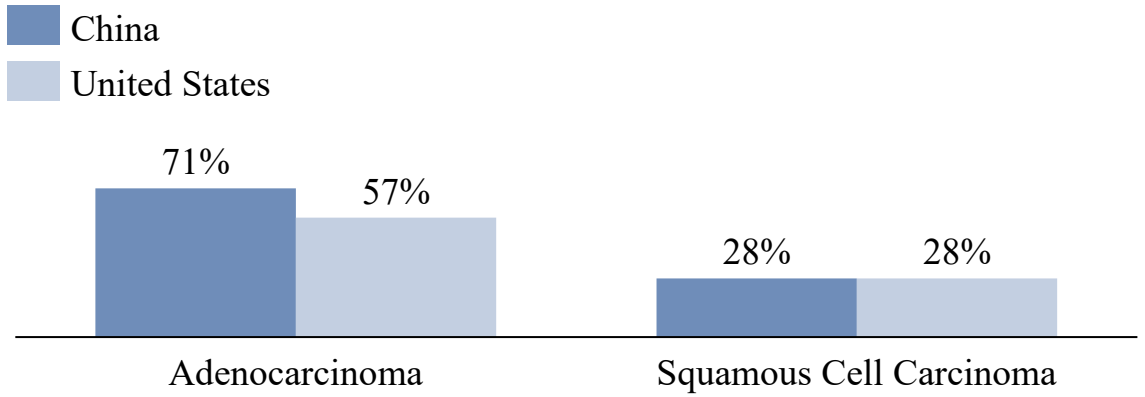
Source: China Insights Consultancy

A higher incidence and better survival rate for Chinese patients with NSCLC

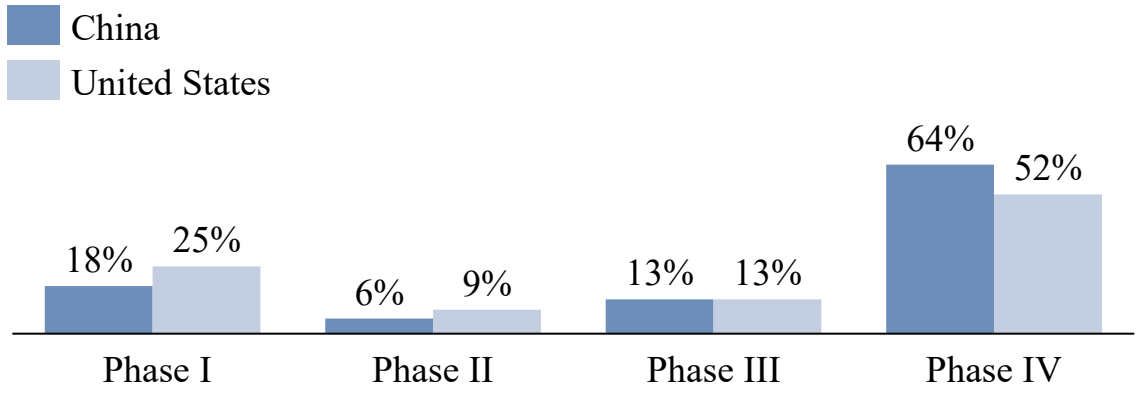
NSCLC Incidence, 2024



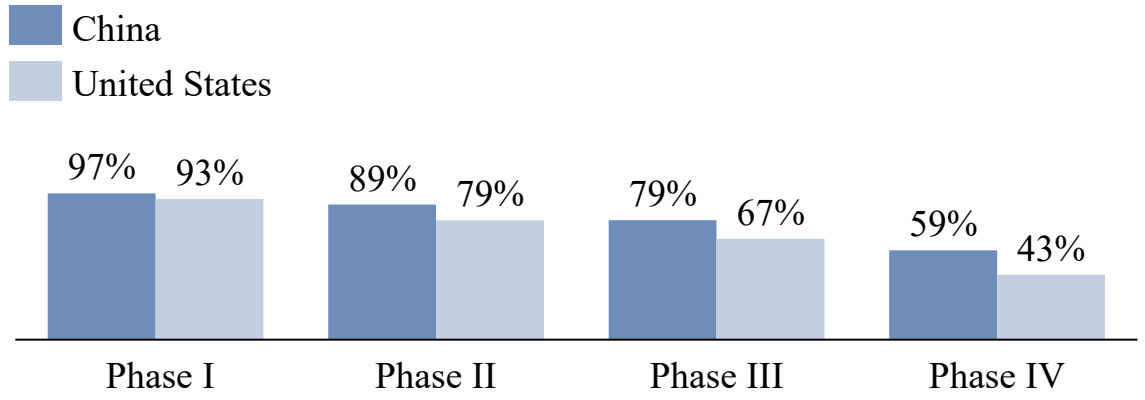
Proportion of Histological Type*



Proportion of Newly Diagnosed NSCLC by Stage*



1-year Survival Rate of NSCLC*



Notes: *: The sample data for the Chinese population is from NSCLC patients in Shanghai from 2011 to 2013; the sample data for the American population is from NSCLC patients in the SEER-18 database from 2010 to 2017.

Source: National Cancer Center, IARC, GLOBOCAN, BMJ Open, JAMA Oncology, China Insights Consultancy

Advancements in NSCLC gene typing and targeted therapy

- **Percentage:** Lung cancer is the most common type of cancer and the second leading cause of death globally. NSCLC accounted for approximately 85% of all lung cancer cases
- **Classification:** Adenocarcinoma (AC) and Squamous Cell Carcinoma (SCC) are the two most common pathological types, accounting for 70%-90% of NSCLC
- **Driver Genes:** NGS technologies can more accurately determine NSCLC gene typing. Approximately 60% of driver genes have been identified in AC
- **Targeted Therapy:** Clinically effective targeted therapies for driver genes mainly target EGFR, ALK, KRAS, ROS1, and other targets in AC patients

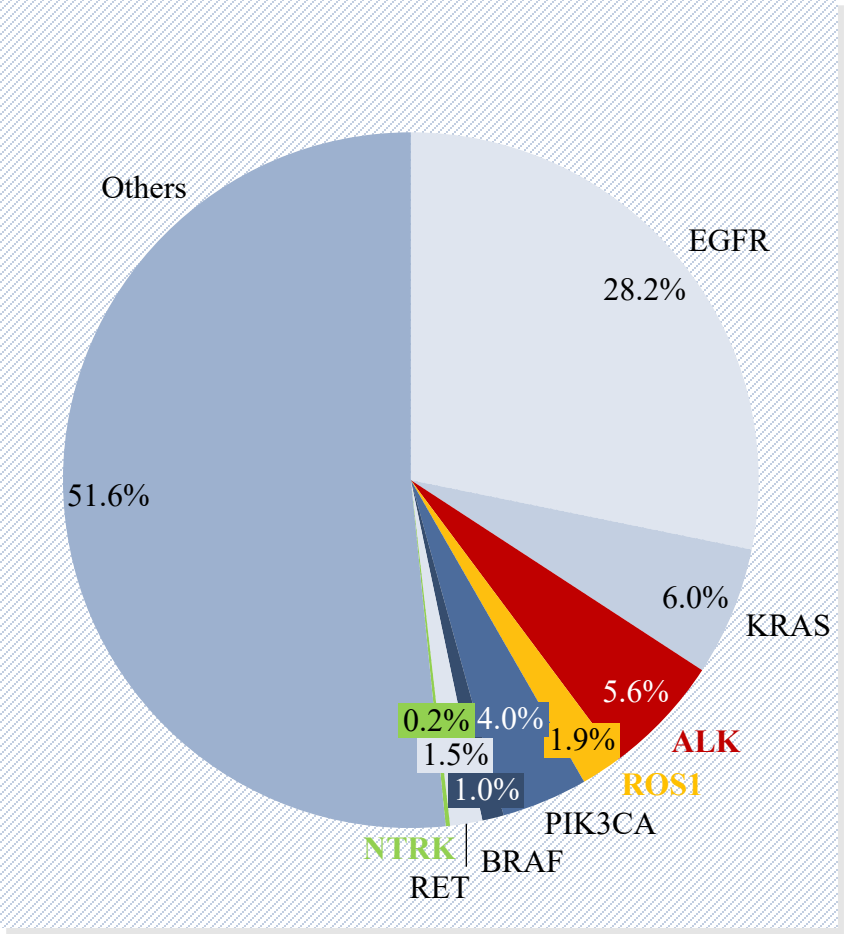
Driver Genes in AC

1. KRAS, EGFR mutations, and ALK fusion are common driver genes, accounting for ~40% in Chinese
2. There are also reports related to ROS1, RET fusion genes, etc
3. EGFR-TKIs, ALK-TKIs, and other targeted therapies have shown clear benefits

Driver Genes in SCC

1. KRAS, EGFR mutations, and ALK fusion are common driver genes, accounting for ~8% in Chinese
2. Genetic typing has not brought clear clinical benefits to SCC
3. Driver genes such as PI3KCA are expected to become new treatment targets

Frequency of driver mutation in Chinese NSCLC



Source: WHO, Transl Lung Cancer Res., Dovepress, Cancer Treat Rev, CHINA ONCOLOGY, China Insights Consultancy

CSCO 2025: Treatment path for ALK fusion NSCLC

Stage I~III ALK fusion NSCLC

Ineligible for surgery	Eligible for surgery
• Radiotherapy ± Chemotherapy	• Surgical resection + Mediastinal lymph node dissection

Adjuvant therapy for postoperative stage II~III patients:
- Atezolizumab following curative surgery (Restricted to PD-L1 TC ≥ 1%, Grade I)
- Platinum-based doublet chemotherapy (Stage IIB, Grade I)
- Platinum-based chemotherapy combined with toripalimab (Stage III, Grade I)
- **Alectinib for ALK-positive patients (Grade I)**

Stage IV ALK fusion NSCLC

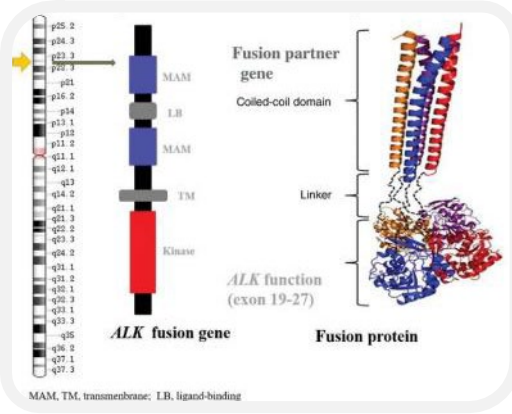
	Grade I	Grade II	Grade III
First line therapy	• Preferred: Alectinib, Brigatinib, Lorlatinib • Ceritinib, Ceritinib, Crizotinib, Iruplinalkib, Envonalkib	• Platinum-based doublet chemotherapy ± Bevacizumab (Non-squamous carcinoma)	• N/A
Subsequent targeted therapy	• Oligoprogress/CNS metastasis: – Initial ALK-TKI ± local therapy – Alectinib, Ceritinib, Ceritinib, Brigatinib, Lorlatinib, Lorlatinib, Envonalkib (Restricted to post-Crizotinib treatment) • Extensive progession: – Next-generation ALK-TKI – Platinum-based doublet chemotherapy± Bevacizumab (Non-squamous carcinoma)	• Extensive progession: – Platinum-based doublet chemotherapy ± Bevacizumab, biopsy to assess resistance mechanisms	• N/A
Post-failure therapy	• PS=0~2: – Single-agent chemotherapy	• PS=0~2: – Single-agent chemotherapy + Bevacizumab (Non-squamous carcinoma)	• PS=0~2: – Anlotinib

Source: CSCO2025, China Insights Consultancy

ALK rearrangement in NSCLC

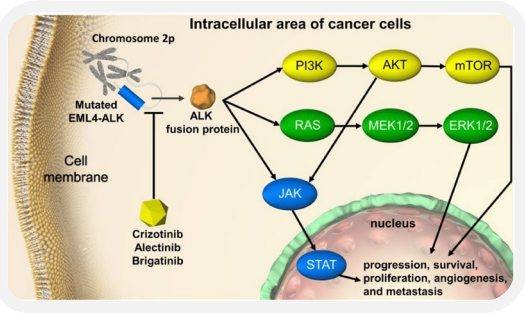
NSCLC | ALK gene

ALK rearrangement in NSCLC



- The ALK gene encodes a transmembrane tyrosine kinase receptor
- 3 types of ALK gene mutations: rearrangement (ALK-R), amplification (ALK-A), and point mutation
- ALK gene rearrangement is a driving mutation underlying the development of NSCLC, and has been identified in 5–6% of NSCLC cases

First-line targeted therapy: ALK inhibitors



- ALK tyrosine kinase inhibitors act on the ATP-binding site of the ALK kinase region, inhibiting the autophosphorylation of the ALK protein and the phosphorylation of the downstream target protein STAT3. This inhibition suppresses the proliferation, growth, and survival of tumor cells

Resistance to ALK inhibitors

- Mutations in the ALK kinase domain are one of the most common mechanisms of resistance to ALK inhibitors. These ALK mutations are dispersed throughout the kinase domain, affecting its function. Amplification of the ALK fusion gene can result in the inhibitor's inability to fully suppress downstream signaling
- To overcome the resistance to first-generation inhibitors, second-generation ALK inhibitors such as ceritinib and alectinib, which have stronger inhibitory capabilities and higher blood-brain barrier permeability, as well as third-generation ALK inhibitors like lorlatinib, have been subsequently developed

	1st generation	Next generation	
Pros	• Directly used for first-line treatment	• Approved for first- and second-line treatment • Better blood-brain barrier permeability compared to the first generation	• Approved for first-, second-, and third-line treatment • Better blood-brain barrier permeability and ALK mutation resistance compared to first- and second-generation • Excellent efficacy for intracranial lesions in patients with brain metastases
Cons	• Limited to first-line use • Suboptimal clinical efficacy	• Relatively high cost	

Source: Thorac Cancer, MDPI, China Insights Consultancy

NMPA approved ALK targeted therapies for ALK-positive NSCLC

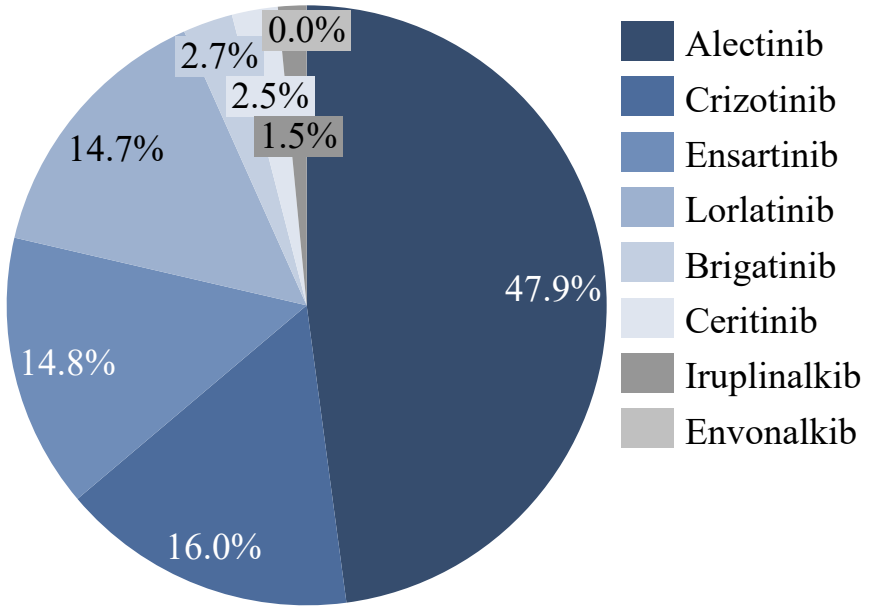
NSCLC | Marketed drug

NMPA approved ALK targeted drugs for ALK-positive NSCLC, as of LPD

Drug Name	Original manufacturer	Treatment line	Indication	NMPA Initial Approved Date	NRDL	NRDL price
Alectinib	Roche	Adjuvant	• Postoperative adjuvant treatment of patients with ALK-positive stage IB to stage IIIA NSCLC	2024.06	YES	54.91/150mg
Crizotinib	Pfizer	1L	• a/m ALK-positive NSCLC	2013.01		171.6/250 mg
Ceritinib	Novartis	1L; 2L	• a/m ALK-positive NSCLC	2018.05		108.2/150 mg
Alectinib	Roche		• a/m ALK-positive NSCLC	2018.08		54.91/150mg
Ensartinib	Betta		• a/m ALK-positive NSCLC	2020.11		142.0/100 mg
Brigatinib	Takeda		• a/m ALK-positive NSCLC	2022.03		339.0/180 mg
Lorlatinib	Pfizer		• a/m ALK-positive NSCLC	2022.04		526.8/100 mg
Iruplinalkib	Qilu		• a/m ALK-positive NSCLC	2023.06		145.0/60 mg
Envonalkib	CTTQ		• a/m ALK-positive NSCLC	2024.06		27.4/100mg
Dirozalkib	Our Company	1L	• a/m ALK-positive NSCLC	2025.08	No	/

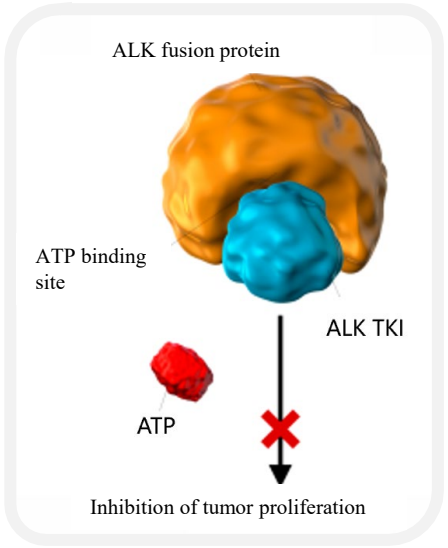
Source：CDE, China Insights Consultancy

Competitive landscape of ALK inhibitors in China, 2024

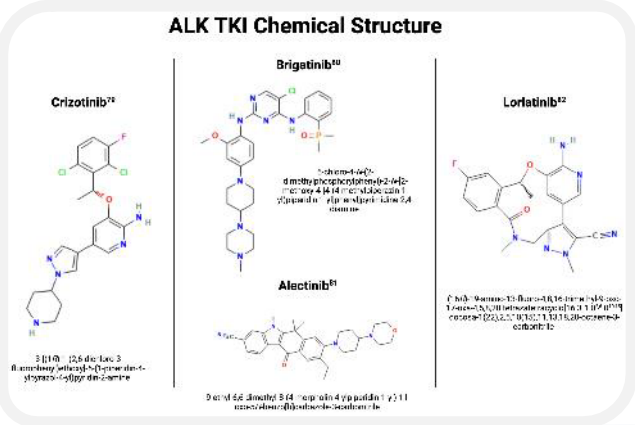


Source：Menet, China Insights Consultancy

Characteristics of different ALK inhibitors



- ALK fusion proteins have a specific kinase domain, which is the adenosine triphosphate (ATP) binding site. When the ALK fusion protein binds with ATP, it activates a series of downstream signaling pathways that promote tumor survival, growth, and progression
- Although crizotinib can significantly prolong the response rate and PFS of patients with ALK-p NSCLC, disease progression inevitably occurs after treatment because of the acquired resistance of 1–2 years

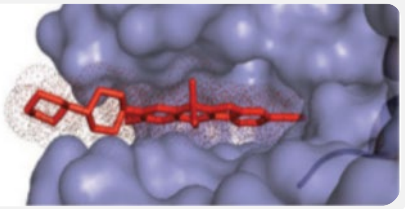


- **Acquired resistance:**
  - ➢ ALK-dependent resistance mechanisms, such as secondary ALK resistance mutations and ALK amplification
  - ➢ ALK-independent resistance mechanisms, such as bypass signaling pathway activation and lineage changes

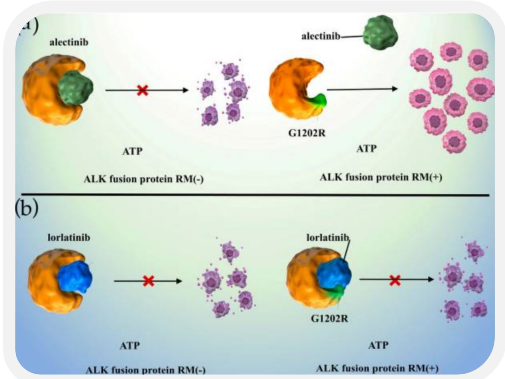
2nd-generation ALK inhibitors

- 2nd-generation ALK inhibitors, such as alectinib and brigatinib, have been developed and approved clinically to overcome crizotinib-resistant mutations. These inhibitors are potent against common crizotinib-resistant mutations, L1196M, and G1269A
- For patients who develop resistance due to brain metastases, 2nd-generation drugs are capable of crossing the blood-brain barrier and maintaining high concentrations

Compared to crizotinib, alectinib binds more tightly to the ALK protein in the ATP binding pocket



3rd-generation ALK inhibitors



- The G1202R mutation is the most frequent resistance mutation following the administration of 2nd-generation ALK inhibitors
- Due to the macrocyclic amide structure, lorlatinib displays activity against all potential ALK-TKI resistance mutations, including L1196M, G1269A, and G1202R

Source：Int J Mol S, Cancer Drug Resist, Ann Oncol, China Insights Consultancy

CDE-registered ALK inhibitors pipeline for NSCLC/solid tumor

Pipelines of ALK inhibitors, CDE-registered, as of LPD (Phase III or beyond)

Product	Target	Company	Phase	Line	Indication	First Posted Date	Trial Number
Conteltinib	FAK1; FAK2; ALK; IGF1R	Centaurus	NDA	≤2L	ALK-positive NSCLC	2024-10-22	N/A
Foritinib	ALK; ROS1	Fochon	NDA	1L	ALK-positive NSCLC	2025-03-06	N/A
TGRX-326	ALK; ROS1	TargetRx	III	≤2L	ALK-positive NSCLC	2023-11-07	CTR20233380
CT-3505	ALK	Shouyao	III	1L	ALK-positive NSCLC	2024-01-19	CTR20240005
Ensartinib	ALK; ROS1; c-Met	Betta	III	Adjuvant therapy	Stage II-IIIB ALK-positive NSCLC	2022-04-19	CTR20220895

Source：CDE, China Insights Consultancy

Clinical data of ALK inhibitors

Clinical data of ALK inhibitors

Product	Phase	Line	Therapy	ORR (%)	mPFS (months)	Grade≥3 TRAE (%)
ALK-positive advanced NSCLC treatment-naive patients						
Crizotinib	III	1L	Crizotinib vs Chemotherapy	74 vs 45	10.9 vs 7.0	50 vs 53
Ceritinib	III	1L	Ceritinib vs Chemotherapy	73 vs 27	16.6 vs 8.1	78 vs 62
Alectinib	III	1L	Alectinib vs Crizotinib	79 vs 72	25.7 vs 10.4	41 vs 50
Ensartinib	III	1L	Ensartinib vs Crizotinib	74 vs 67	25.8 vs 12.7	N/A
Brigatinib	III	1L	Brigatinib vs Crizotinib	74 vs 62	24.0 vs 11.0	72 vs 55
Iruplinalkib	III	1L	Iruplinalkib vs Crizotinib	93 vs 89	27.7 vs 14.6	84 vs 82
Envonalkib	III	1L	Envonalkib vs Crizotinib	82 vs 71	24.9 vs 11.6	56 vs 43
XZP-3621	I	1L	XZP-3621	84	NR; the 21-month PFS rate is 53.1%	35
Lorlatinib	III	1L	Lorlatinib vs Crizotinib	76 vs 58	>60.0 vs 9.3	61 vs 55
ALK-positive advanced NSCLC patients previously treated with 1st-generation inhibitors						
Ceritinib	I	2L	Ceritinib	55	6.9	N/A
Alectinib	II	2L	Alectinib	48	N/A	27
Ensartinib	II	2L	Ensartinib	52	11.2	23
Brigatinib	II	2L	Brigatinib	54	NR	N/A
Iruplinalkib	II	2L	Iruplinalkib	70	19.8	N/A
Envonalkib	I	2L	Envonalkib	56	NR	N/A
XZP-3621	I	2L	XZP-3621	50	NR; the 21-month PFS rate is 37.5%	N/A
Lorlatinib	II	2L	Lorlatinib	70	NR	31

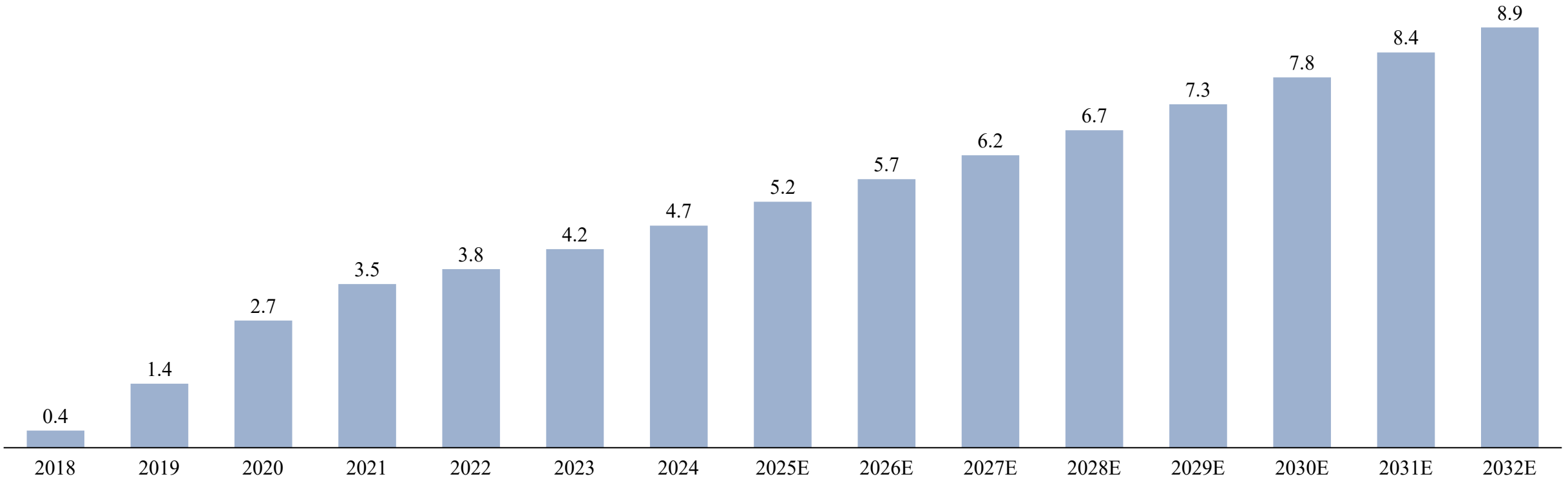
Source：CDE, ClinicalTrials, ASCO, Pharmacodia, China Insights Consultancy

Market size of ALK inhibitors in China, 2018-2032E

Market size of ALK inhibitors in China, 2018-2032E

CAGR	2018-24	2024-32E
ALK inhibitors	53.2%	8.3%

Billion RMB



Source：Menet, China Insights Consultancy

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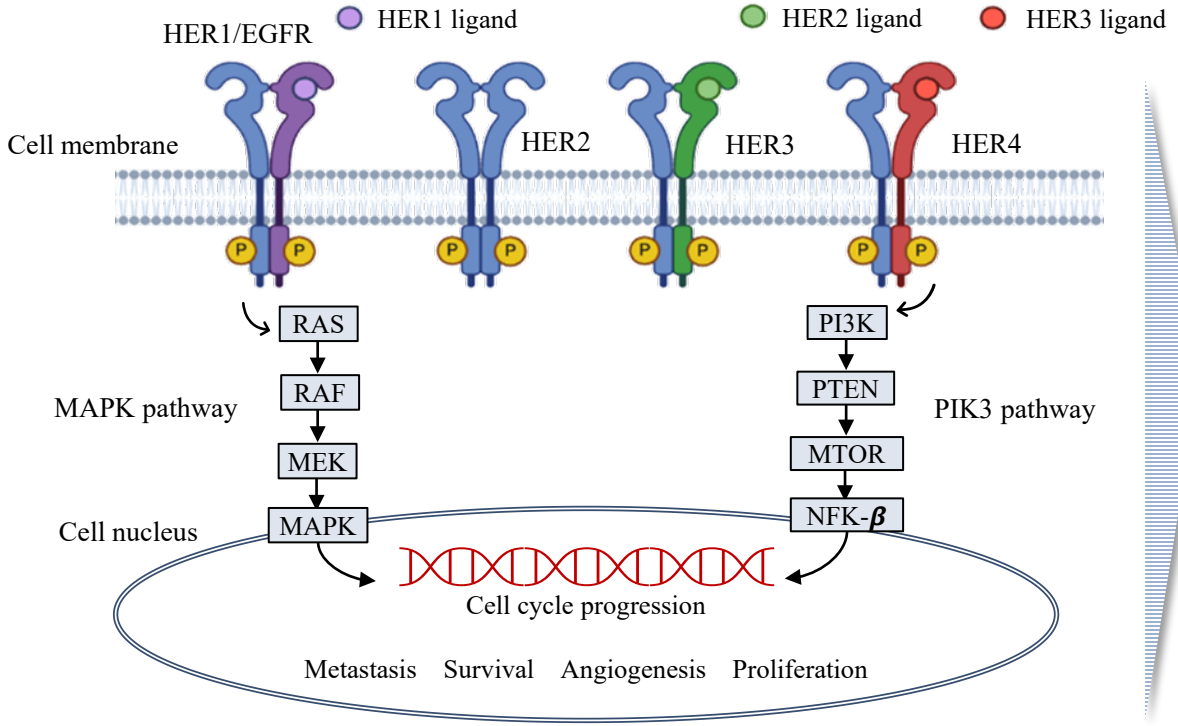
Introduction and mechanism of HER2

Introduction to HER2

- **Human epidermal growth factor receptor 2 (HER2)** is a member of the human epidermal growth factor receptor family. HER2 is a transmembrane receptor tyrosine kinase and a member of the ErbB family, which also includes HER1 (EGFR), HER3, and HER4. Unlike the other three members, HER2 does not bind to EGF-like ligands but relies on forming heterodimers with other members to activate signaling pathways that regulate cell proliferation and survival. HER2 is overexpressed in various cancers such as BC, GC, lung cancer, ovarian cancer (OC), among others
- In recent years the HER2 has become an important biomarker and anti-HER2 treatments are expected to be standard therapy for those cancers with HER2 over-expression



Mechanism of action of HER2 signal pathway

- HER stands for Human Epidermal Growth Factor Receptor, also known as ERBB. The HER family comprises four members: EGFR (HER1 or ERBB1), HER2 (ERBB2), HER3 (ERBB3), and HER4 (ERBB4).
- Human Epidermal Growth Factor Receptor 2 (HER2) is a tyrosine kinase on chromosome 17 (17q21). It contains three recognizable functional domains: an extracellular domain that binds to members of the HER2 family, a hydrophobic transmembrane domain, and an intracellular domain with tyrosine kinase activity.
- Upon activation, HER2 triggers **the phosphorylation of intracellular tyrosine substrates, initiating signaling pathways that have oncogenic implications**. HER2 does not rely on extracellular ligands for activation and can form heterodimers with any of the other three receptors (HER1, HER3, HER4), making it an ideal dimer partner. After activation, HER2 triggers the **phosphorylation of intracellular tyrosine substrates,** initiating subsequent signaling pathways. **Activating PI3K/AKT/mTOR/NFK-β and the RAS/RAF/MEK/MAPK signaling pathway** promotes cell proliferation, metastasis, angiogenesis, and survival while inhibiting cell apoptosis.

Source: Biomed Pharmacother, China Insights Consultancy

Classification of HER2 and incidence rate of HER2-high/low expression of major cancer types

Introduction to HER2

Incidence rate of HER2-high/low expression of major cancer types

Cancer type	Incidence rate of HER2-low expression	Incidence rate of HER2-high expression	Incidence rate of HER2 expression
Breast	47.1%	10.3%	57.4%
Gastric	34.7%	13.9%	48.6%
Biliary tract	42.2%	5.0%	47.2%
Colorectal	28.5%	3.3%	31.8%
Pancreas	31.4%	1.5%	32.9%
Endometrial	46.5%	12.6%	59.1%
Ovarian	32.9%	4.7%	37.6%
Cervical	21.4%	14.3%	35.7%
Urothelial	46.0%	21.6%	67.6%
Lung	46.9%	2.8%	49.7%
HNSCC	21.7%	8.7%	30.4%

HER2 expression classification

HER2 expression classification	IHC				FISH		
	3+	2+	1+	0	Positive	Equivocal	Negative
HER2-High	√						
		√			√		
HER2-Low		√				√	√
			√				
HER2-Negative				√			

Key Analysis

- The HER2 expression status of cancer can be described as High, Intermediate, Low or Negative according to immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH). For instance, HER2 High expression is IHC 3+ or IHC 2+ with FISH-positive.

Source: ESMO, The Oncologist, Annals of Oncology, China Insights Consultancy

Classification of HER2 and incidence rate of HER2-high/low expression of major cancer types

Incidence rate of HER2 expression of major cancer types

Cancer type	IHC 1+	IHC 2+	IHC 3+
Breast cancer	27.8%	19.3%	10.3%
Lung cancer	32.2%	14.7%	2.8%
Gastric cancer	21.2%	13.5%	13.9%
Biliary tract cancer	27.3%	14.9%	5.0%
Ovarian cancer	12.9%	20.0%	4.7%
Cervical cancer	7.1%	14.3%	14.3%
Pancreatic cancer	23.9%	7.5%	1.5%
Colorectal cancer	20.5%	8.0%	3.3%
Head and neck squamous cell carcinoma	17.4%	4.3%	8.7%

Source: Annals of Oncology, China Insights Consultancy

Classification of HER2 and incidence rate of HER2-high/low expression of major cancer types

Incidence of HER2-high/low expression of major cancer types in China

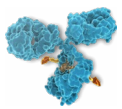
Cancer type	Incidence of cancer in China (k ppl.)			CAGR		Incidence rate of HER2 expression	Incidence of HER2 expression cancer in China (k ppl.)			CAGR	
	2018	2024	2032E	2018-2024	2024-2032E		2018	2024	2032E	2018-2024	2024-2032E
Breast cancer	322.2	374.7	435.0	2.5%	1.9%	57.4%	184.9	215.1	249.7	2.5%	1.9%
NSCLC	764.4	973.2	1,236.4	4.1%	3.0%	49.7%	379.9	483.7	614.5	4.1%	3.0%
Gastric cancer	383.5	347.8	315.9	-1.6%	-1.2%	48.6%	186.4	169.0	153.5	-1.6%	-1.2%
Biliary tract cancer	122.2	98.3	83.5	-3.7%	-2.1%	47.2%	57.7	46.4	39.4	-3.7%	-2.1%
Total							808.9	914.2	1057.1	2.1%	1.8%

Source: ANNALS OF ONCOLOGY; China Insights Consultancy

NMPA has 9 approved HER2 mAb/ADC products, with indications mainly focusing on breast cancer

HER2 mAb/ADC | Marketed drug

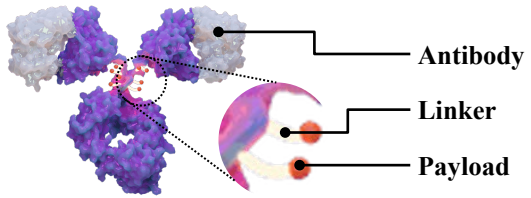
HER2 mAb/ADC products comparison

MoA	Product Name	Generic Name	Original Company	Indication	NMPA Approved Date	NRDL
mAb 	Herceptin®	Trastuzumab	Roche	Early/advanced breast cancer	2002-09-05	YES
				Locally advanced or metastatic gastric cancer	2012-01-01	
	Perjeta®	Pertuzumab	Roche	Early/advanced breast cancer	2018-12-17	YES
	Cipterbin®	Inetetamab	三生国健 guojian pharmaceutical	Advanced breast cancer	2020-06-17	YES
	Margenza®	Margetuximab	MacroGenics	Advanced breast cancer	2023-09-01	NO
	Phesgo®	Trastuzumab/ Pertuzumab	Roche	Early/advanced breast cancer	2023-12-26	YES
ADC 	Kadcyla®	Trastuzumab Emtansine	Roche	Early/advanced breast cancer	2020-01-21	YES
	Aidixi®	Disitamab Vedotin	RemeGen 荣昌生物	Locally advanced or metastatic gastric cancer	2021-06-08	
				Locally advanced or metastatic urothelial carcinoma	2023-08-21	
	Enhertu®	Trastuzumab Deruxtecan	Daiichi-Sankyo AstraZeneca	Advanced breast cancer	2023-02-21	YES
	艾维达®	Trastuzumab rezetecan	Hengrui	HER2 (ERBB2) mutated Locally advanced or metastatic NSCLC	2025-05-29	NO

Source: NMPA, China Insights Consultancy

Introduction to HER2/HER2 Bispecific ADC

Introduction HER2/HER2 Bispecific ADC



- **ADC (Antibody-Drug Conjugate)** is a revolutionary cancer treatment method that combines **antibodies, cytotoxic drug(payload), and linker.** The working principle of ADC involves antibodies specifically binding to antigens on the surface of tumor cells, internalizing into the cell, and releasing payload to kill tumor cells, thus inhibiting tumor growth and spread
- **Bispecific ADC combines the advantages of bispecific antibodies and ADCs**: compared to monoclonal antibodies, bispecific ADCs can more specifically target tumor cells through their bispecificity, overcoming drug resistance while increasing drug safety. Additionally, by crosslinking and promoting the synergistic endocytosis of dual-targets, they enhance the efficiency of toxin entry into tumor cells. This further inhibits tumor cell growth signals by reducing the expression of receptor proteins on the cell membrane, leading to better therapeutic outcomes

Potential of HER2/HER2 dual-target

- In 2017, the FDA approved the trastuzumab + pertuzumab + chemotherapy regimen. The success of this regimen has drawn increased interest from researchers in dual targeting of HER2
- The underlying mechanism is the dual HER2 inhibition
  - ➢ Trastuzumab kills HER2-positive cancer cells through antibody-dependent cell-mediated cytotoxicity (ADCC), but it is insufficient to completely eradicate cancer cells and block downstream signaling pathways
  - ➢ Pertuzumab is a HER2 dimerization inhibitor. Pertuzumab inhibits the proliferation of breast cancer cells by blocking the dimerization pathway of HER2. The binding site of pertuzumab on HER2 does not interfere with that of trastuzumab, making the combination of these two monoclonal antibodies complementary and possible

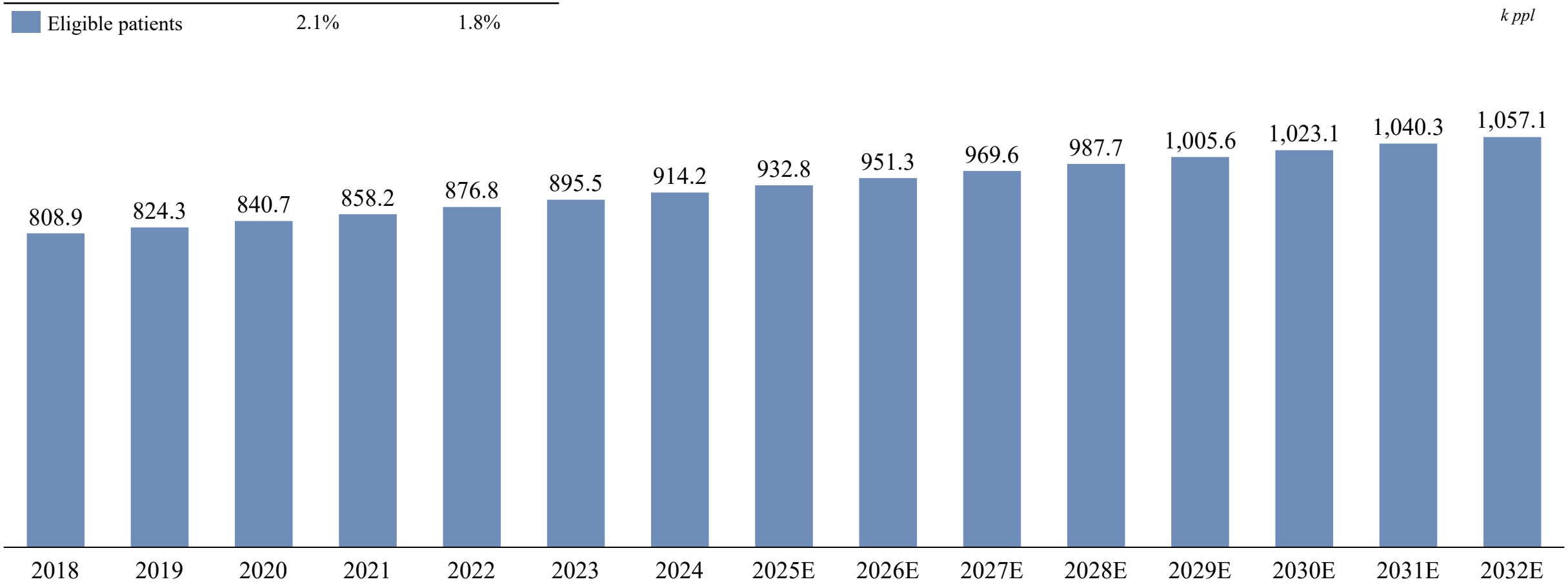
Drug Modalities	Monoclonal Antibody (mAb)	Bispecific Antibody (BsAb)	Antibody–drug conjugate (ADC)
Description	• Laboratory-produced molecules engineered to target specific antigens	• Recombinant molecules designed to target two antigens or epitopes	• ADC combines cytotoxic drugs with monoclonal antibodies for targeted tumor destruction
Pros	• High specificity • Low toxicity	• Enhanced tumor specificity • Reducing off-target toxicity • Enhancing activation of immune cells • Potential for synergistic therapeutic effects	• High specificity • High selectivity • Low systemic toxicity
Cons	• Targeting only one antigen • Limited efficacy in some cancers	• Higher risk of immunogenicity • Cytokine storm • Limited clinical experience	• Challenges in payload stability and conjugation • Safety concerns
Challenge of Development and Production	• Low yield • High time and monetary costs • Challenges in process scaling	• Low druggability • Targets selecting • Constructing expression vectors • Achieving production purification	• Site-specific quantitative conjugation of antibodies, payload, and linkers • Downstream production purification

Source: The Lancet, Mol Biol Int, Signal Transduction And Targeted Therapy, STTT, China Insights Consultancy

Eligible patients of HER2/HER2 Bispecific ADCs in China

Eligible patients of HER2/HER2 Bispecific ADCs in China, 2018-2032E

CAGR	2018-2024	2024-2032E
Eligible patients	2.1%	1.8%



Note: including NSCLC, melanoma, CRC, GC.

Source: China Insights Consultancy

Clinical pipelines targeted HER2/HER2 bispecific ADC registered in CDE

Pipelines of HER2/HER2 bispecific ADC, CDE-registered, as of LPD

Drug Name	Company	Phase	Line	Indication	First Posted Date	Trial Number
JSKN003	Alphamab Oncology 康宁杰瑞	III	2L&3L	HER2 low expression recurrent/metastatic breast cancer HER2低表达复发/转移性乳腺癌	2023-10-07	CTR20232959
		III	≥1L	Recurrent epithelial ovarian cancer/primary peritoneal carcinoma/fallopian tube cancer 复发上皮性卵巢癌、原发性腹膜癌或输卵管癌	2024-12-27	CTR20244822
		III	≥2L	Unresectable locally advanced/metastatic HER2-positive breast cancer 不可切除局部晚期或转移性HER2阳性乳腺癌	2025-02-05	CTR20250049
		II	1L	HER2-positive unresectable locally advanced/metastatic gastric cancer or stage II–Iva resectable gastric cancer HER2阳性不可切除局部晚期或转移性癌或II-IVa期可切除的胃癌	2025-05-20	CTR20251968
		I/II	N/A	Advanced malignant solid tumor 晚恶性实体瘤	2024-12-25	CTR20244896
TQB2102	Chiatai Tianqing Pharmaceutical Group 正大天晴	III	1L	HER2 low expression recurrent/metastatic breast cancer HER2低表达复发/转移性乳腺癌	2024-08-19	CTR20242868
		III	≥2L	HER2-positive unresectable locally advanced/metastatic breast cancer HER2 阳性、不可切除的局部晚期或转移性乳腺癌	2025-05-15	CTR20251922
		II	N/A	HER2 genetic aberration locally advanced or metastatic NSCLC HER2 基因异常局部晚或转移性非小细胞肺癌	2024-06-11	CTR20242017
		II	≥2L	Unresectable locally advanced/recurrent/metastatic HER2-positive gastroesophageal adenocarcinoma 不可切除的局部晚期、复发性或转移性HER2阳性胃食管腺癌	2024-10-29	CTR20243929
		Ib/II	N/A	HER2-positive locally advanced/metastatic biliary tract cancer HER2阳性局部晚或转移性胆道癌	2024-05-22	CTR20241862
XZP-KM501	**Xuanzhu Biopharma 轩竹生物**	**I**	**≥2L**	**Advanced solid tumors with HER2 expression, amplification, or mutation HER2表达、扩增或突变的晚实体瘤**	**2023-03-10**	**CTR20230726**

*Note: *Two different antigen epitopes*

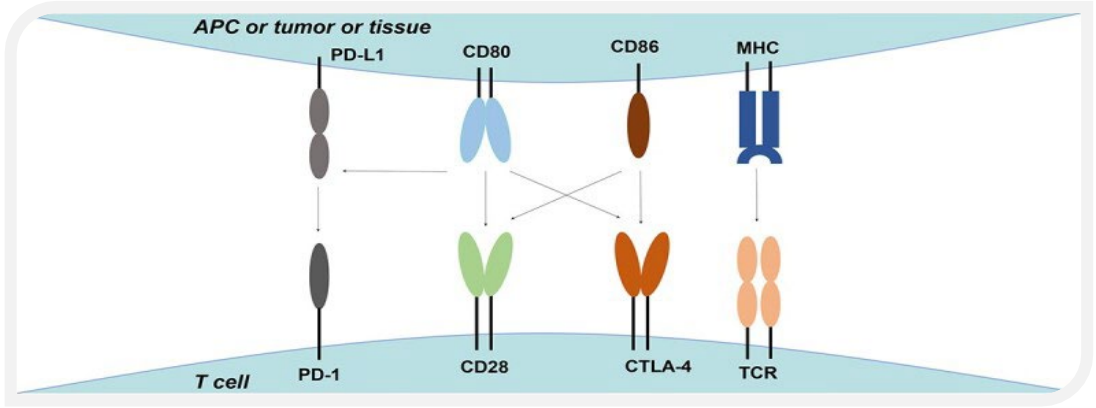
Source: CDE, China Insights Consultancy

Introduction and mechanism of CD80-Fc

Introduction to CD80-Fc

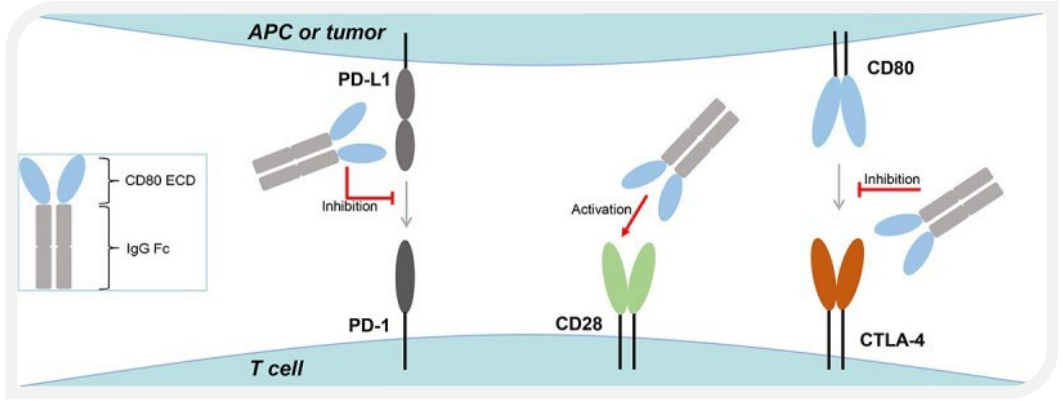
- Cluster of differentiation (CD) 80, also known as B7-1, is a costimulatory molecule and plays an important role in the T-cell activation
- CD80 is usually expressed on antigen-presenting cells (APCs), which can interact with cluster of differentiation 28 (CD28) or programmed cell death ligand 1 (PD-L1) to promote T-cell proliferation, differentiation and function by activating costimulatory signal or blocking inhibitory signal. Simultaneously, CD80 on the APCs also interacts with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on the surface of T cells to suppress the response of specific effector T cells, particularly in the context of persistent antigenic stimulation
- Due to the pivotal role of CD80 in the immune response, the CD80-Fc fusion protein has emerged as a promising approach for cancer immunotherapy

The CD80/86 costimulatory pathway



- During T cell activation, the inhibitory receptor CTLA4 on T cells is induced, and subsequently, the binding of CTLA4 to CD80/CD86 can limit T cell activation. CD80 is expressed on activated T/B lymphocytes, monocytes stimulated by IFN-γ, and dendritic cells

Mechanism of CD80-Fc fusion protein



- CD80-Fc fusion protein consists of the ECD of CD80 and the structural domain of IgG Fc. Soluble CD80-Fc fusion protein binds to CD28 to generate T-cell costimulatory signal, whereas its binding to PD-L1 blocks inhibitory signals. Meanwhile, soluble CD80-Fc fusion protein also can bind to CTLA-4 to exert a CTLA-4-trap effect

Source: Nature reviews, Antib Ther, China Insights Consultancy

Clinical pipelines of anti-tumor CD80-FC fusion protein, CDE-registered

Clinical pipelines of anti-tumor CD80-FC fusion protein, CDE-registered, as of LPD

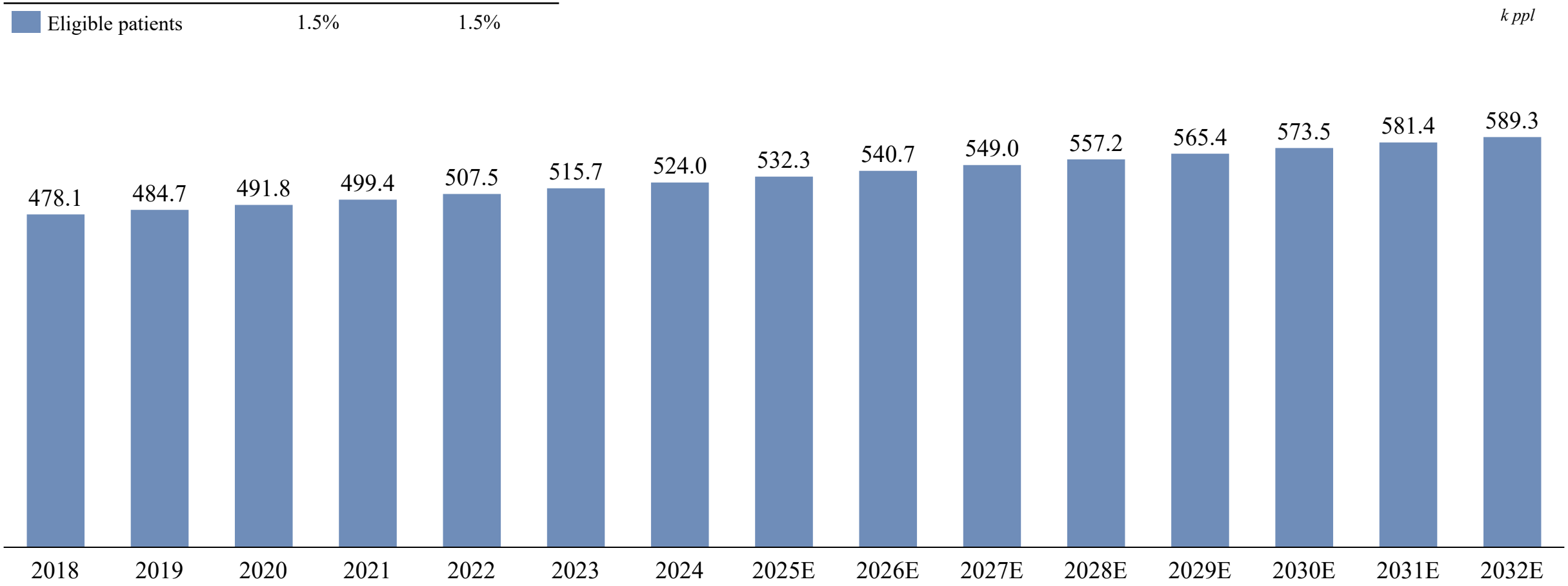
Drug Name	Company	Phase	Line	Indications	First Posted Date	Trial Number
XZP-KM602	Our Company	I	≥1L	Solid tumors	2023-03-02	CTR20230600
SG1827	SumgenBio	I	≥1L	Advanced solid tumors	2023-09-25	CTR20232894

Source: CDE, China Insights Consultancy

Eligible patients of KM602 in China, 2018-2032E [major* PD-L1 positive solid tumors incidence]

Eligible patients of KM602 in China, 2018-2032E

CAGR	2018-2024	2024-2032E
Eligible patients	1.5%	1.5%

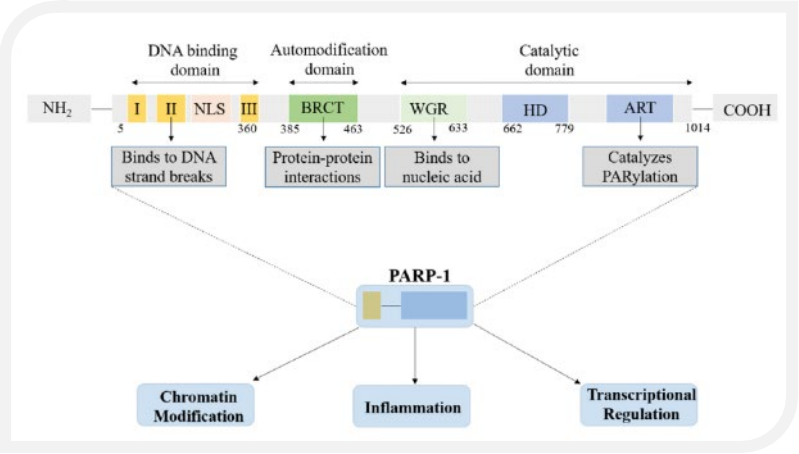


Note: including NSCLC, melanoma, CRC, GC.

Source: China Insights Consultancy

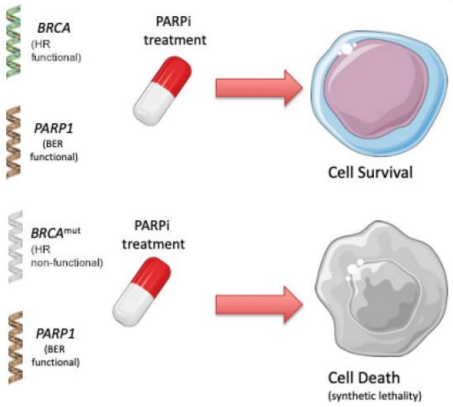
Introduction to PARP1

Introduction to PARP1



- Poly (ADP-ribose) polymerase 1 (PARP1), the best-studied isoform of the nuclear enzyme PARP family, plays a pivotal role in cellular biological processes, such as DNA repair, gene transcription, and so on
- PARP family of enzymes are composed of 18 member proteins. Among the 18 PARP family members, PARP1 is the most abundant and best-characterized nuclear enzyme. PARP1 comprises three distinct functional domains: N-terminal DNA binding domain (DBD), central auto-modification domain (AD), and C-terminal catalytic domain (CAT)
- PARP1 is considered to promote tumor development potentially through many pathways. Briefly, PARP1 regulates gene transcription through interacting with transcription factors, transcription machinery, and chromatin modulators. Hyperactivated PARP1 upregulates inflammatory signal factors in tumors

Mechanism of PARP1 inhibitors



- Up until now, preclinically studied PARP1 inhibition methodologies are divided into two types: pharmacological inhibition, and genetic knockdown. PARP1 inhibitors include chemical compounds and nucleic acids. In general, the antineoplastic mechanism of currently mature PARP1 inhibitors mainly focuses on DNA repair pathways
- **Synthetic lethality:** a lethal combination of perturbations in two pathways is exploited as an anti-cancer therapeutic. Mutations in or targeting either pathway alone do not affect cell viability. However, if one pathway is mutated in cancer cells (such as defects in HRR), the cell becomes overly reliant on other closely related pathways for survival. If one of these related pathways (such as PARP-driven base excision repair [BER]) is pharmacologically inhibited, the tumour cell will die. The recent success of PARPi in BRCA mutant ovarian cancers is the first clinical example of using synthetic lethality to target tumour suppressor gene loss

Source: Pharmacological Research, Int J Mol Sci, Cancers (Basel), China Insights Consultancy

NMPA has 7 approved PARP products, but no PARP1 selective inhibitors have been approved

PARP1 | Marketed drug

Product Name	Generic Name	Original manufacturer	Target	Indication	Line	Initial NMPA Approval	Mono/ Combo	NRDL
Lynparza®	Olaparib	AstraZeneca	PARP 1/2	• Maintenance treatment of adults with HRD+/BRCA mutations advanced or recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are in complete or partial response to ≥1L platinum-based chemotherapy	Maintenance treatment	2018-08-22	Mono& Combo	2019
				• ≥2L treatment of metastatic castration-resistant prostate cancer carrying germline or somatic BRCA mutations	≥2L	2021-06-23	Mono	2022
Zejula®	Niraparib	Zai Lab	PARP 1/2	• Maintenance treatment of adults with advanced or recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are in complete or partial response to ≥1L platinum-based chemotherapy	Maintenance treatment	2019-12-26	Mono	2020
AiRuiYi®	Fluzoparib	Hengrui	PARP 1/2	• ≥3L treatment of patients with platinum-sensitive recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have undergone chemotherapy and have gBRCA mutations	≥3L	2020-12-11	Mono	2021
				• Maintenance treatment of platinum-sensitive adults with advanced or recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are in complete or partial response to ≥1L platinum-based chemotherapy	Maintenance treatment	2021-06-24	Mono	2021
Partruvix®	Pamiparib	Beone	PARP 1/2	• ≥3L treatment of patients with recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have undergone chemotherapy and have gBRCA mutations.	≥3L	2021-04-30	Mono	2021
Akeega®	Niraparib/ Abiraterone	Johnson & Johnson	PARP 1/2	• ≥1L treatment for mCRPC patients with germline and / or systemic BRCA mutation	≥1L	2024-10-21	Combo	No
Talzenna®	Talazoparib	Pfizer	PARP 1/2	• ≥1L treatment for male patients of mCSPC with DDR-mutation	≥1L	2024-10-29	Combo	No
Shupaining® 派舒宁®	Senaparib	IMPACT	PARP 1/2	• Maintenance treatment of adults with advanced or recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who are in complete or partial response to ≥1L platinum-based chemotherapy	Maintenance treatment	2025-01-14	Mono	No

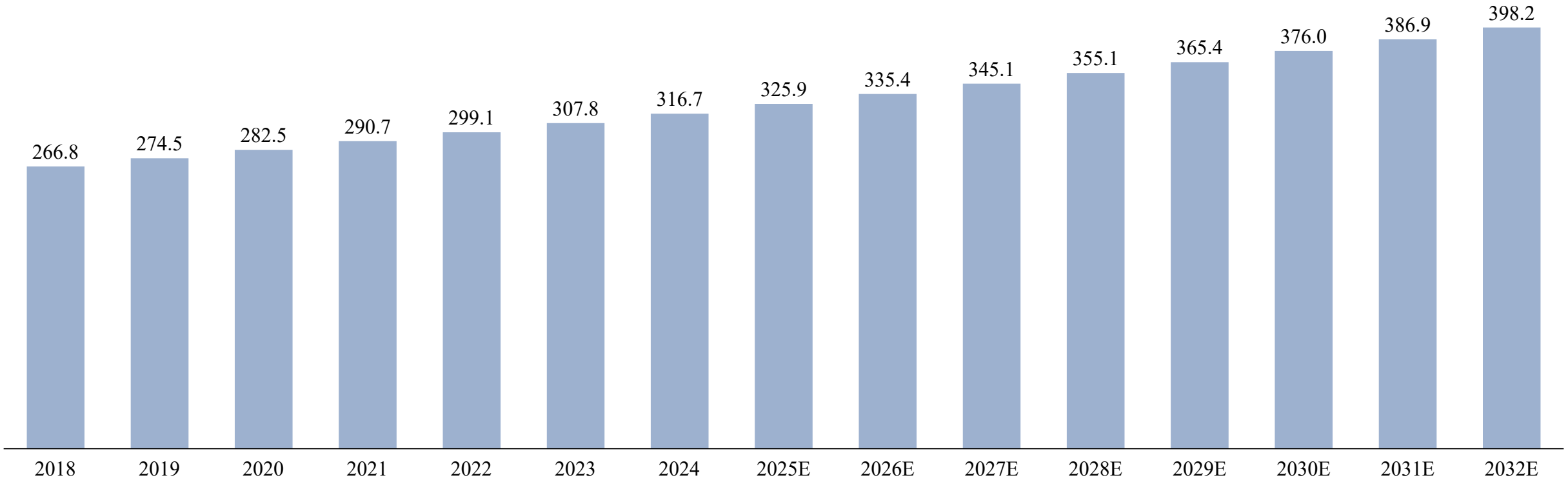
Source: CDE, China Insights Consultancy

Eligible patients of USP1 inhibitors in China, 2018-2032E

Eligible patients of USP1 inhibitors in China, 2018-2032E

thousand ppl

CAGR	2018-24	2024-32E
USP1 inhibitors	2.9%	2.9%

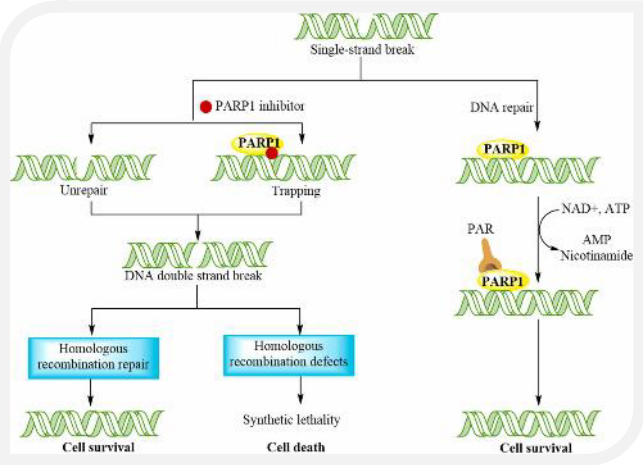


Source: China Insights Consultancy

Clinical Advantages of next-generation PARP1 Selective Inhibitors

Next-generation of PARP1 Selective Inhibitors

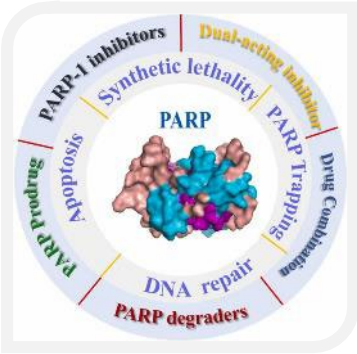
Unmet demand of first-generation PARP inhibitors



- PARP1 and PARP2 are the most extensively studied PARPs due to their crucial roles in DNA damage repair
- Currently, there are four PARP inhibitors approved for market in China: Olaparib, Niraparib, Fluzoparib, Pamiparib, all of which are PARP1/2 inhibitors

- The advent of PARP1/2 inhibitors has brought significant changes to the treatment of recurrent ovarian cancer and has provided additional treatment options for breast cancer, prostate cancer, and pancreatic cancer
- However, these first-generation PARP1/2 inhibitors may have several limitations, such as poor water solubility, lower bioavailability, and limited tissue distribution. Notably, adverse reactions primarily related to hematologic toxicity are prominent, which restricts their clinical application

Trend of PARP1 selective inhibitors



- The synthetic lethality with BRCA mutations was only driven by PARP1, and that PARP2 was not required. Therefore, selective inhibition of PARP1 may reduce toxicity and improve therapeutic index. Therefore, in cases of homologous recombination deficiency, selective inhibition of PARP1 alone can achieve synthetic lethality. The current research trend is to develop next-generation inhibitors that selectively target PARP1

Example: Saruparib for HRR-Deficient Breast Cancer

- Saruparib (AZD-5305) is a next-generation oral inhibitor that selectively targets PARP1. Compared to first-generation dual PARP1/2 inhibitors, it does not need to target both PARP1 and PARP2 simultaneously, resulting in lower toxicity and higher safety. This allows for administration at higher doses, improving efficacy
- Results from the phase I/II PETRA trial:
  - Among the 31 breast cancer patients treated with 60 mg saruparib, the ORR was 48.4%, the mDOR was 7.3 months, and the mPFS was 9.1 months
  - In the cohort of 141 patients across all cancer types, adverse events were observed in 12.1% of patients experienced a serious adverse event

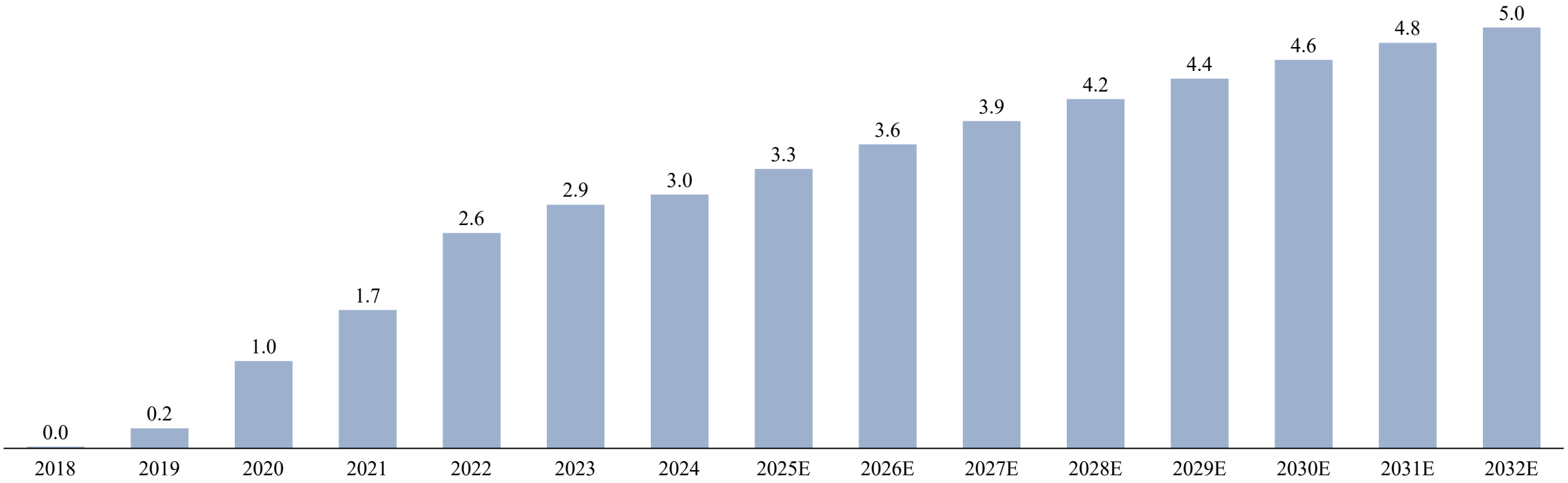
Source: Pharmacological Research, AACR, China Insights Consultancy

Market size of PARP1 inhibitors in China, 2018-2032E

Market size of PARP1 inhibitors in China, 2018-2032E

CAGR	2018-24	2024-32E
PARP1 inhibitors	131.2%	6.5%

Billion RMB



Source: Menet, China Insights Consultancy

Clinical pipelines of PARP target drugs, CDE-registered

Clinical pipelines of PARP-target drugs, CDE-registered, as of LPD*

Drug Name	Target	Company	Phase	Line	Indications	First Posted Date	Trial Number
Saruparib	PARP1	AstraZeneca	III	≥2L	Metastatic castration-sensitive prostate cancer	2024-04-15	CTR20241066
			III	1L	Patients with advanced breast cancer who have BRCA1, BRCA2, or PALB2 mutations and are hormone receptor-positive and HER2-negative (IHC 0, 1+, or 2+/ISH non-amplified)	2024-12-24	CTR20244809
			I/II	N/A	Advanced solid tumors	2022-03-03	CTR20220423
Senaparib	PARP1/2	IMPACT	III	≥3L	Advanced ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	2019-04-04	CTR20190652
			II	2L	Advanced small cell lung cancer	2022-05-23	CTR20221169
TQB-3823	PARP1/2	Chia Tai Tianqing	Ib/III	1L	Maintenance therapy for advanced ovarian cancer, fallopian tube cancer, and primary peritoneal cancer	2023-06-05	CTR20231645
HRS-1167	PARP1	Hengrui	Ib/II	2L&3L	Recurrent ovarian cancer	2024-02-26	CTR20240646
CVL218	PARP1/2	Cisen	II	N/A	Metastatic castration-resistant prostate cancer with BRCA gene mutation	2021-06-21	CTR20211367
HWH-340	PARP1/2	Humanwell	II	≥2L	Prostate cancer	2022-12-22	CTR20223238
HTMC-0435	PARP1/2	Huilun	II	≥2L	Advanced pancreatic cancer	2023-03-14	CTR20230616
			II	≥2L	Advanced cholangiocarcinoma	2023-03-06	CTR20230615
			Ib/II	2L&3L	Advanced small cell lung cancer and other solid tumors	2022-10-11	CTR20222504
			I/II	≥1L	Advanced solid tumors	2020-04-14	CTR20200573

Source: CDE, China Insights Consultancy

Clinical pipelines of PARP target drugs, CDE-registered

Clinical pipelines of PARP-target drugs, CDE-registered, as of LPD*

Drug Name	Target	Company	Phase	Line	Indications	First Posted Date	Trial Number
ACE-86225106	PARP1	Acerand	I/II	N/A	Advanced solid tumors	2024-01-23	CTR20240158
VB15010	PARP1	Yangli	I/II	N/A	Advanced solid tumors	2024-09-13	CTR20243267
IMP-1734	PARP1	IMPACT	I/II	N/A	Advanced solid tumors	2024-02-26	CTR20240637
IMP1707	PARP1	IMPACT	I/II	N/A	Advanced solid tumors	2025-05-07	CTR20251737
Simmiparib	PARP1/2	Shanghai Institute of Materia Medica	Ib	≥2L	HER-2 negative advanced breast cancer with gBRCA1/2 mutations	2023-07-17	CTR20232031
HS-10502	PARP1	Hansoh	I	N/A	Advanced solid tumors	2025-01-13	CTR20250035

Source: CDE, China Insights Consultancy

Clinical pipelines of selectively PARP1-target drugs, CDE-registered

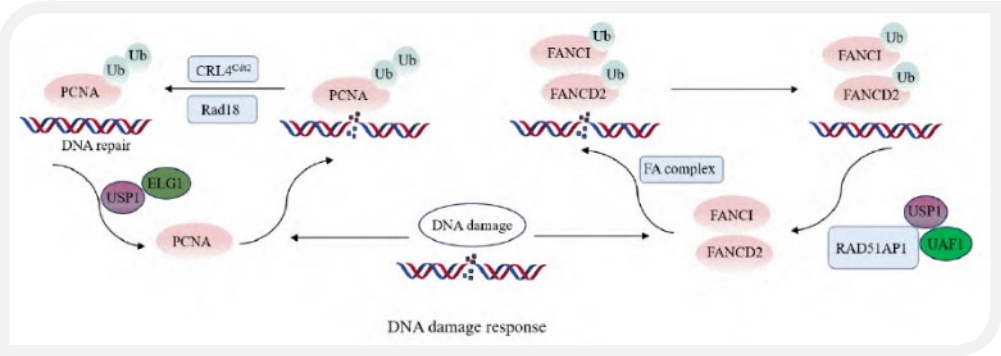
Clinical pipelines of selectively PARP1-target drugs, CDE-registered, as of LPD

Drug Name	Target	Company	Phase	Line	Indications	First Posted Date	Trial Number
Saruparib	PARP1	AstraZeneca	III	≥2L	Metastatic castration-sensitive prostate cancer	2024-04-15	CTR20241066
			III	1L	Patients with advanced breast cancer who have BRCA1, BRCA2, or PALB2 mutations and are hormone receptor-positive and HER2-negative (IHC 0, 1+, or 2+/ISH non-amplified)	2024-12-24	CTR20244809
			I/II	N/A	Advanced solid tumors	2022-03-03	CTR20220423
HRS-1167	PARP1	Hengrui	Ib/II	2L&3L	Recurrent ovarian cancer	2024-02-26	CTR20240646
ACE-86225106	PARP1	Acerand	I/II	≥1L	Advanced solid tumors	2024-01-23	CTR20240158
VB15010	PARP1	Yangli	I/II	≥1L	Advanced solid tumors	2024-09-13	CTR20243267
IMP-1734	PARP1	IMPACT	I/II	N/A	Advanced solid tumors	2024-02-26	CTR20240637
IMP1707	PARP1	IMPACT	I/II	N/A	Advanced solid tumors	2025-05-07	CTR20251737
HS-10502	PARP1	Hansoh	I	N/A	Advanced solid tumors	2025-01-13	CTR20250035

Source: CDE, China Insights Consultancy

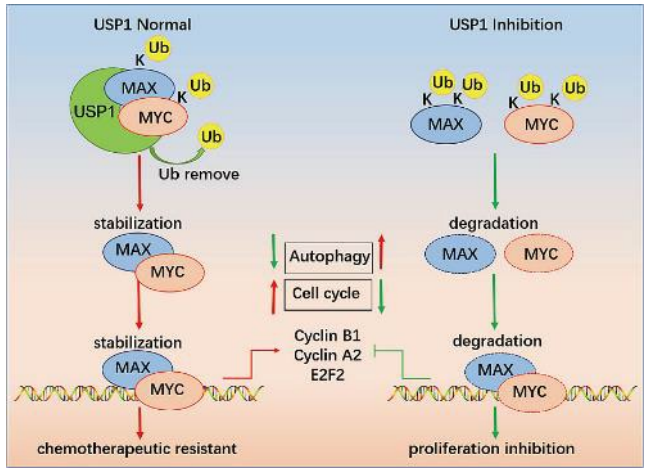
Introduction to USP1

Introduction to USP1



- Ubiquitin-specific protease 1 (USP1) is an important subtype of them and is a deubiquitinase involved in DNA damage repair by modulating the ubiquitination of major regulators, such as PCNA and FANCD2
- The primary function of USP1 is to participate in the DNA damage response (DDR). USP1 regulates the DNA repair process by modulating the monoubiquitinated heterodimer FANCD2Ub-FANCIUb in the Fanconi anemia (FA) pathway and the polyubiquitinated homotrimer proliferating cell nuclear antigen (PCNA) in the translesion DNA synthesis (TLS) pathway

Mechanism of USP1 inhibitors



- Overexpression of USP1 is a characteristic of many types of tumors. According to database records, USP1 is most highly expressed in cervical squamous cell carcinoma and cervical adenocarcinoma. Furthermore, compared to normal tissue samples, USP1 is also significantly overexpressed in invasive breast cancer, sarcoma, cholangiocarcinoma, glioblastoma multiforme, and head and neck squamous cell carcinoma. The increased expression of USP1 in various types of cancer is associated with affected cell homeostasis, proliferation, and apoptosis, potentially mediated through the stabilization of inhibitors of differentiation (ID) family proteins ID1, ID2, and ID3, or FANCD2
- USP1 inhibitors primarily form non-covalent interactions with USP1 and bind to an allosteric regulatory site, making them allosteric inhibitors. In 2020, KSQ Therapeutics published a potential first-in-class USP1 small molecule inhibitor, KSQ-4279. Its potent efficacy, high selectivity, and ability to overcome PARP inhibitor resistance have rekindled researchers' interest in the potential of the USP1 target

Source: Leukemia, Acta Pharmaceutica Sinica, China Insights Consultancy

Clinical pipelines of USP1-targeted drugs, CDE-registered

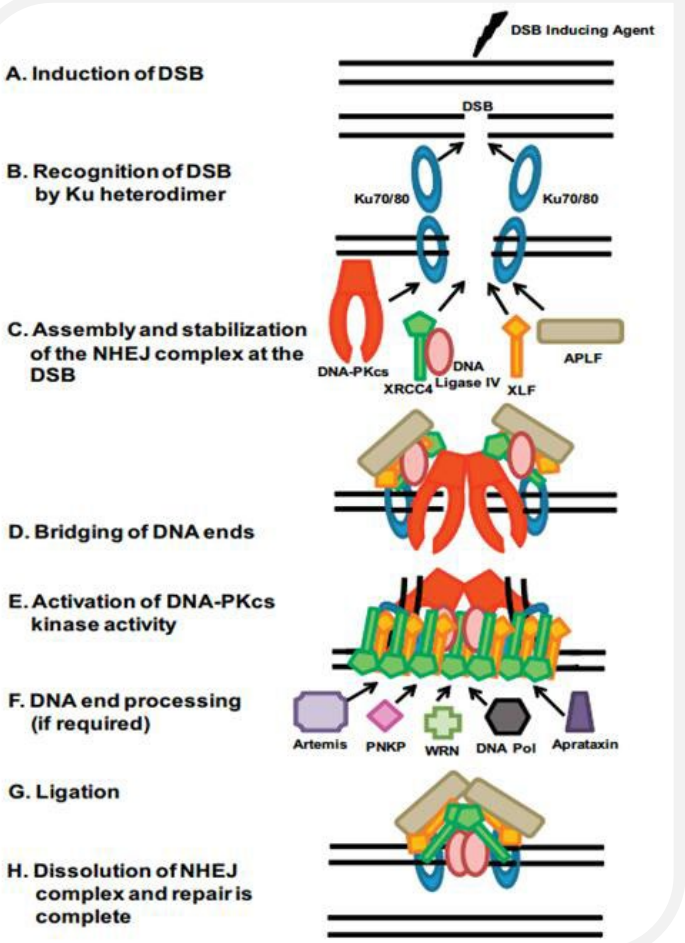
Clinical pipelines of USP1 target drugs, CDE-registered, as of LPD

Drug Name	Company	Indications	Phase	Lines	First Posted Date
HSK39775	Haisco	Advanced solid tumors	I/II	≥2L	2024-02-27
ASN-3186	Asieris	Advanced solid tumors	I/IIa	≥2L	2025-01-26
SIM-0501	Simcere	Advanced solid tumors	I	≥2L	2024-02-26
ISM-3091	InSilico	Advanced solid tumors	I	≥2L	2023-07-10

Source: CDE, China Insights Consultancy

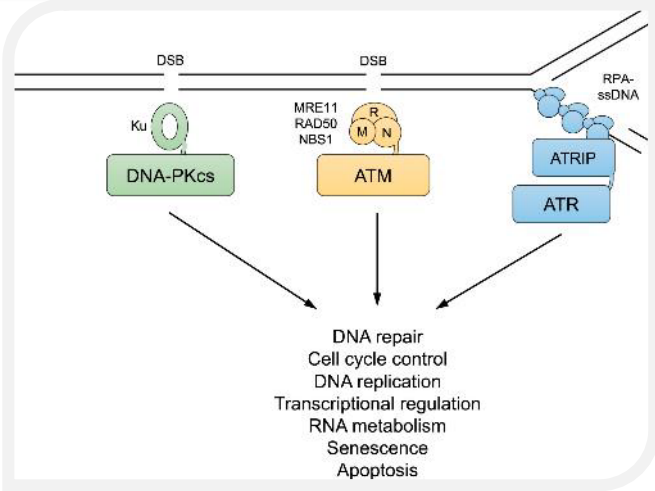
Introduction to DNA-PK

Introduction to DNA-PK



- The DNA-dependent protein kinase (DNA-PK) is a serine/threonine protein kinase consisting of a catalytic subunit (DNA-PKcs) and a Ku heterodimer that is made up of the Ku70 and Ku80 subunits
- DNA-PK is highly expressed in almost all mammalian cells and is a core kinase in the classical non-homologous end joining (c-NHEJ) repair pathway. DNA-PK itself cannot recognize damage sites and requires an auxiliary protein factor, Ku. When a DSB is present, NHEJ recognizes the DSB ends through the KU70/80 heterodimer, which then recruits the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs) to the DNA damage site. This binding stabilizes the DNA ends, followed by the recruitment of other core NHEJ factors to align and join the ends closely together

Mechanism of DNA-PK inhibitors



- There is a synthetic lethal interaction between DNA-PKcs and ATM. ATM and DNA-PKcs are key kinases in the homologous recombination (HR) and non-homologous end joining (c-NHEJ) pathways, respectively. If both are inactivated simultaneously, it results in synthetic lethality.
- The development of DNA-PK inhibitors primarily focuses on the catalytic activity of DNA-PKcs, aiming to reduce DSB repair by inhibiting the expression or activity of DNA-PK. This, in turn, increases the sensitivity of tumor cells to radiotherapy and chemotherapy

Source: Molecular Cell, Sec. Molecular and Cellular Oncology, China Insights Consultancy

Clinical pipelines of DNA-PK targeted drugs, CDE-registered

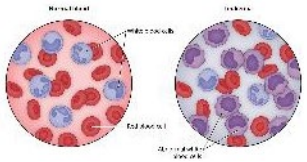
Clinical pipelines of DNA-PK target drugs, CDE-registered, as of LPD

Drug Name	Company	Phase	Indications	First Posted Date	Trial Number
BY-101298	Chengdu Baiyu	I	Advanced solid tumors	2023-04-03	CTR20230997

Source: CDE, China Insights Consultancy

Introduction to hematologic malignancy

Introduction to hematologic malignancy



- **Hematologic malignancies** begin in the cells of the immune system or in blood-forming tissue, such as the bone marrow
- Common types of hematologic cancer are **lymphoma, myeloma, and leukemia**

The main classifications of hematologic cancer

Myeloid neoplasm (MN)

- AML
- MPN
  - CML
  - Classical BCR-ABL1-negative MPN
    - PV
    - ET
    - PMF
  - CNL
  - CEL
- MDS
- MDS/MPN Syndrome
- Myeloid Neoplasm with TP53 Mutation
- CMML
- Atypical CML
- SF3B1-mutant MDS/MPN

Lymphoid neoplasm (LN)

- Precursor lymphoid neoplasm
  - B-Cell ALL/LBL
  - T-Cell ALL/LBL
- Mature B-cell neoplasm
  - Chronic CLL/SLL
  - MGUS
  - PCN
  - LPL
  - MZL
  - HCL
  - FL
  - MCL
  - DLBCL
  - BL
- Mature T/NK-cell neoplasm
- HL
  - cHL
  - NLPHL

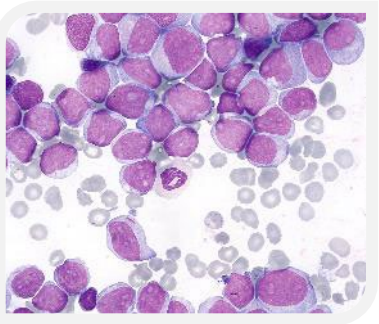
Other categories

- Myeloid/lymphoid neoplasms with eosinophilia and gene fusions involving tyrosine kinase genes
- Dendritic cell neoplasm
- Mastocytosis
- Mixed or undifferentiated cell neoplasm
- Disorders associated with children and/or lineage-specific mutations

Source: China Insights Consultancy

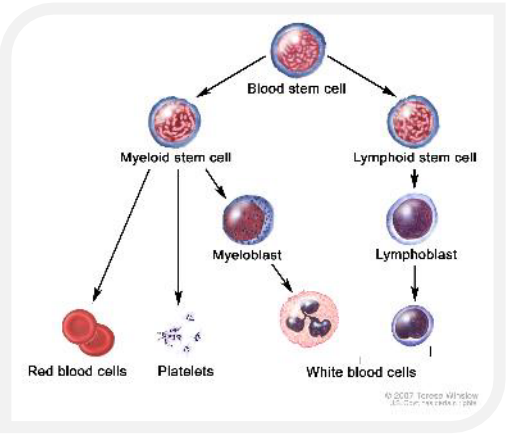
Introduction to AML

Introduction to AML



- Acute myeloid leukemia (AML) is a rapidly progressing myeloid neoplasm characterized by the clonal expansion of primitive hematopoietic stem cells, known as blasts, in the bone marrow. This expansion results in ineffective erythropoiesis and megakaryopoiesis, clinically manifesting as relatively rapid bone marrow failure compared to chronic and indolent leukemias. This leads to inadequate production of red blood cells and platelets
- AML is the most common subtype of leukemia in China, accounting for 51.7% of all leukemia cases. It is estimated that over 40,000 new AML patients are diagnosed annually in China. The incidence of AML significantly increases with age, with the median age of onset being between 68 and 70 years. This indicates that over 50% of AML cases occur in patients aged 60 and above

Pathogenesis of AML



- Normally, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time. Blood stem cells mature into cells in the myeloid line or the lymphoid line. AML occurs due to a problem with blood stem cell development in the myeloid line
- In AML, there is an increase in the number of immature white blood cells called myeloblasts (or myeloid blasts). The myeloblasts in AML are abnormal and do not become healthy white blood cells. As the number of these cells, also called leukemia cells, increases in the blood and bone marrow, there is less room for healthy platelets, red blood cells, and other white blood cells. This may lead to easy bleeding, anemia, and infection

Etiology of AML

- Smoking, previous chemotherapy treatment, and exposure to radiation may increase the risk of AML
- Possible risk factors for AML include
  - being male
  - older age
  - smoking
  - having had treatment with chemotherapy or radiation therapy in the past
  - being exposed to radiation in the environment (such as nuclear radiation) or to the chemical benzene
  - having a personal history of a blood disorder such as myelodysplastic syndrome
  - having certain syndromes or inherited disorders

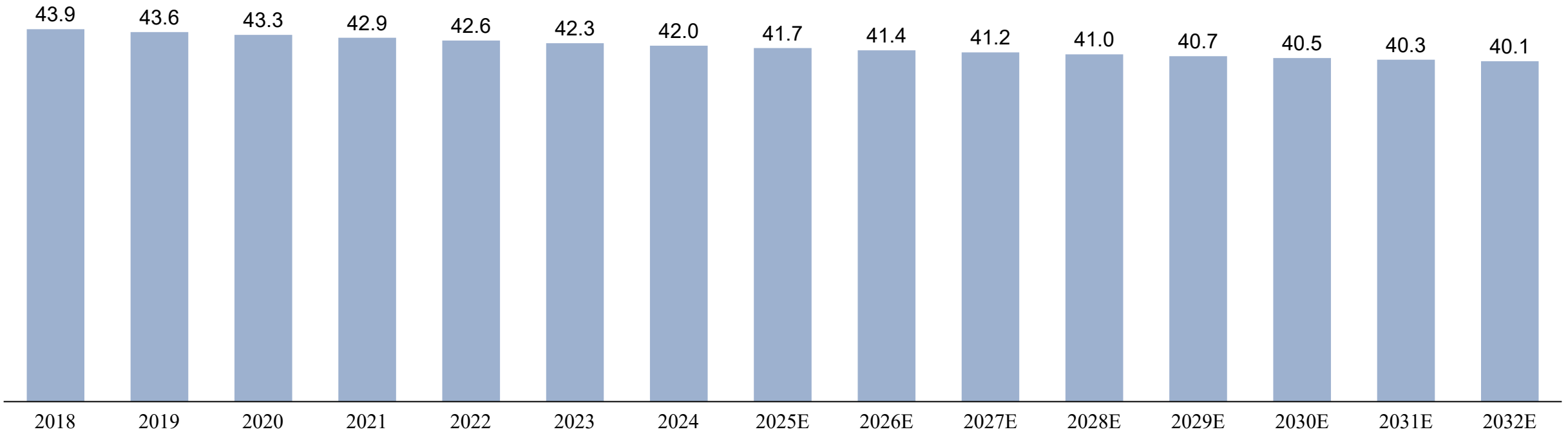
Source: American Cancer Society, StatPearls, NIH, Chinese Journal of Internal Medicine, China Insights Consultancy

AML incidence in China, 2018-2032E

AML incidence in China, 2018-2032E

CAGR	2018-24	2024-32E
Total	-0.8%	-0.6%

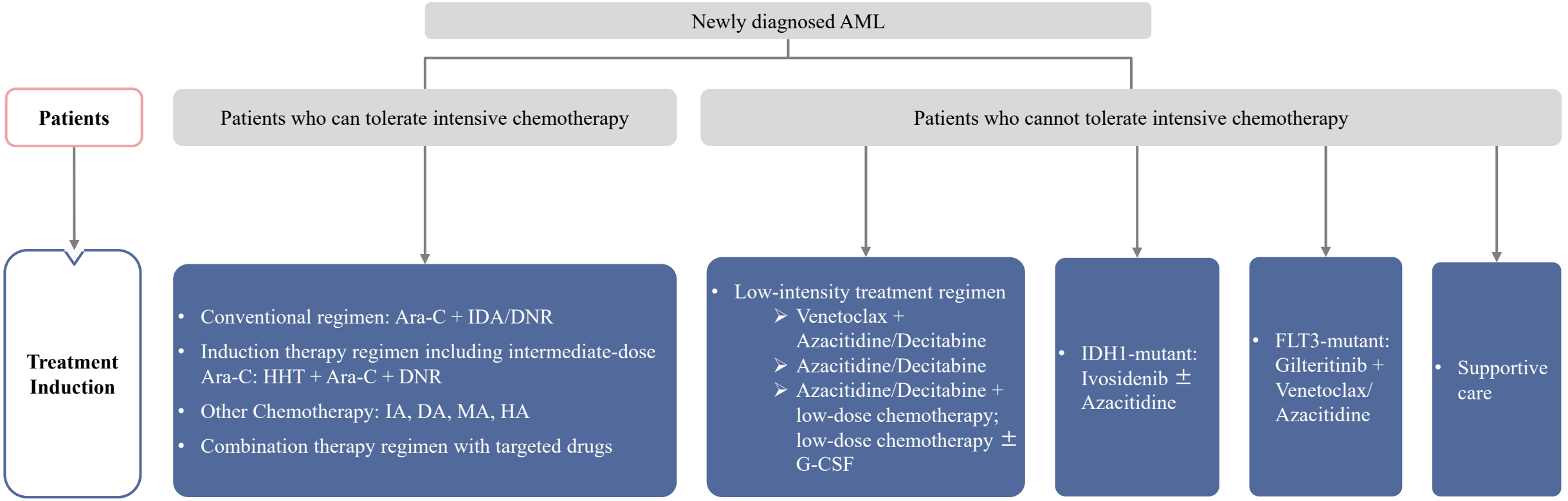
k ppl



Source: China Insights Consultancy

Treatment path of newly diagnosed AML in China

Treatment path of newly diagnosed AML in China

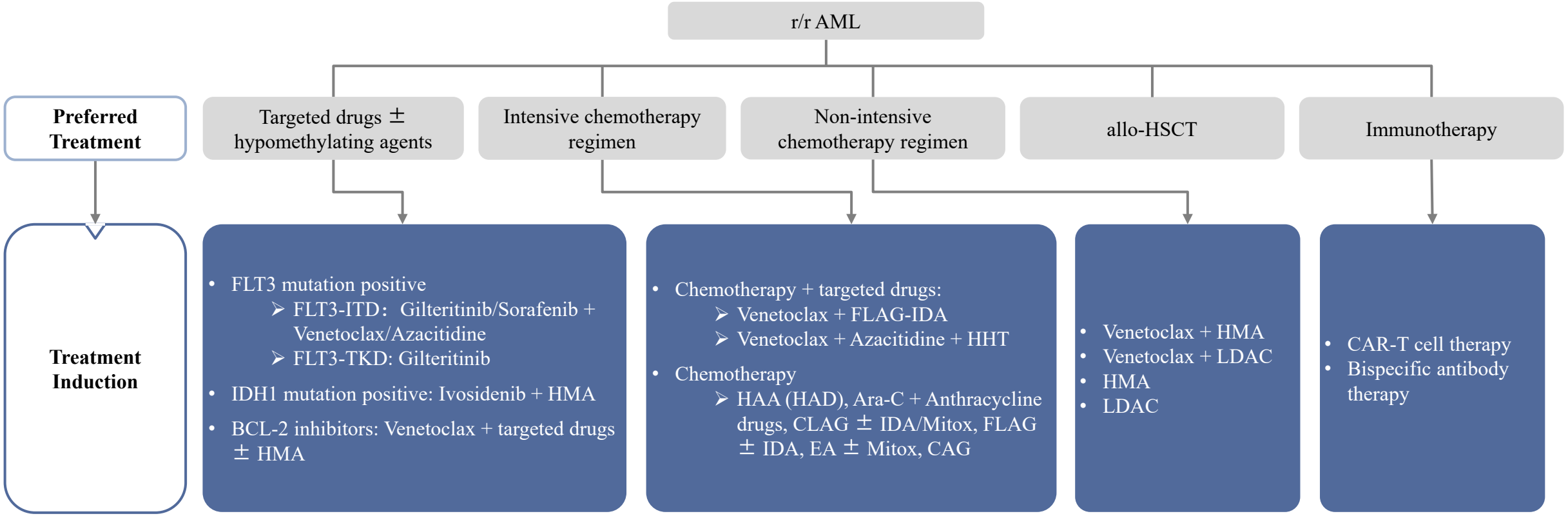


- **All AML patients are advised to participate in clinical trials if they are eligible**
- **The treatment of AML primarily involves chemotherapy, hematopoietic stem cell transplantation (HSCT), and newly emerging targeted therapies**
- **Intensive chemotherapy remains the recommended treatment plan for AML patients who can tolerate it**

Source: Chinese Journal of Hematology, China Insights Consultancy

Treatment path of r/r AML in China

Treatment path of r/r AML in China



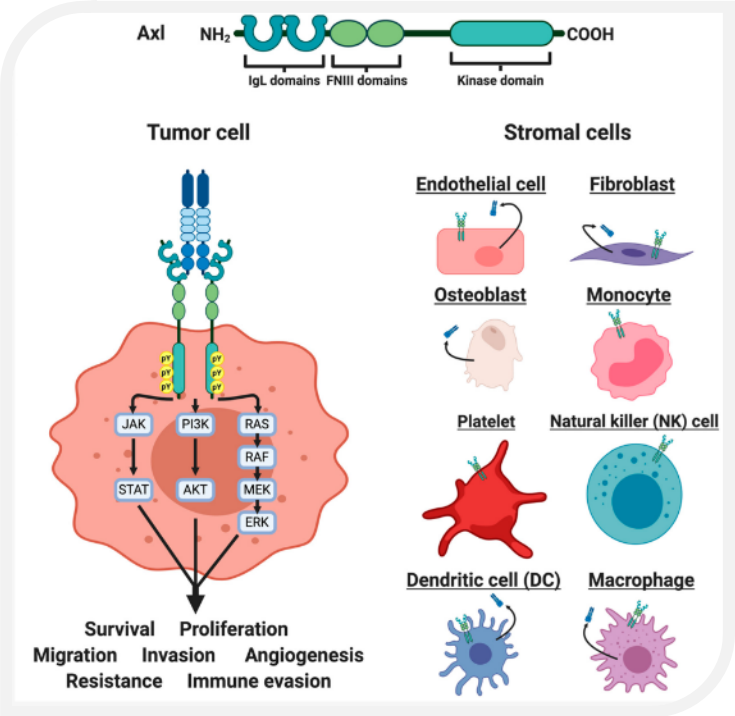
- **Eligible patients with r/r AML should primarily consider participating in clinical trials**
- **Other treatment options mainly include targeted therapy or sequential allogeneic hematopoietic stem cell transplantation (allo-HSCT) after chemotherapy**

Source: Chinese Journal of Hematology, China Insights Consultancy

Introduction to AXL

Introduction to AXL

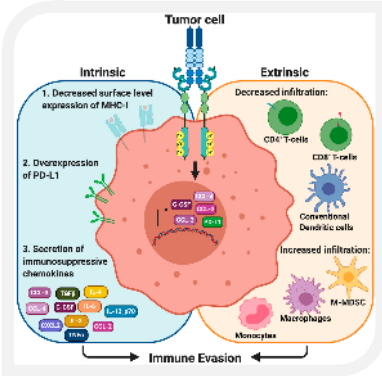
Structures and expression profiles of AXL



- AXL belongs in the Tyro3, AXL, MerTK (TAM) subfamily of the receptor tyrosine kinases. AXL consists of immunoglobulin-like (IgL) domains, two fibronectin domains, and a kinase domainAXL is expressed in a number of tumor types
- The AXL signaling promotes tumor cell survival, proliferation, migration, invasion, angiogenesis, therapeutic resistance, and immune evasion

- AXL is expressed by host stromal cells, including endothelial cells, fibroblasts, osteoblasts, monocytes, platelets, natural killer (NK) cells, dendritic cells (DCs), and macrophages

The Gas6/AXL signaling promotes the immunosuppressive tumor microenvironment



- AXL signaling modulates surface level expression of major histocompatibility complex I (MHC-I) and programmed death ligand-1 (PD-L1) on neoplastic cells
- The Gas6/AXL signaling also promotes secretion of immunosuppressive chemokines, including CCL3-5, G-CSF, IL-3, IL-4, IL-6, IL-12_p70, TGFβ, and TNFα. The Gas6/AXL signaling promotes infiltration of macrophages, monocytes, and myeloid-derived suppressor cells (MDSCs)

Targeting AXL in therapeutic research

- The leading drugs targeting the AXL-Gas6 signaling pathway mainly include AXL small-molecule inhibitors, AXL nucleic acid aptamers, AXL therapeutic antibodies, and AXL-Fc fusion proteins. Most of the drugs that have entered clinical research are AXL small-molecule inhibitors, while research on AXL therapeutic antibodies is still in the preclinical stage
- AXL inhibitors can be classified into two categories based on their binding sites with AXL. Type I inhibitors can bind to the aspartate-phenylalanine-glycine (DFG) motif of the AXL kinase domain, while Type II inhibitors are able to bind to regions outside of the DFG motif

Source: MDPI, China Insights Consultancy

Clinical pipelines of highly selective AXL-targeted drugs, CDE-registered

Clinical pipelines of highly selective AXL target drugs, CDE-registered, as of LPD

Drug Name	Target	Company	Phase	Line	Indications	First Posted Date	Trial Number
XZB-0004		Xuanzhu Biopharma	I	≥1L	Advanced solid tumors	2023-02-24	CTR20230435
			I	≥1L	Hematologic malignancies	2023-02-15	CTR20230215
FC-084-CSA		Medical Novishen	I	≥1L	Advanced solid tumors	2023-02-23	CTR20230518
NTQ-2494		Chia Tai Tianqing	I	N/A	Hematologic malignancies	2023-04-12	CTR20231086

Source: CDE, China Insights Consultancy

Drivers of China’s anti-tumor drug market

➢ **The aging population and the increasing number of cancer cases each year are driving the expansion of demand in the anti-tumor drug market**

- According to data from the National Bureau of Statistics, in 2021, China had about 200 million people aged 65 and above, making up about 14.2% of the total population. From 2015 to 2021, this age group's population grew at a compound annual rate of around 5.6%. With the aging population increasing rapidly, the incidence of malignant tumors is rising, leading to higher demand for medication. This growth is driving the rapid development of China's pharmaceutical market

➢ **Advances in medical technology, including accelerated new drug development and the progress of precision medicine, are gradually meeting the diverse treatment needs of patients**

- The number of global innovative anti-tumor drugs has been continuously increasing. With ongoing research and technological advancements, more innovative drugs with new targets or novel mechanisms of action will cover a broader range of patient populations. They can selectively bind to designated target molecules, showing good clinical efficacy in treating various diseases that previously lacked effective treatment options. This will significantly stimulate the clinical demand for innovative drugs and drive the growth of the pharmaceutical market

➢ **The government supports the research and production of domestic anti-tumor drugs, promoting domestic substitution through policy guidance and market access**

- In 2013, the CFDA introduced measures to speed up the review of innovative drugs for major diseases, those with independent intellectual property, and those in national science projects. The NMPA's 2017 policy further prioritized reviews for innovative drugs not yet marketed in China or abroad and those in key national R&D plans. In 2020, new regulations streamlined drug registration and approval processes, enhancing support for innovative drug development. These policies encourage drug innovation and prioritize treatments for serious diseases, benefiting domestic R&D efforts

Source: China Insights Consultancy

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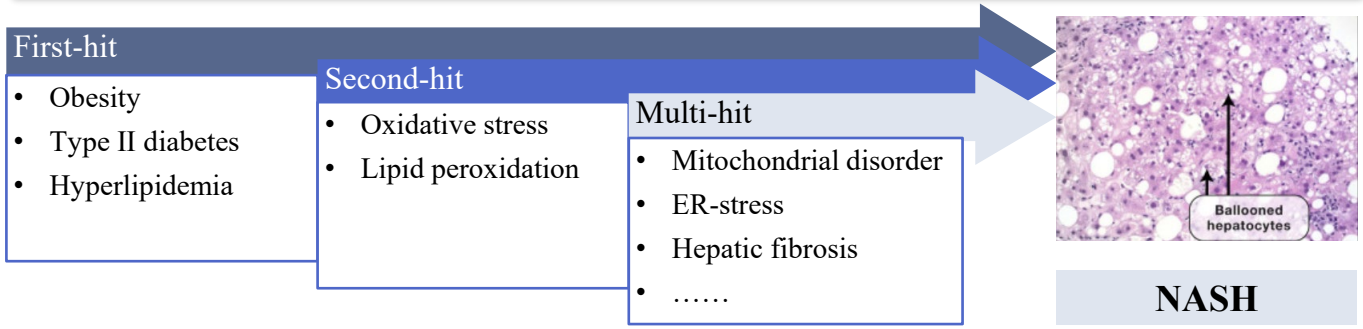
Introduction to non-alcoholic steatohepatitis (NASH)

Introduction to NASH

- NAFLD refers to a series of non-alcohol-related pathological disorder, characterizing by hepatic steatosis. NAFLD starts from NAFL and can develop into NASH, fatty hepatic fibrosis, cirrhosis, or even hepatoma. It is considered as the **most common hepatic disease globally**.

Pathogenesis of NASH

- The 'multi-hit' theory is the mainstream of the pathogenesis of NAFLD and NASH, believing the successive impact from a series of in vivo and in vitro factors can explain the onset and development of NAFLD and NASH.
- The 'first-hit' is defined as the hepatocytic lipid deposition caused by metabolic disorders including obseity, type II diabetes, and hyperlipidemia. The damaged hepatocytes will experience oxidative stress and lipid peroxidation leading to the inflammation and necrosis, which is defined as the 'second-hit'. The successive mitochondrial disorder, ER-stress, and hepatic fibrosis will keep impacting on hepatocytes, being part of the 'multi-hit'.



Symptoms of NASH

- NASH used to be developed from NAFL with its onset being insidious. Patients may suffer from a series of non-specific symptoms, including fatigue, mild pain of liver region, and gastrointestinal symptoms. The symptoms may aggravate as the disease develops. Patients suffering from severe NASH are with jaundice, hepatosplenomegaly, and inappetence.

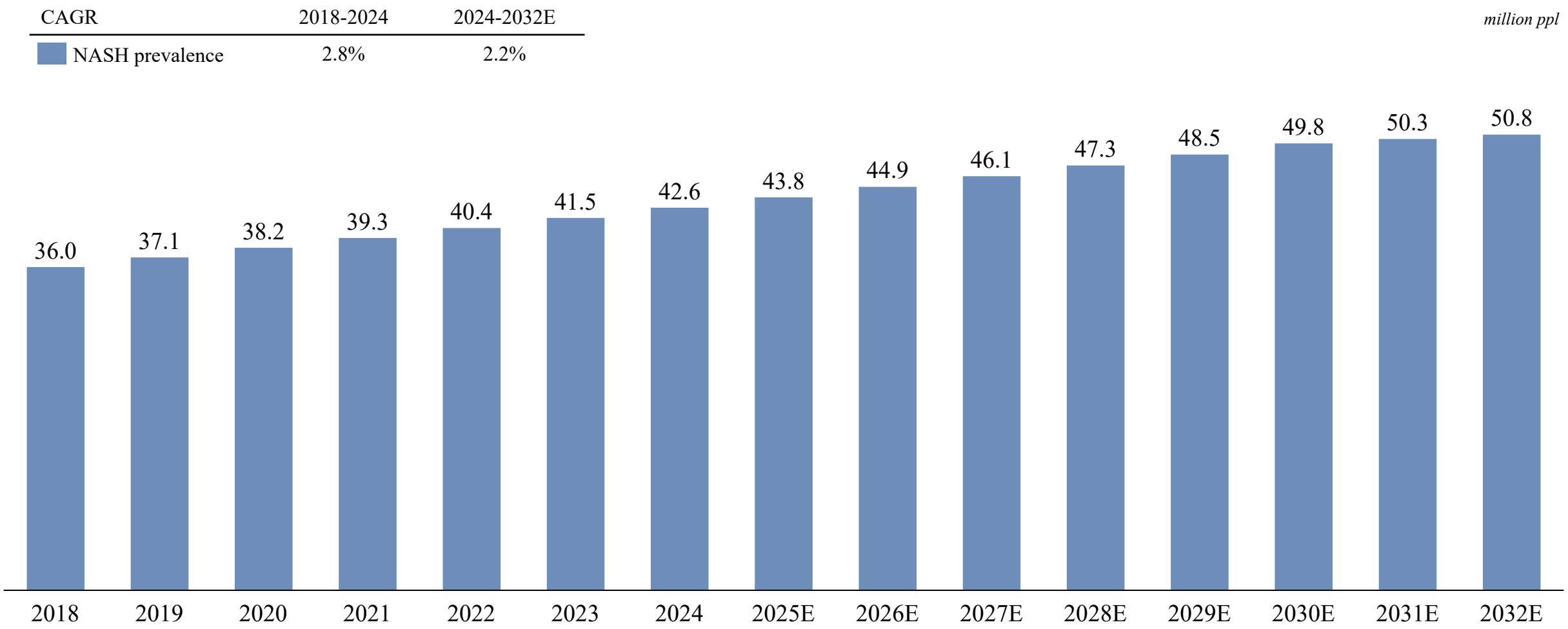
Diagnosis and pathological features of NASH

- Pathological examination is the most vital examination for the diagnosis of NASH. Patients with the symptoms of hepatic damage and typical pathological features can be diagnosed as NASH.
- Typical pathological features of NASH includes ballooned hepatocytes in hepatic acinus zones-3, hepatic spotty necrosis, inflammation at the portal area, and bridging fibrosis.

Source: Internal Medicine; Pathology; CELL; China Insights Consultancy

The prevalence of NASH in China, 2018-2032E

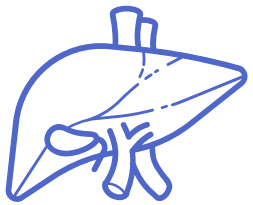
The prevalence of NASH in China, 2018-2032E



Source: China Insights Consultancy

Treatment for NASH

Symptomatic Treatment



- **Relieving hepatic damage and reversing hepatic fibrosis**

Being the first granted medication by FDA for NASH in the last 40 years, **Resmetirom** is an activator for THR-β receptor, which can reduce the hepatic lipoid accumulation.

OCA, which is used for primary biliary cirrhosis, is another potential candidate for the treatment for NASH. As a FXR activator, OCA can partially recover the histological presentation of hepatic tissue and relieve the hepatic fibrosis. As the clinical trials and pharmaceutical research progresses, it can be expected that more innovative small molecule drugs will be put into market.

Systematic Treatment

- **Restoring metabolic homeostasis**

It is suggested that NASH patients combined with diabetes should control blood glucose level carefully, using medication like **metformin and glibenclamide.** Those with hyperlipidemia can receive **antihyperlipidemic agents** with their liver function under close supervise. **Intestinal probiotics** is another optional medication for patients with NASH to reduce the production of endotoxin and energy intake.

Supplementary Treatment

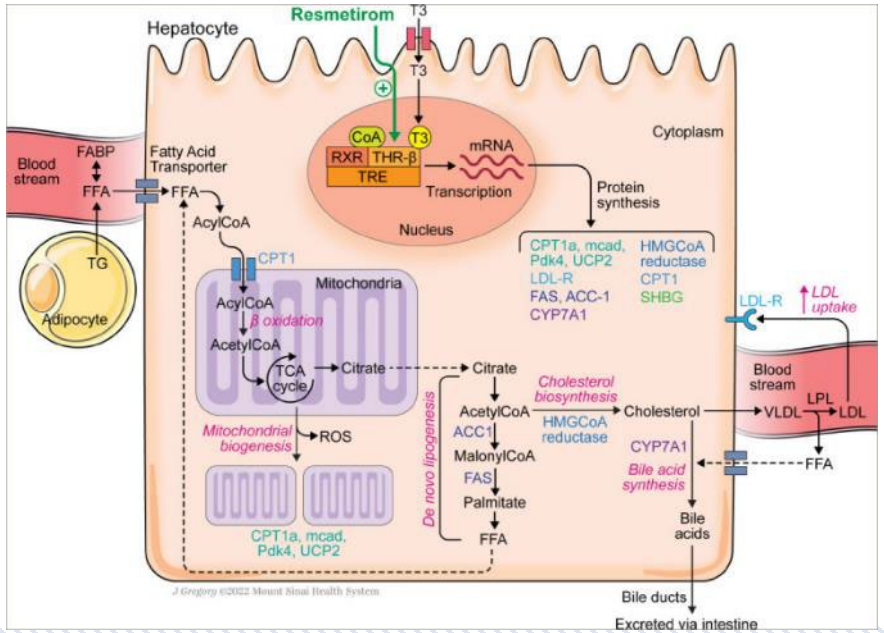
- **Improving lifestyle** The main reason for the metabolic disorders of NASH patients is their unhealthy lifestyle. It has been reported that losing 3%-5% weight can recover the liver function of the patients, and 7%-10% can partially restore the enzymatic and histological abnormalities. Therefore, doing enough exercises and having a healthy diet is of great help for the NASH patients.
- **Surgery** Those patients who are not sensitive to drugs or having poor compliance can accept bariatric surgery.

Source: Internal Medicine; CNKI; Drug instructions; China Insights Consultancy

As the only approved small molecule drug for NASH, Resmetirom can partially reserves the hepatic damage through activating THR-β selectively

Introduction to Resmetirom

Mechanism of Resmetirom



- The activation of THR-β will lead to the expression of a series of downstream genes responsible for the regulation of metabolic homeostasis. As a THR-β activator, the intake of resmetirom will **inhibit the intrahepatic triglycerides accumulation, promote bile acid synthesis and LDL intake**.

Drug name	Resmetirom
Original manufacture	• Madrigal Pharma.
Initial approval	• 2024/03/15
Indications	• NASH with moderate to advanced liver fibrosis
Target	• THR-β activator
Characteristics	• Resmetriom can selectively activate THR-β without effecting THR-α which is abundantly expressed in cardiomyocyte, leading to the improvement of hepatic metabolic homeostasis without causing cardiovascular reactions
Clinical trials results	• No significant differences were observed in ADRs rate compared to placebo • 25.9% (80mg)-29.9% (100mg) RR of NASH • 24.2% (80mg)-25.9% (100mg) of the patient experienced reversal of hepatic fibrosis • 13.6% (80mg)-16.3% (100mg) reduction in LDL level

Source: N Engl J Med; touchREV Endocrinol; Drug instructions; China Insights Consultancy

Market opportunity analysis of NASH treatment

Unmet clinical needs of current NASH treatment

1

Lack of efficacious drug approved for NASH

- Up to now, there has been no NMPA approval of any specifically treatment for NASH. According to the latest treatment guideline, management of NASH patients relies on the use of other metabolic drugs from weight, hypertension and diabetes aspects. Therefore, there is huge clinical gap to be filled by new treatments of NASH.

2

Large patient pool expected to continuously grow

- NASH is among the top causes of liver cancers and the most aggressive type in NAFLD, accounting for 12-14%. In 2022, over 300 million people around the globe have NASH and the number is projected to continuously increase in the coming decade. The risk of NASH is especially higher, 2-3 times in persons with obesity and/or T2D.

3

Complicated pathogenesis making it hard to progress R&D

- NASH/ NAFLD can have a series of manifestations of metabolic syndrome in the liver. Clinically, it is often a combination of liver and extrahepatic comorbidities in different severity. These complex clinical phenotypes will not only influence disease progression, but also have an impact on drug efficacy, which have impeded the implementation of new drug experiments.

Future trends of NASH therapies

Combination therapy on multiple targets	• Considering the complex factors regulating metabolism, the future treatment will focus on multiple targets through a combination of existing and new drugs. The management of NASH will be comprehensively carried from dietary, medical and physical sides.
Innovative therapy	• With the development of medical technology, new related drugs such as RNA drugs, gene therapy and gut and microbiome related therapies are emerging, several of which have entered into clinical phase of research.
Individualized treatment	• NASH is a multifactorial disease that involves complicated pathogenesis. Some drug candidates are shown to be effective for some phenotypes in, but ineffective or even harmful for some phenotypes, driving the personalization of NASH treatment based on individual metabolism.

Source: China Insights Consultancy

Clinical pipelines of innovative drugs for NASH in China (1/3)

Clinical pipelines of innovative drugs for NASH in China (1/3), as of LPD

Drug name	Target	Company	Phase	Indications	First Posted Date	Trial Number
Ecnoglutide	GLP-1R	Sciwind Biosciences	III	T2DM; NASH; obesity; AD	2023/03/15	CTR20230745
Lanifibranor	PPARα/γ/δ	Inventiva S.A./Chiatai Tianqing/ Delpharm Reims/ Fisher Clinical Services	III	NASH; IPF	2023/09/11	CTR20232876
Survodutide	GLP-1R/GCGR	Boehringer Ingelheim	III	T2DM; NASH; obesity	2023/12/15	CTR20234043
HTD1801	AMPK/PCSK9/FXR /TGR5	Hightide Therapeutics	III	NASH (MASH); T2DM; advanced hypertriglyceridemia; primary sclerosing cholangitis; PBC	2024/03/25	CTR20240991
TQA3526	FXR	Chia Tai Tianqing	II	NASH; PBC	2020/01/10	CTR20200055
TVB-2640	FAS	Sagimet Bioscieces	II	NASH	2020/04/30	CTR20192369
MK-3655	FGFR1/KLB	MSD	II	NASH	2021/01/21	CTR20210074
PF-06865571	DGAT2	Pfizer	II	NASH with hepatic fibrosis	2021/03/15	CTR20210412
HEC96719	FXR	HEC Pharma	II	NASH	2021/07/27	CTR20211428
ASC41	THR-β	Ascletis Pharma	II	NASH;NAFL	2022/06/21	CTR20221529
ZSP1601	PDE	Zhongsheng Pharma	II	NASH	2022/12/30	CTR20223378
CS0159	FXR	Cascade Pharma	II	NASH; PBC; PSC; IBD	2023/05/12	CTR20231402
MT2004	FXR	Aolitai Pharma	II	NASH; cholestatic and drug-induced hepatic damage	2023/07/07	CTR20232066

Notes: AD stands for Alzheimer's disease; IPF stands for idiopathic pulmonary fibrosis; IBD stands for inflammatory bowel disease

Source: Pharmacodia; CDE; China Insights Consultancy

Clinical pipelines of innovative drugs for NASH in China (2/3)

Clinical pipelines of innovative drugs for NASH in China (2/3), as of LPD

Drug name	Target	Company	Phase	Indications	First Posted Date	Trial Number
AZD2693	PNPLA3	AstraZeneca	II	NASH with PNPLA3 rs738409 148M homozygous	2023/07/11	CTR20232127
recombinant human FGF21-Fc fusion protein for injection	FGF21	Ampsource Biopharma	II	NASH	2023/08/11	CTR20232280
HEC88473	FGF21R/GLP-1R	HEC Pharma	II	T2DM; NASH; obesity	2023/08/17	CTR20232481
VSA006	HSD17β13 (mRNA)	Visirna Therapeutics	II	NASH	2023/10/13	CTR20233245
MK-6024	GLP-1R/GCGR	MSD	II	NASH; obesity; T2DM; cirrhosis; hepatic steatosis	2023/10/19	CTR20233311
HSK31679	THR-β	Haisco Pharma	II	NASH; primary hypercholesterolemia in adults	2023/11/09	CTR20233629
BGT-002	ACL	Bojiyuan Biopharma	II	primary hypercholesterolemia; NASH	2024/03/05	CTR20240756
ZSP0678	PPAR	Zhongsheng Pharma	I	NASH; PBC	2019/11/05	CTR20191375
TQA3563	Caspase family	Chia Tai Tianqing	I	NASH	2019/11/11	CTR20192073
SH2442	ACC	Sanhome Pharma	I	NASH	2020/02/04	CTR20200136
HS-10356	unknown	Hansoh Pharma	I	NASH	2020/11/03	CTR20202161
HPN-01	SREBF1/2	Hepanova Pharma	I	NASH	2021/03/25	CTR20210551
XZP-5610	FXR	Xuanzhu Biopharm	I	NASH; PBC	2021/04/14	CTR20210737
SYHA1805	FXR	CSPC	I	NASH	2021/06/29	CTR20211453

Source: Pharmacodia; CDE; China Insights Consultancy

Clinical pipelines of innovative drugs for NASH in China (3/3)

Clinical pipelines of innovative drugs for NASH in China (3/3), as of LPD

Drug name	Target	Company	Phase	Indications	First Posted Date	Trial Number
HPG1860	FXR	Hepagene Therapeutics	I	NASH (MASH); IBD; PBS/PSC	2021/11/18	CTR20212697
ENN0403	unknown	Ennovabio Pharma	I	NASH	2021/12/20	CTR20213238
XZP-6019	KHK	Xuanzhu Biopharm	I	NASH	2021/10/13	CTR20212402
Cotadutide	GCGR/GLP-1R	AstraZeneca	I	NASH	2022/01/14	CTR20220073
GST-HG151	ASK1/JNK/p38 MAPK	Consunter Pharma	I	NASH with fibrosis	2022/03/03	CTR20220395
NNC0194-0499	FGF21	Novo Nordisk	I	NASH	2023/01/18	CTR20230074
Kylo-0603	THR-β	Kylonva/Hygieia	I	NASH	2023/02/22	CTR20230472
GH509	unknown	1Globe Biomedical	I	NASH	2023/03/10	CTR20230547
RJ4287	THR-β	Ruijie Pharma	I	NASH	2023/05/29	CTR20231621
UBT251	GCGR/GIPR/GLP-1R	United Laboratories	I	T2DM; NASH; obesity	2023/12/14	CTR20234009
IMM-H014	Nrf2	CAMS/Intell Crown	I	NASH	2023/12/20	CTR20234134
CS060304	THR-β	Cascade Pharma	I	NAFLD/NASH	2024/07/23	CTR20242690

Source: Pharmacodia; CDE; China Insights Consultancy

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Introduction to primary biliary cholangitis (PBC)

Introduction to PBC

- PBC is an autoimmune diseases characterized by chronic progressive non-suppurative inflammation of the small bile duct, leading to the onset of cirrhosis eventually. The incidence rate of women is significantly higher than that of men and that in America and Europe is significantly higher than in Asia.

Pathogenesis of PBC

- **Humoral immunity** AMA plays an important role in the onset of PBC with a positive rate over 90% in PBC patients. It may recognize pyruvate dehydrogenase complex and damage the mitochondrion.
- **Cellular immunity** HLA-DR and DQ antigen may be abnormally expressed in biliary epithelial cells, leading to the T-cell-induced cytotoxic effects, damaging bile ducts continuously.

Natural history and symptoms of PBC

Stage	Symptoms	Duration
Pre-clinical	No obvious symptoms with normal hepatic function; AMA test being positive	>10 years
Hepatic function compensated	No obvious symptoms with abnormal biochemical indicators	2-4 years
Hepatic function decompensated	Pruritus; fatigue; progressive jaundice; pain in hepatic region	10-15years
Cirrhosis	Severe hepatic function damage; hepatic encephalopathy	

Diagnosis of PBC

Patients meet two of the following three standards can be diagnosed as PBC.

- Biochemical evidence of cholestasis based mainly on the elevation of ALP and GGT with the exclusion of extrahepatic biliary obstruction by imaging studies;
- Presence of AMA or other PBC-specific ANAs including anti-sp100 or anti-gp210;
- Histologic evidence of non-suppurative destructive cholangitis mainly affecting the interlobular bile ducts.

Prognosis of PBC

- Prognosis of PBC varies among patients, the average survival time of patients with obvious symptoms is 10-15 years. The 3-year survival rate of PBC patients with esophageal and gastric varices can be less than 60%.

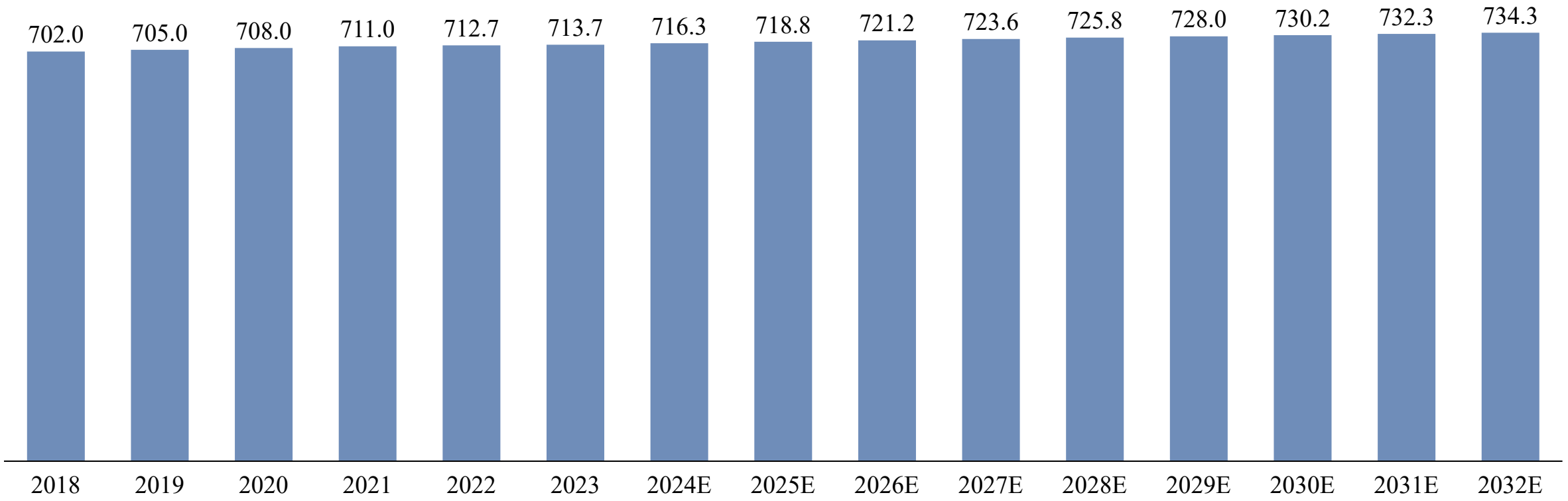
Source: Internal Medicine; Hepatol Int; CNKI; China Insights Consultancy

The prevalence of PBC in China, 2018-2032E

The prevalence of PBC in China, 2018-2032E

CAGR	2018-2023	2023-2032E
PBC prevalence	0.3%	0.3%

thousand cases



Source: China Insights Consultancy

Treatment path for PBC, CMA

First-line

- **UDCA** The preferred treatment for PBC is UDCA which can increase the bile acid secretion and protect hepatocytes and cholangiocytes. More than 90% patients will show significant improvement in 6 to 9-month treatment.

Second-line

- **OCA**

OCA is the only approved small molecule drugs for PBC by FDA. It can improve the abnormalities in biochemical indicators and hepatic histology of the patients who are unsensitive to UDCA. According to clinical trials data, after 3-year treatment, PBC patients' hepatic damage showed improvement or no progress.

- **Budesonide**

Budesonide is a second-generation glucocorticoid, which participates in the regulation of bile acid with minimized systematic effect. According to randomized controlled trials, the combination of UDCA and Budesonide can better improve the abnormalities in biochemical indicators and hepatic histology.

- **Fibrates**

- Fibrates inhibits the secretion of bile acid through PPAR pathway. According to clinical trials, the combination of UDCA and Fibrates can largely improve the abnormity in biochemical indicators.

Third-line

- **Liver transplantation** For patient progressed to the decompensation stage with MELD rating >15 or Mayo risk rating >7.8, liver transplantation is a vital option. The long-term survival rate of patients who received liver transplantation will be largely improved with high risks of PBC reoccurrence.

Source: Internal Medicine; CNKI; China Insights Consultancy

Clinical pipelines of innovative drugs for PBC in China

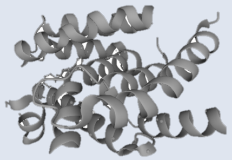
Clinical pipelines of innovative drugs for PBC in China, as of LPD

Drug name	Target	Company	Phase	Indications	First Posted Date	Trial Number
Linerixibat	ISBT	GSK	III	PBC; T2DM; cholestatic itch	2021/09/07	CTR20212220
TQA3526	FXR	Chia Tai Tianqing	II	NASH; PBC	2020/01/10	CTR20200055
ASC42	FXR	Ascletis Pharma	II	chronic hepatitis B; PBC	2021/12/10	CTR20213229
CS0159	FXR	Cascade Pharma	II	NASH; PBC; PSC; IBD	2023/05/12	CTR20231402
ZSP0678	PPAR	Zhongsheng Pharma	I	NASH; PBC	2019/11/05	CTR20191375
XZP-5610	FXR	Xuanzhu Biopharma	I	NASH; PBC	2021/04/14	CTR20210737
HPG1860	FXR	Hepagene Therapeutics	I	NASH (MASH); IBD; PBS/PSC	2021/11/18	CTR20212697
TB-001	GCCR/GLP-1R	Turier Biotech	I	cirrhosis; chronic hepatitis B; NAFLD; PBC	2021/12/16	CTR20213310

Source: Pharmacodia; CDE; China Insights Consultancy

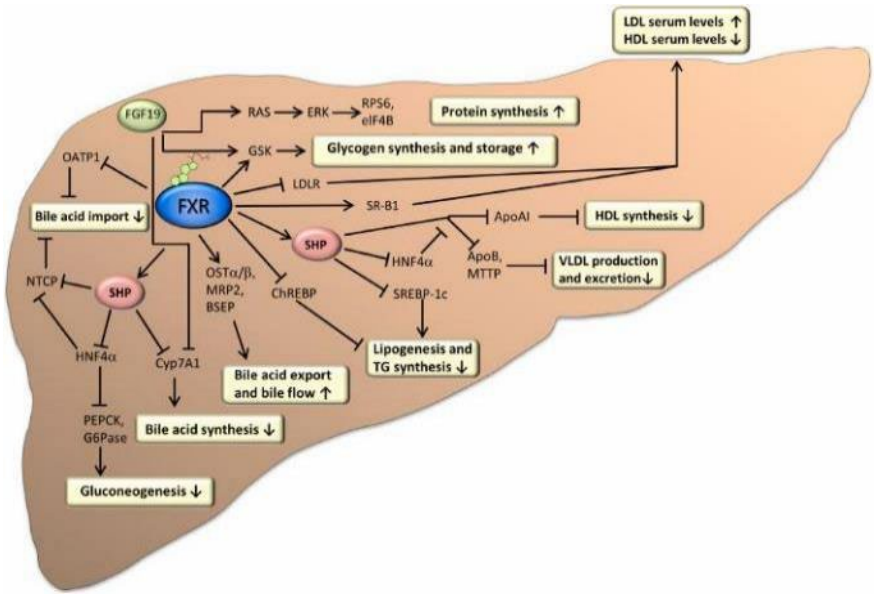
Introduction to FXR

Introduction to FXR



3D structure of FXR

- FXR is a member of nuclear receptor superfamily. Since bile acid can be its endogenous ligand, it is also named as bile acid receptor (BAR). FXR participates in the regulation of target gene expression after forming a dimer with RXR. It is abundantly expressed in hepatocytes and ileum tissue.
- The target genes of FXR are related to the process of bile acid, lipid and glucose metabolism, making FXR essential in the maintenance of homeostasis and a series of pathophysiological processes.



FXR signaling and metabolic effects in normal liver

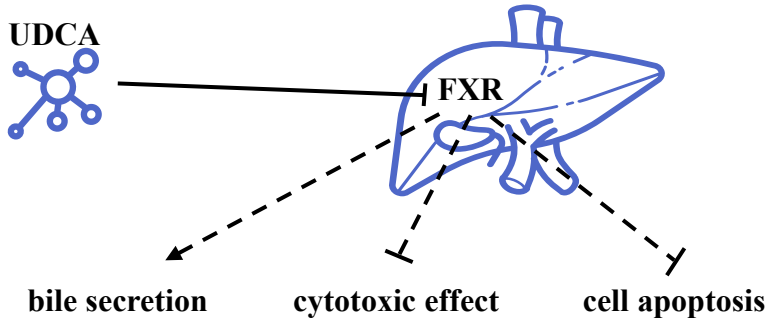
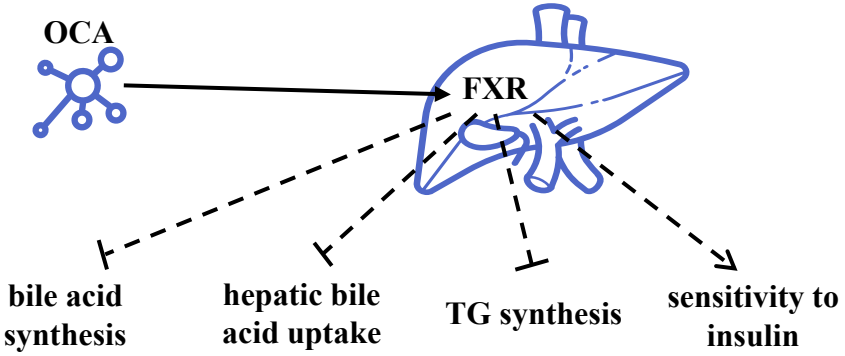
Metabolic and therapeutic effect of FXR

- **Metabolic effect of FXR** FXR is abundantly expressed in hepatocytes. As a core molecule in metabolic regulation, FXR participates in a series of biological process, including bile acid synesis, bile acid transportation, gluconeogenesis, and the regulation of lipoprotein, making it one of the potential therapeutic targets for progressive hepatic diseases.
- **Therapeutic effect of FXR-targeting drugs** Due to its essential role in metabolic regulation, both FXR activators and inhibitors are found that can improve the metabolic process of hepatocytes, which can largely improve the metabolic homeostasis and partially reverse the progress of hepatic damage. As a FXR inhibitor, UDCA is a classic drug for PBC, which can promote bile secretion and inhibit the cytotoxic effect and cell apoptosis induced by hydrophobic bile acid. FXR activator, OCA, is approved for the second-line treatment for PBC. For those PBC patients who are unsensitive to UCDA, OCA can largely reduce their ALP, GGT, and ALT level. Both of the drugs show strong therapeutic effects for progressive hepatic damage.

Source: UniProt; Mol Cell Endocrinol.; Gastroenterology; CNKI; China Insights Consultancy

Through different mechanism pathways, UDCA and OCA can improve hepatic homeostasis, targeting FXR

Summary of UDCA and OCA

Drug name	UDCA	OCA
Original manufacture	• Mitsubishi Tanabe Pharma	• Intercept Pharma
Initial approval	• 1961/11/27	• 2016/05/27
Indications	• Cholesterol gallstones • PBC • Bile reflux gastritis	• PBC
Target	• FXR inhibitor	• FXR activator
Characteristics	• As a classic drug for progressive hepatic damage, UDCA can improve hepatic homeostasis through promoting bile secretion and inhibiting the cytotoxic effect and cell apoptosis induced by hydrophobic bile acid.	• OCA can activate the core molecule for metabolism regulation in hepatocytes, FXR, which enables it to improve the hepatic homeostasis and partially reverse the fibrosis.
Mechanism		

Source: Lancet; CNKI; Drug instructions; China Insights Consultancy

Innovative clinical pipelines for FXR-targeting drugs in China

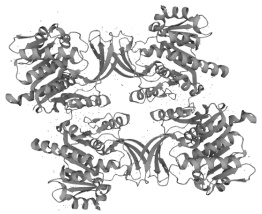
Summary of innovative clinical pipelines for FXR-targeting drugs in China, as of LPD

Drug name	Type	Company	Phase	Indications	First Posted Date	Trial Number
TQA3526	FXR activator	Chia Tai Tianqing	II	NASH; PBC	2020/01/10	CTR20200055
HEC96719	FXR activator	HEC Pharma	II	NASH	2021/07/27	CTR20211428
CS0159	FXR activator	Cascade Pharma	II	NASH; PBC; PSC; IBD	2023/05/12	CTR20231402
MT2004	FXR activator	Aolitai Pharma	II	NASH; cholestatic and drug-induced hepatic damage	2023/07/07	CTR20232066
XZP-5610	FXR activator	Xuanzhu Biopharma	I	NASH; PBC	2021/04/14	CTR20210737
SYHA1805	FXR activator	CSPC	I	NASH	2021/06/29	CTR20211453
HPG1860	FXR activator	Hepagene Therapeutics	I	NASH (MASH); IBD; PBS/PSC	2021/11/18	CTR20212697

Source: Pharmacodia; CDE; China Insights Consultancy

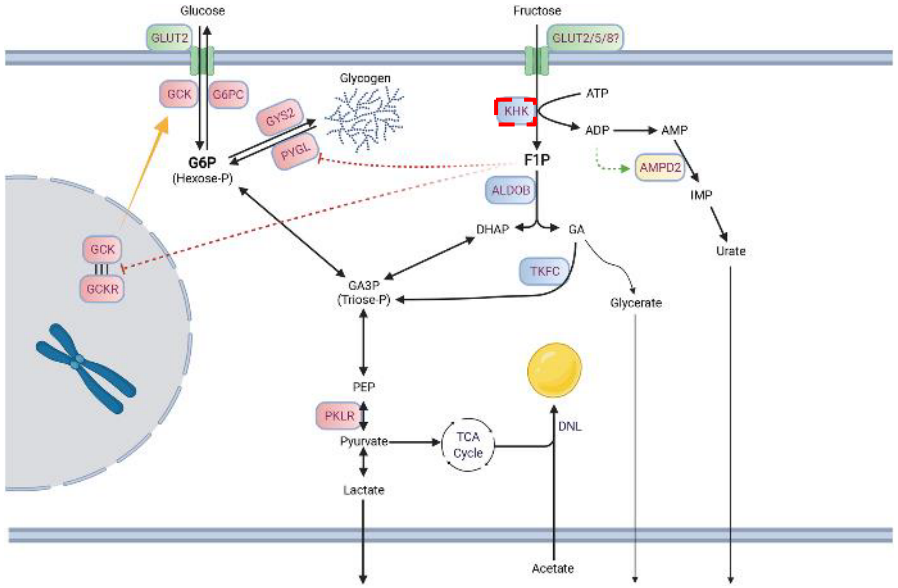
Introduction to KHK

Introduction to KHK



3D structure of KHK

- KHK is encoded by the gene on 2p23 with 9 exons. There are two spliced variants of KHK, KHK-A and KHK-C. KHK-A is widely expressed with low abundance while KHK-C is abundantly expressed in hepatocytes, renal tubular epithelial cells, and intestinal epithelial cells .
- KHK is the rate-limiting enzyme of fructose metabolism process through which the hepatic de novo lipogenesis is strongly increased. According to former reports, NAFLD patients are with higher serum KHK level and experimental animals with Khk knockdown showed better metabolism homeostasis, making KHK a potential target for metabolic diseases.



Fructose metabolism and associated biochemistry

Metabolic and therapeutic effect of KHK

- **Metabolic effect of KHK** It is widely agreed that a long-term high-fructose and high-fat diet will lead to metabolic disorders including obesity, T2DM, and NAFLD. As a vital enzyme in fructose metabolism, the level of KHK may be directly related to metabolism homeostasis. According to animal experiments, the knockdown of Khk gene would protect the individuals from metabolic disorders, which made KHK a potential target for metabolic disorder treatment.
- **Therapeutic effect of KHK-targeting drugs** Though no KHK-targeting drugs has been approved yet, a few clinical trials reported promising results. The highly-selective KHK inhibitor developed by Lilly, LY-3522348, can significantly reduce the lipid deposition in hepatocytes among patients suffering from NAFLD and T2DM with extraordinary safety assurance in a phase-II trial.

Source: UniProt; Cell Metab.; CNKI; China Insights Consultancy

Clinical pipelines of KHK-targeting drugs in China

Clinical pipelines of KHK-targeting drugs in China, as of LPD

Drug name	Type	Company	Phase	Indications	First Posted Date	Trial Number
XZP-6019	KHK inhibitor	Xuanzhu Biopharma	I	NASH	2021/10/13	CTR20212402

Source: Pharmacodia; CDE; China Insights Consultancy

Appendix

- **Digestive diseases**. Digestive diseases are increasingly prevalent as modern lifestyles with irregular diet, long working hours and nutritional imbalance become more common. According to the "China Health Statistical Yearbook 2022", digestive diseases ranked among the top five in both two-week prevalence and chronic disease prevalence in China in 2018. In 2021, digestive diseases were the 7th highest contributor to mortality in China. The prevalence of peptic ulcers in China is expected to increase from approximately 73.5 million in 2023 to approximately 81.2 million in 2032, and that for RE is expected to grow from 37.8 million in 2023 to approximately 42.4 million in 2032. Oral PPI drugs are the mainstay treatment for these diseases, with a market size over RMB10.0 billion in China and projected to grow to RMB11.0 billion by 2032.
- **XZP-3287, a Near-commercial Potential Best-in-class CDK4/6 Inhibitor for HR+/HER2-BC, a Core Product.** XZP-3287 is a proprietary CDK4/6 inhibitor we developed with complete intellectual property rights for the treatment of HR+/HER2- BC. BC is the most prevalent cancer in the world with approximately 2.3 million new cases in 2022, of which HR+/HER2- patients account for approximately 75%. CDK4/6 inhibitors in combination with endocrine therapy are the first-line treatment for HR+/HER2- advanced or metastatic BC. CDK4/6 inhibitors have a market size of RMB2.7 billion in 2023 in China for the treatment of advanced BC, which is expected to increase to RMB13.0 billion by 2032.
- **Competitive advantages.** Potentially the First and Only CDK4/6-targeted Monotherapy in China. While CDK4/6 inhibitors are only approved in China as combination therapies thus far, CDK4/6 inhibitor monotherapy is underexplored and could significantly benefit patients who fail multiple rounds of chemotherapy or endocrine therapy. To date, our XZP-3287 is the only CDK4/6 inhibitor that has been investigated in clinical trial as a monotherapy in China for HR+/HER2- advanced or metastatic BC. In its phase II clinical trial, XZP-3287 monotherapy demonstrated good efficacy as of the data cut-off date (November 30, 2022) (objective response rate (ORR): 29.0%; median progression-free survival (mPFS): 11.0 months) in HR+/HER2- advanced BC patients who have progressed after endocrine therapy and chemotherapy. Also, it marks the lowest hazard ratios among all CDK4/6 inhibitors. Abemaciclib, which is the only CDK4/6 monotherapy approved in the world for advanced or metastatic HR+/HER2- BC, was reported to have an ORR of 17.4% and mPFS of 5.9 months in its non-head-to-head phase II trial.
- **KM602, the First and Only CD80 Mutant — Fc Fusion Protein in China.** KM602 is the only clinical-stage anti-tumor CD80 Fc fusion protein drug in China, with the potential for first-in-class. It has better safety with the potential to be First-In-Class.
- **KM501, a Potential First-in-class Bispecific ADC with the Potential to be the First Patented Therapy of Its Kind in China.** KM501 is a potential FIC HER2/HER2 bispecific ADC and the first patented bispecific ADC of its kind in China. It is intended for the treatment in solid tumors with HER2-low or HER2-moderate expressing, including breast, gastric, and lung cancers.
- **Market Opportunity and Competition.** As of the Latest Practicable Date, there were no HER2/HER2 bispecific ADCs approved for marketing in China. As of the same date, there were three HER2/HER2 bispecific ADC candidates under clinical development in China. To date, DS-8201 is the only ADC approved for HER2 low expressing BC globally. The addressable market for HER2/HER2 bispecific ADCs primarily includes patients with HER2-expressing cancers. The major indication of HER2/HER2 bispecific ADC candidates under clinical development is HER2-expressing BC, with the incidence being forecasted to reach 100.1 thousand in 2032. As of the Latest Practicable Date, there were no USP1 inhibitors approved for marketing in China. As of the same date, there were two USP1 inhibitor candidates under clinical development in China. Eligible patients for USP1 inhibitors primarily include patients with drug resistance after PARP inhibitor treatment. It is estimated that the number of patients eligible for USP1 inhibitors will reach 398.2 thousand in 2032.

Appendix

- **XZP-6877, Potentially the First DNA Dependent Protein Kinase (DNA-PK) Inhibitor in China.** XZP-6877 is potentially the first DNA-PK inhibitor in China, with leading research and development progress and technical advantages. Preclinical data indicate that it has good drug forming ability, and is expected to fill the domestic market gap in this field.
- **XZP-5610, a Novel, First-in-class, Non-bile Acid Farnesoid X Receptor (FXR) Agonist.** XZP-5610 is a novel, first-in-class, non-bile acid FXR agonist for the treatment of NASH.
- **XZP-6019 a Novel, First-in-class Ketohexokinase (KHK) Inhibitor.** XZP-6019, a novel, first-in-class KHK inhibitor, is being developed for the treatment of NASH.
- Anaprazole is the first and only PPI independently developed by a PRC domestic company
- Entry barriers to innovative drug industry:
- 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
- Law enforcement authorities are increasingly focusing on enforcing these laws
- Cancer therapies may be characterized as first line, second line or later line therapy depending on options for treatment and prior treatments received. For indications with well-established standard of care therapies, the NMPA and other comparable regulatory authorities may approve new therapies initially only for later lines of therapy
- The average labor cost in the global pharmaceutical market, particularly for highly skilled and experienced personnel, has been steadily increasing as the competition for qualified employees has become more intense