Global Innovative Drugs Market Study

Independent Market Research Report

Date : October 23, 2024

For and on behalf of
Frost & Sullivan (Beijing) Inc., Shanghai Branch Co.

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Title: Executive Director

Confidential For

华昊中天 Biostar

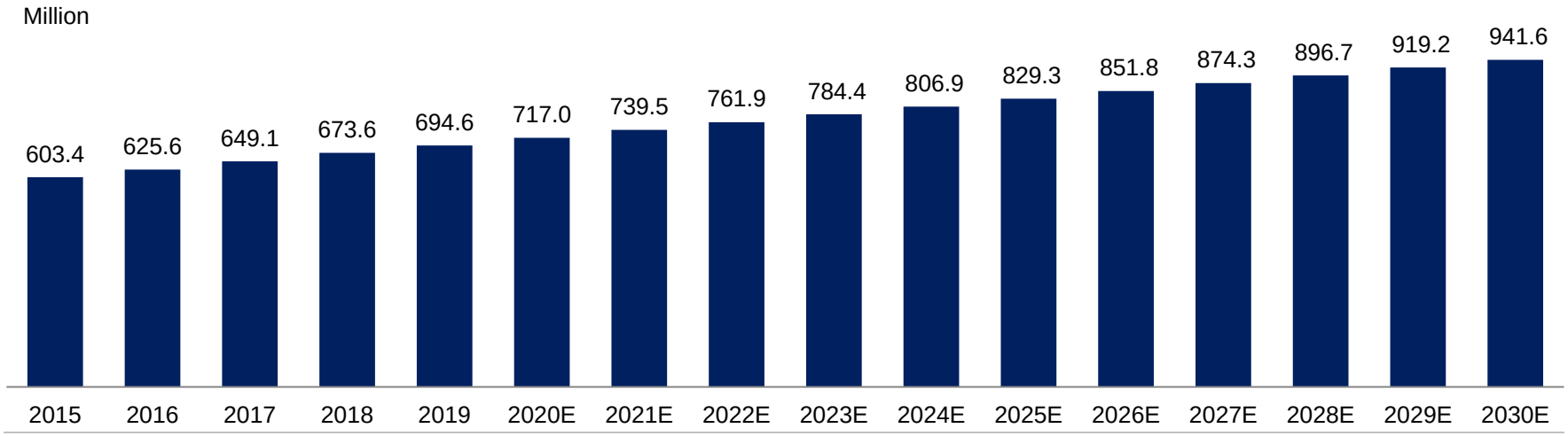
Frost &Sullivan
Oct 2024

Global Aging Population Trend, 2015-2030E

- The world's aging population is experiencing growth in terms of both number and proportion. In 2019, It is estimated that there are 694.6 million people aged over 65 years old in the world, accounting for 8.2% of the world's population. The population over 65 years old grows at a CAGR of 3.6% during the period of 2015 to 2019.
- Declining fertility and increasing longevity are the key drivers of population aging globally. It is estimated that the number of people aged over 65 in the world would reach 806.9 million in 2024, accounting for 10.0% of the total population, with a CAGR of 3.0% from 2019 to 2024. Size of aging population will keep the upward tendency, it is anticipated to reach 941.6 million by 2030.

Global Aging Population Trend, 2015-2030E

Period	CAGR
2015-2019	3.6%
2019-2024E	3.0%
2024E-2030E	2.6%



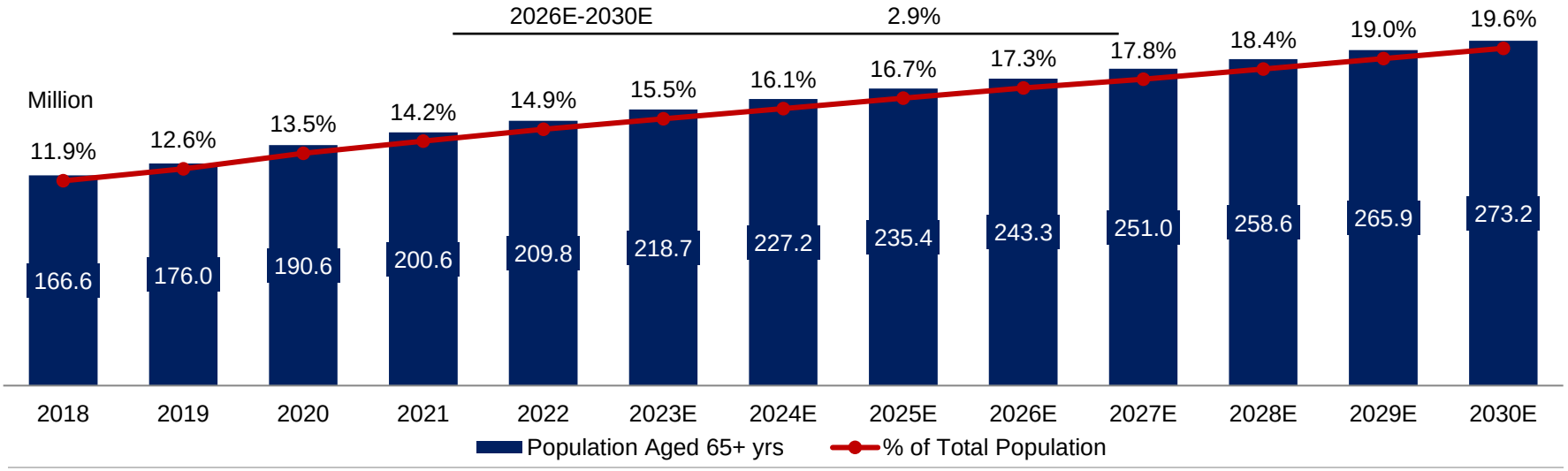
Source: Aging population refers to people aged over 65 years old.
World Bank, Frost & Sullivan analysis

Aging Population Trend in China, 2018-2030E

- With the implementation of the 'One Child Policy' and increasing life expectancy, China has entered an aging society. From 2018 to 2022, the population was aging rapidly in China with people aged above 65 growing at a CAGR of 5.9%. According to the National Bureau of Statistics of China (NBSC), individuals aged above 65 years old were 209.8 million in 2022. The number of individuals aged above 65 years old is growing at a fairly fast pace and is expected to continue its growth momentum into the future. This number of people is expected to reach 273.2 million by 2030, representing a CAGR of 2.9% from 2026 to 2030.
- China's demographic shift offers immense opportunities for healthcare market, as elder people generally have a greater need for medications and scientific disease management.

Aging Population Trend in China, 2018-2030E

Period	CAGR
2018-2022	5.9%
2022-2026E	3.8%
2026E-2030E	2.9%



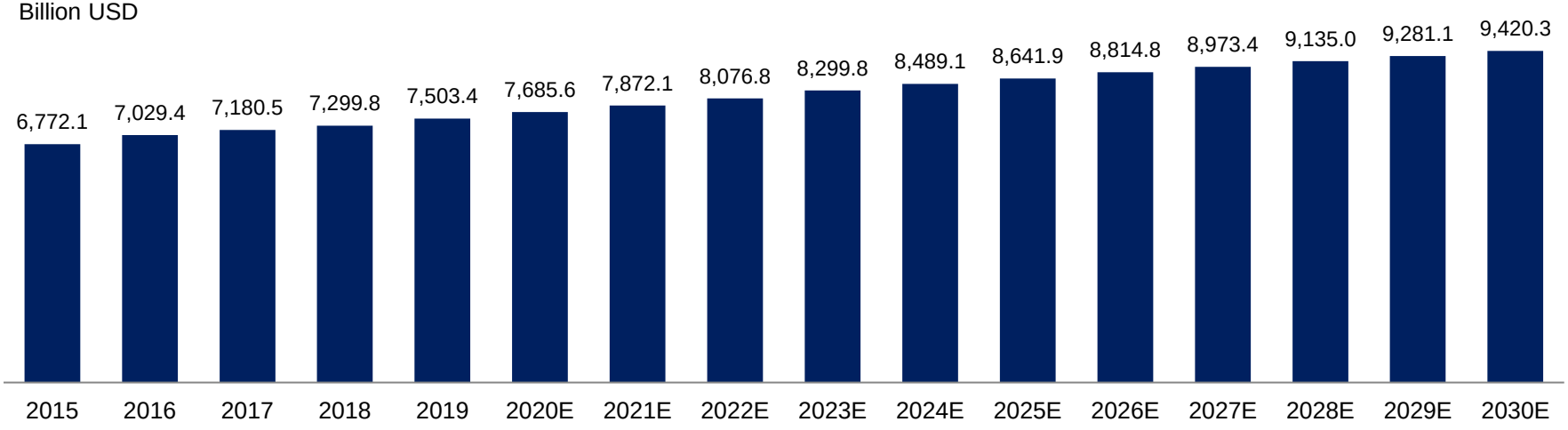
Source: NBSC, Frost & Sullivan Analysis

Global Total Healthcare Expenditure, 2015-2030E

- Healthcare expenditure is one of important means of achieving social equity and protecting the health of residents. Generally speaking, global healthcare expenditure is growing steadily. Total global healthcare expenditure reached USD7,503.4 billion in 2019, and is expected to grow at a CAGR of 2.6% from 2019 to 2024. Global healthcare expenditure is inevitably increased with expansion of aging population. Total healthcare expenditure is expected to be USD9,420.3 billion in 2030 with a CAGR of 1.7% from 2024 to 2030.

Global Total Healthcare Expenditure, 2015-2030E

Period	CAGR
2015-2019	2.6%
2019-2023E	2.5%
2024E-2030E	1.7%



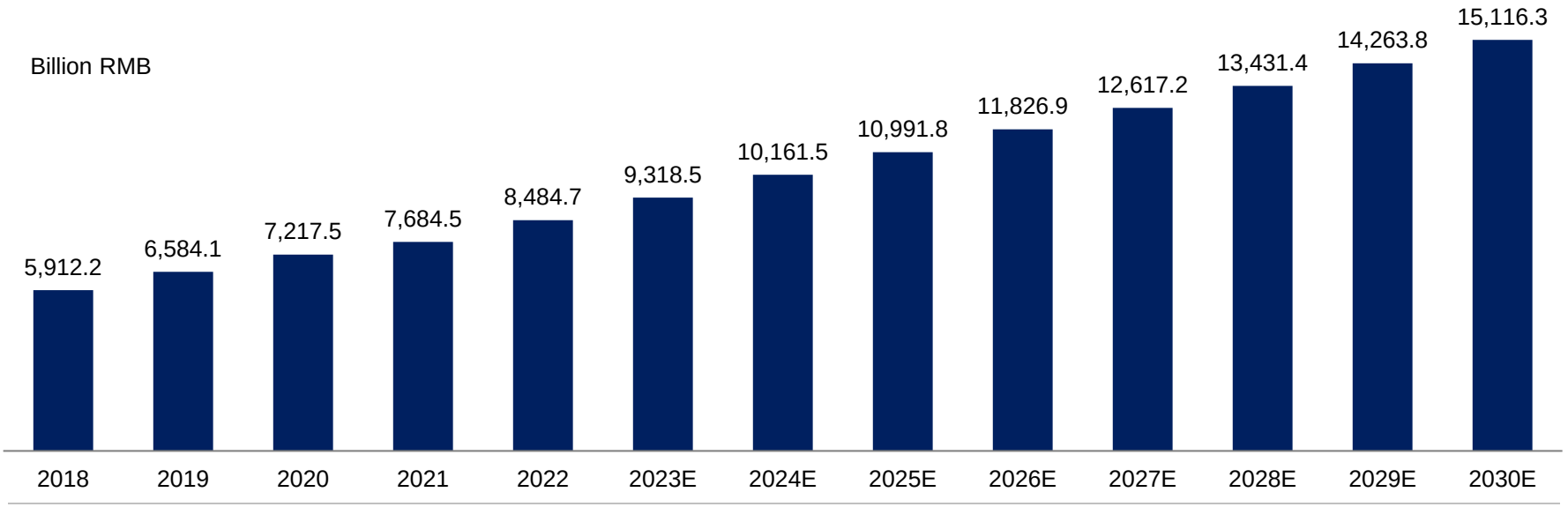
Source: WHO, Frost & Sullivan analysis

Total Healthcare Expenditure in China, 2018-2030E

- In 2022, China ranked 2nd largest globally in terms of total healthcare expenditure, amounting RMB8,484.7 billion in total healthcare expenditure in the same year, compared to RMB5,912.2 billion in 2018, a CAGR of 9.5% is presented over this period. The total healthcare expenditure is expected to further grow to RMB11.826.9 billion in 2026 with a CAGR of 8.7% from 2022 to 2026. With the increase of health awareness and personal disposable income, the total expenditure is projected to boost up to RMB15,116.3 billion in 2030 with a CAGR of 6.3% from 2026 to 2030.

China Healthcare Expenditure, 2018-2030E

Period	CAGR
2018-2022	9.5%
2022-2026E	8.7%
2026E-2030E	6.3%



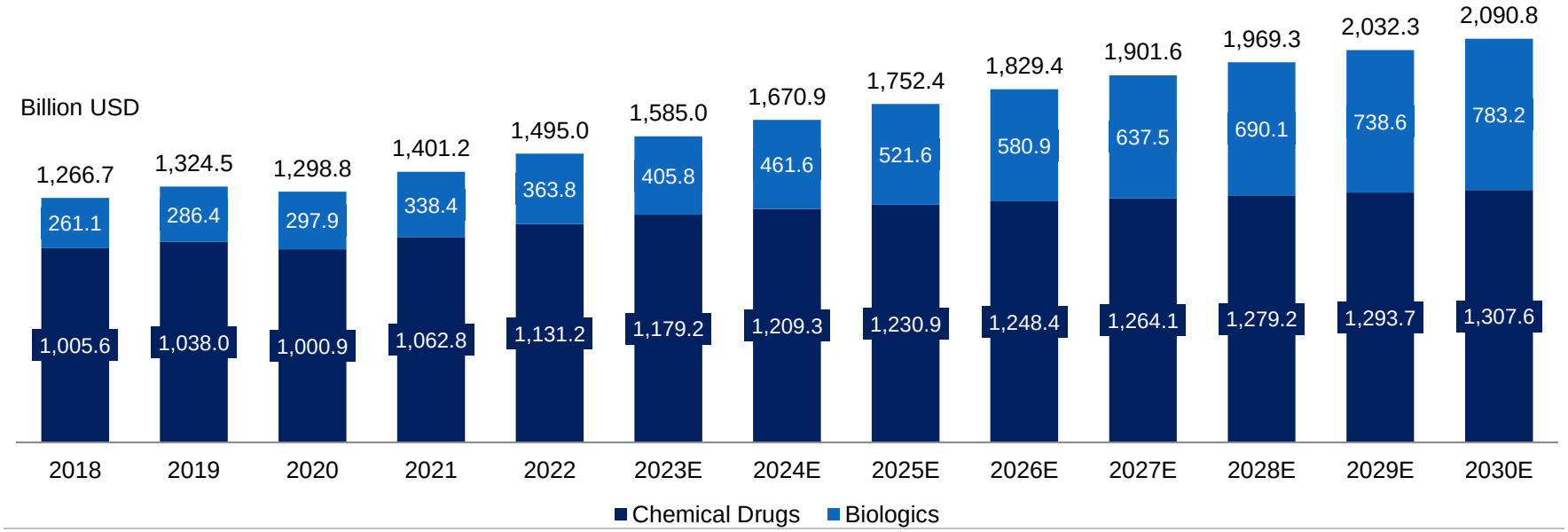
Source: NBSC, Frost & Sullivan Analysis

Global Pharmaceutical Market, 2018-2030E

- Global pharmaceutical market is composed of two segments, namely chemical drugs and biologics. The size of global pharmaceutical market was USD1,495.0 billion in 2022, and is expected to reach to USD2,090.8 billion in 2030, representing a CAGR of 4.3% from 2022 to 2030.
- The chemical drugs took USD1,131.2 billion market size in 2022, and is expected to reach to USD1,307.6 billion in 2030.

Global Pharmaceutical Market, 2018-2030E

Period	CAGR		
	Chemical Drugs	Biologics	Total
2018-2022	3.0%	8.6%	4.2%
2022-2026E	2.5%	12.4%	5.2%
2026-2030E	1.2%	7.8%	3.4%



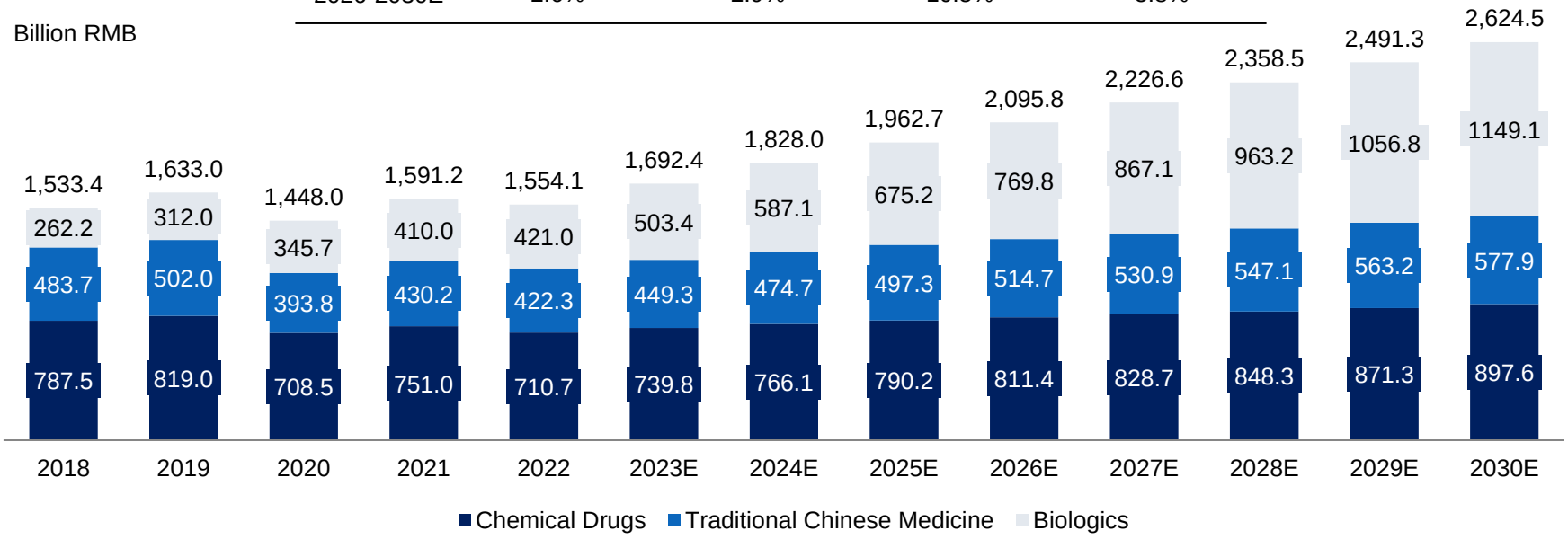
Source: Frost & Sullivan Analysis

China Pharmaceutical Market, 2018-2030E

- China pharmaceutical market, accompanying with the growth of economy and healthcare demand, increased from RMB 1,533.4 billion in 2018 to RMB1,554.1 billion in 2022 with CAGR of 0.3%. China pharmaceutical market will further increase to RMB2,624.5 billion in 2030, with CAGR of 6.8%.

China Pharmaceutical Market, 2018-2030E

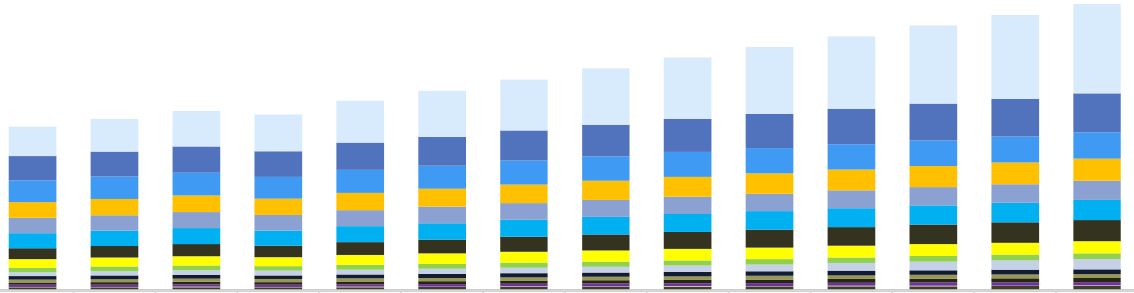
Period	CAGR			
	Chemical	TCM	Biologics	Total
2018-2022	-2.5%	-3.3%	12.6%	0.3%
2022-2026E	3.4%	5.1%	16.3%	7.8%
2026-2030E	2.6%	2.9%	10.5%	5.8%



Source: Frost & Sullivan Analysis

Breakdown of Global Pharmaceutical Market by Therapeutic Area, 2017-2030E

Billion USD



	2017	2018	2019	2020	2021	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Anti-neoplastic and immunomodulating agents	216.7	241.8	260.4	270.9	309.4	341.2	376.4	415.0	452.9	493.5	534.3	576.0	618.5	660.5
Alimentary tract and metabolism	178.2	184.6	193.8	189.0	201.4	211.2	222.2	233.1	243.8	253.2	262.3	270.9	279.2	287.9
Anti-infectives for systemic use	161.9	164.9	168.2	160.6	169.6	172.3	176.1	179.6	182.6	184.9	187.0	188.8	190.8	192.9
Pain & neurology	115.4	119.7	124.5	121.4	127.5	132.3	137.9	143.0	147.5	151.3	154.3	157.4	160.6	164.0
Psychiatry	114.6	115.2	118.0	115.0	119.5	121.0	123.2	125.3	127.4	129.4	131.7	134.3	137.7	142.0
Cardiovascular system	110.1	113.0	116.4	112.3	118.0	121.8	125.8	129.5	133.1	136.3	139.7	142.5	145.4	148.4
Respiratory system	80.9	85.2	90.3	83.9	94.5	102.0	110.3	117.7	125.0	131.5	138.1	144.1	149.9	156.1
Blood and blood forming organs	62.5	66.5	69.8	66.9	72.3	76.6	79.9	82.0	83.7	84.9	86.2	87.2	88.1	89.1
Dermatologicals	33.4	34.0	34.7	33.7	34.9	35.7	36.9	38.3	39.5	40.5	41.3	42.1	42.9	43.6
Ophthalmology	29.2	32.4	33.7	33.5	36.0	38.1	40.5	42.2	45.5	49.9	56.3	62.5	68.1	73.7
Systemic hormonal preparations 1	25.5	27.0	28.4	27.7	29.2	30.1	31.2	32.2	33.1	33.9	34.5	35.2	35.8	36.4
Urology	20.7	21.5	22.6	22.0	23.3	24.0	24.9	25.7	26.4	27.0	27.6	28.1	28.5	28.9
Diagnostic agents	17.6	18.6	19.7	19.1	20.5	21.7	23.1	24.3	25.4	26.5	27.6	28.7	29.8	30.9
Hospital infusions	15.6	16.3	17.1	16.8	17.8	18.4	19.1	19.9	20.7	21.4	22.1	22.8	23.5	24.2
Parasitology	2.8	2.8	2.9	2.7	2.9	3.0	3.1	3.1	3.2	3.2	3.3	3.3	3.3	3.4
Others	23.3	23.3	24.0	23.3	24.3	25.2	26.5	27.7	28.8	29.8	30.7	31.5	32.2	32.9

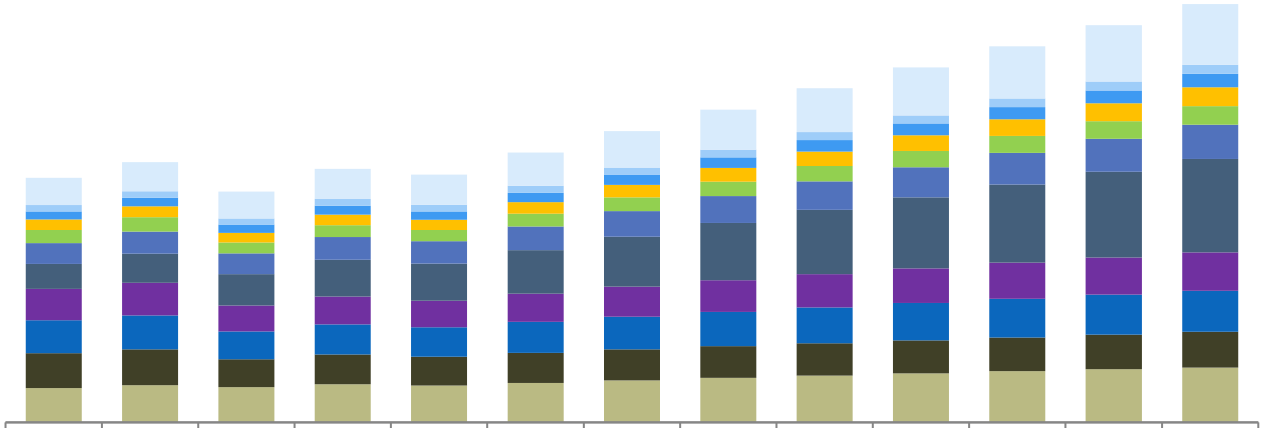
1. Excluding Sex hormones and insulins

Source: Frost & Sullivan Analysis

Breakdown of China Pharmaceutical Market by Therapeutic Area, 2018-2030E

Billion RMB

At wholesale price level



	2018	2019	2020	2021	2022	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Others	170.7	182.8	169.1	189.4	187.8	208.6	229.8	251.7	275.5	300.0	325.7	352.6	380.8
Urology	39.2	41.2	37.9	41.5	41.9	43.1	45.6	47.8	49.9	51.9	54.0	56.0	58.1
Systemic hormonal preparations	50.6	53.7	51.6	56.8	54.0	59.5	63.4	67.3	70.8	74.1	77.2	80.2	82.9
Muscle-skeleton System	64.9	68.2	60.2	65.9	62.6	71.7	78.3	84.9	91.6	98.3	105.1	112.2	118.9
Respiratory System	83.3	90.8	68.3	75.1	71.1	79.4	85.0	90.5	96.0	101.2	106.5	111.6	116.5
Blood And Blood Forming Organs	129.4	138.4	130.1	142.6	140.6	150.2	160.1	169.8	179.3	188.5	197.1	205.4	213.7
Oncology	157.5	182.7	197.5	231.1	233.6	271.3	313.1	357.9	401.9	445.5	490.8	538.1	586.6
Central Nervers System	197.4	204.3	161.4	173.5	165.3	178.4	189.4	199.7	209.3	218.1	226.4	233.6	240.7
Cardiovascular System	206.0	212.2	176.1	189.9	184.8	194.1	204.9	215.4	225.5	234.8	243.7	251.5	258.4
Anti-infective	217.9	225.5	174.2	185.8	181.4	188.0	194.0	198.1	201.6	206.1	211.2	216.9	223.1
Alimentary Tract and Metabolism	216.3	233.2	221.4	239.5	231.1	248.0	264.4	279.6	294.3	308.0	320.8	333.1	344.8

Others includes Skeletal muscle system and Other therapeutic areas

Source: Frost & Sullivan Analysis

Analysis of China Pharmaceutical Industry

Systematic Reform on Pharmaceutical Industry

R&D

Preclinical & IND	Clinical Trials & NDA

Reform of Review and Approval of Pharmaceutical Application

Manufacturing

Manufacturing	CMO

Marketing Authorization Holder (MAH)

Distribution & Retailing

Distributor	Healthcare Institution/Pharmacy

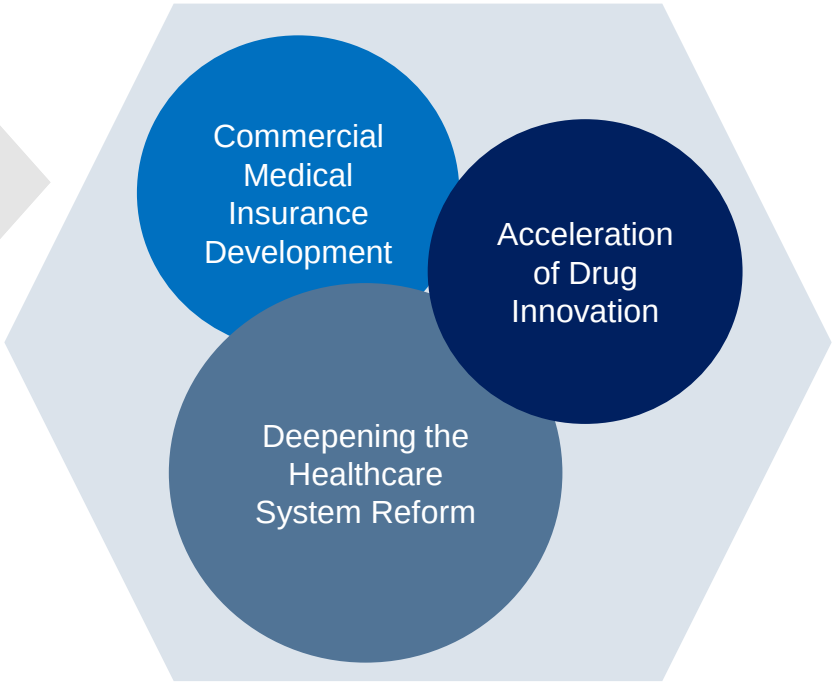
Two-invoice System

Payers

Medical Insurance (NRDL)

Dynamic Adjustment of NRDL via Price Negotiation

- Issued by the State Council on Jan. 2017, the *13th Five-year Health Plan*（“十三五”卫生健康规划）proposed the future development for China healthcare system, which involved every aspect of the pharmaceutical industry from the drug R&D to the end-users including healthcare institutions and patients, such as encouragement of drug innovation, development of medical insurance and supervision of pharmaceutical distribution etc.



Source: Government Website, Frost & Sullivan Analysis

Analysis of China Pharmaceutical Industry

Reform of the Drug and Medical Device Review and Approval

R&D

- Preclinical & IND
- Clinical Trials & NDA

Manufacturing

- Manufacturing
- CMO

Distribution & Retailing

- Distributor
- Healthcare Institution/ Pharmacy

Payers

- Medical Insurance (NRDL)

Reform of the Drug and Medical Device Review and Approval

《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》

	Before	Now
Reforming clinical trial management	• Requiring lengthy approval for clinical trial applications **(12-18 months)**	• Implied CTA approval **(60 days)** • Accepting clinical trial data generated abroad
Accelerating Review and Approval	• Lengthy review and approval process • APIs and formulations are approved separately	• Priority review and enable conditional approval • Linked approval of formulation and API, excipients and packaging • Leveraging eCTD for NDA review
Realizing Global Application	• A drug must be in a Phase II or Phase III clinical study or has received marketing authorization abroad before it begin international multi-center trial ("IMCT") in China	• Accepting foreign clinical data • Removing restrictions on clinical trials and registrations for imported drugs
Protection of Innovators	• Patent declaration system	• Patent linkage system • Drug patent term compensation system • Innovator's data protection • MAH program

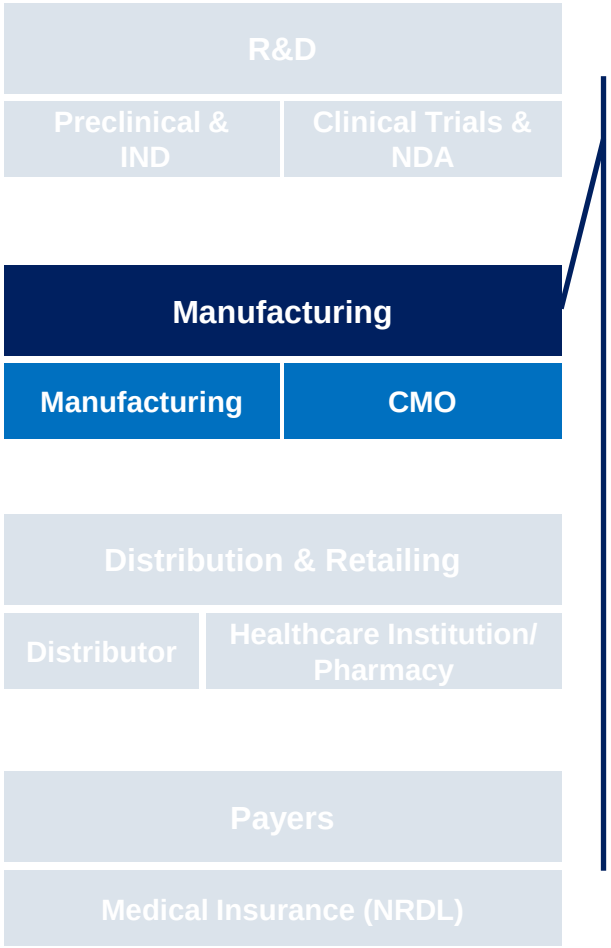
- In Oct 2017, the General Office of the CPC Central Committee and the General Office of the State Council issued the *Opinions on Deepening the Reform of the Evaluation and Approval Systems and Encouraging Innovation on Drugs and Medical Devices* (《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》). With the reform being realized, it leads to availability increase of clinical trial sites, shortening of the IND and NDA approval time, patent term extension and affordability of innovative drugs.

Note: eCTD = electronic common technical document

Source: Government Website, Frost & Sullivan Analysis

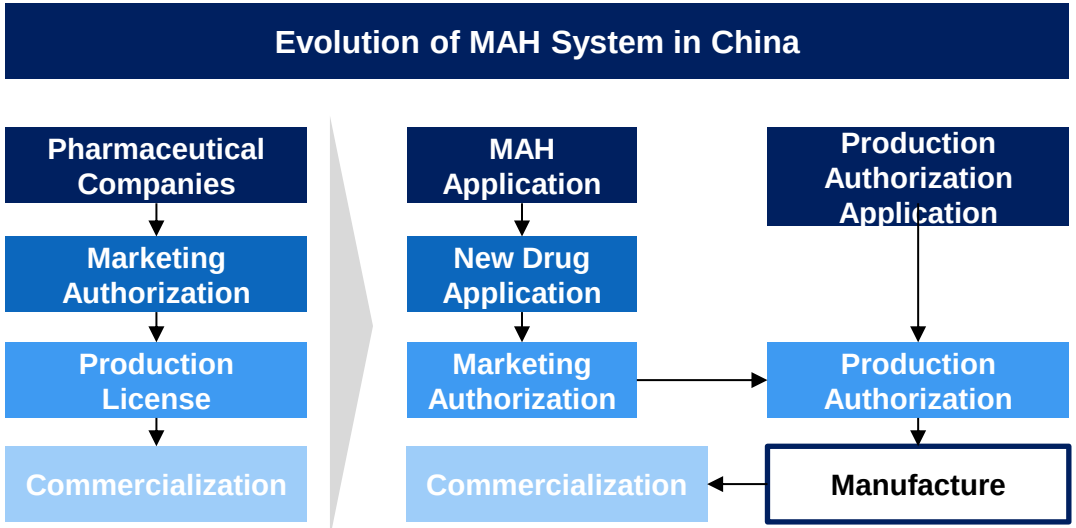
Analysis of China Pharmaceutical Industry

Marketing Authorization Holder (MAH)



Marketing Authorization Holder (MAH)

《国务院办公厅关于印发药品上市许可持有人制度试点方案的通知》



- MAH system enables the R&D organizations or personnel to apply for and obtain drug marketing authorizations and drug approval license, and the MAHs can entrust the CMOs to manufacture drugs instead of obtaining production license themselves, so that they can focus on R&D rather than allocate the manpower and investment on manufacturing.
- MAH system helps to promote R&D innovation, accelerate industrial restructuring and optimize resource allocation.

Source: Government Website, Frost & Sullivan Analysis

Analysis of China Pharmaceutical Industry

Two-Invoice System

R&D

Preclinical & IND | Clinical Trials & NDA

Manufacturing

Manufacturing | CMO

Distribution & Retailing

Distributor | **Healthcare Institution/ Pharmacy**

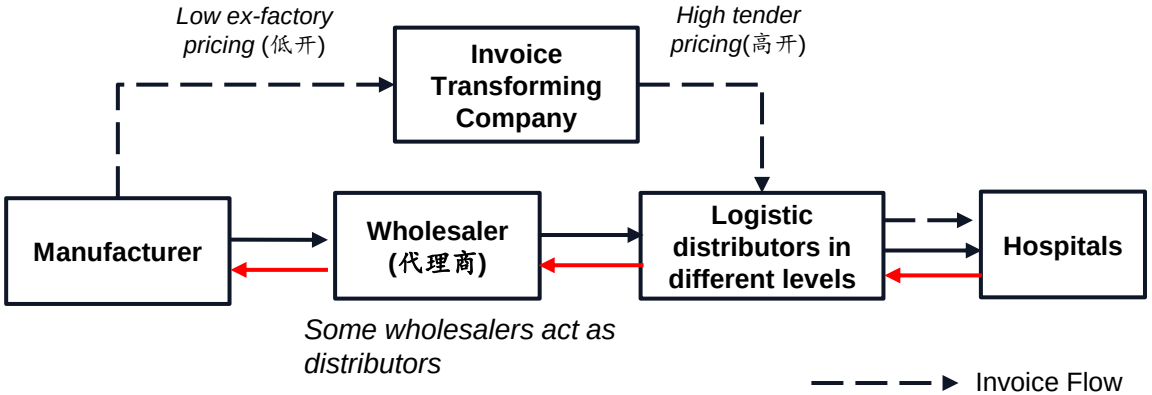
Payers

Medical Insurance (NRDL)

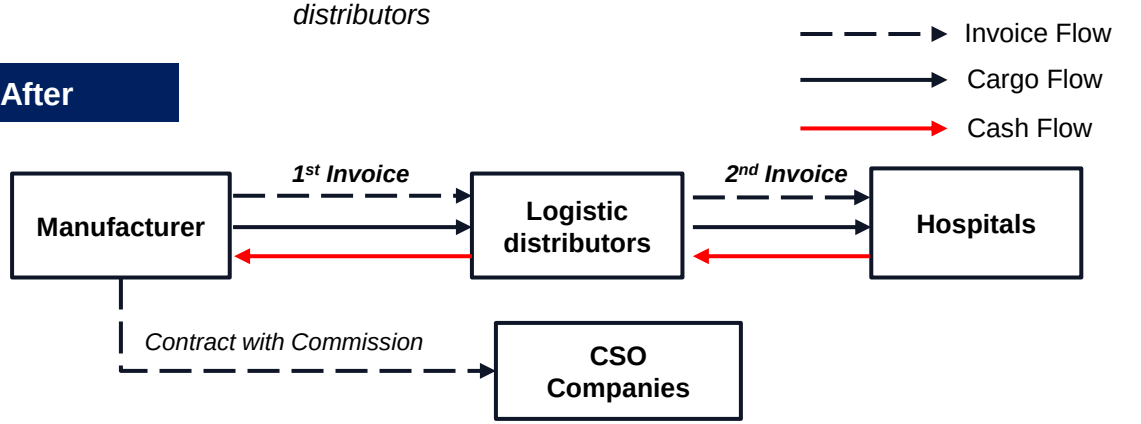
Two-Invoice System

《关于在公立医疗机构药品采购中推行“两票制”的实施意见（试行）的通知》

Before



After



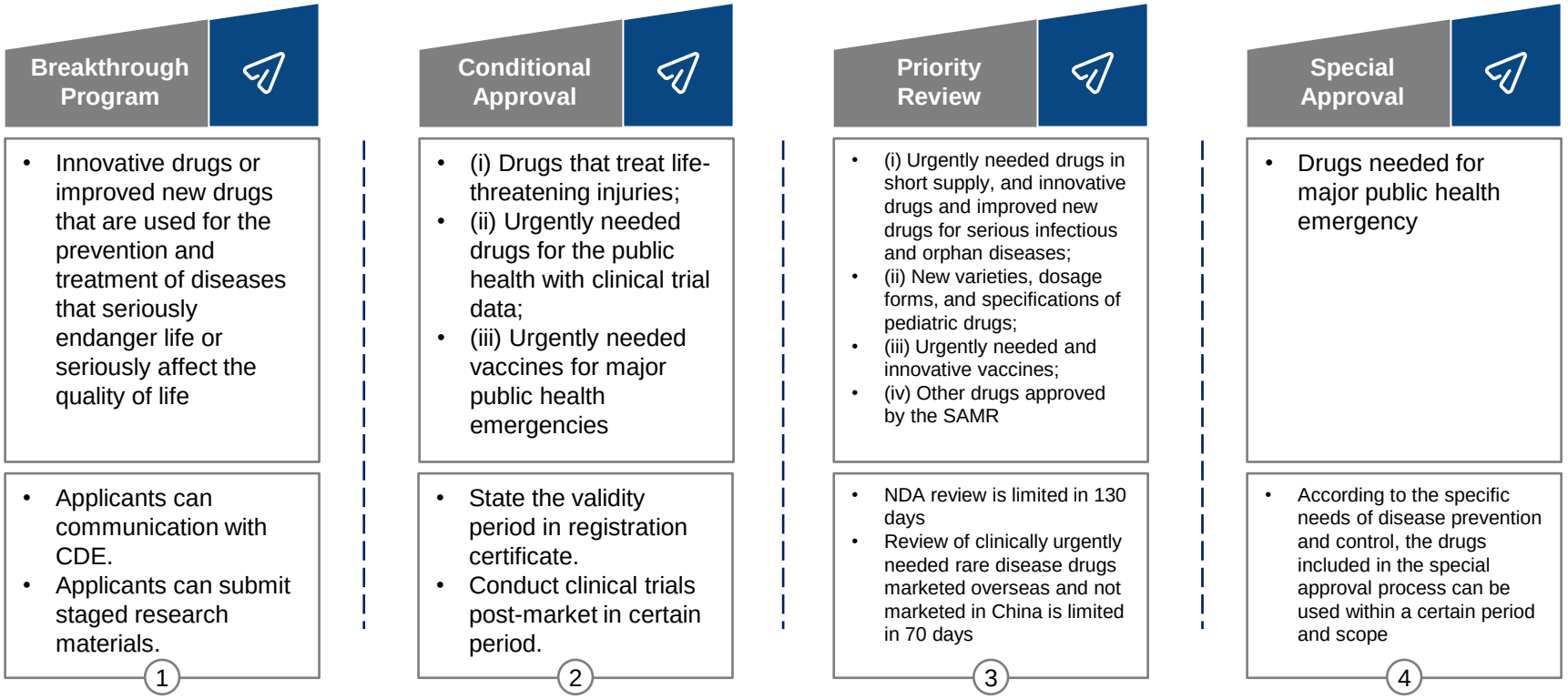
- The two-invoice system, aiming to improve transparency in drug prices and eliminate excessive profit margins associated with multi-tier distribution models, has important implications for pharma companies, distribution companies as well as CSOs.

Source: Government Website, Frost & Sullivan Analysis

Favorable Policies/ Regulations

Review of market access

- On March 30, 2020, the State Administration for Market Regulation (SAMR), released a revised Drug Registration Regulation (Revised DRR) as part of its efforts to strengthen and streamline its regulation of the pharmaceutical industry. According to the revised DDR, four accelerated approval pathways would be established. The revised DRR went into effect on July 1, 2020.



Source: Frost & Sullivan Analysis

Encouraging Policies for Innovative Drugs in China

Accepting Foreign Clinical Trial Data and Bridging Study- I

- In July 2018, in respond to Opinions on Deepening the Reform of the Evaluation and Approval Systems and Encouraging Innovation on Drugs and Medical Devices (《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》), the Guidelines on Accepting Foreign Clinical Data (《接受药品境外临床试验数据的技术指导原则》) was issued, thereby accelerating the marketing process of innovative drugs whose clinical data generated abroad is accepted, making them to continue with the most advanced clinical stage possible directly in China. The overarching principles in determinating the acceptability of the foreign clinical data are authenticity, completeness, accuracy and traceability, with the process of generating data accord with ICH GCP requirement.

Guidelines on Accepting Foreign Clinical Data
《接受药品境外临床试验数据的技术指导原则》

Overarching Principles

Authentic → Complete → Accurate → Traceable → ICH GCP

Scope of Application

Applies to Innovative/Generic Drugs that:

1) Have completed early clinical trials abroad and want to continue with the following trials in China; or
2) Have completed all clinical trials abroad but not yet marketed; or
3) Have been marketed abroad.

Application Material

Foreign Clinical/Market Status			Clinical Data Package Content Required in China			
Clinical Trial	NDA/ANDA	Marketed	BE, PK, PD	Efficacy	Safety	Post Market
			✓	✓	✓	
			✓	✓	✓	
			✓	✓	✓	✓

Acceptability Assessment

1) Data package completeness with respect to the regulatory requirements of China; and
2) The ability of clinical data to extrapolate to China those parts of the application (which could be most or all of the application) based on studies from the foreign region.

Source: NMPA, ICH, Frost & Sullivan Analysis

Encouraging Policies for Innovative Drugs in China

Accepting Foreign Clinical Trial Data and Bridging Study - II

- Based upon the acceptability assessment result, a bridging study might be necessary for the successful extrapolation of the part of foreign clinical data that is aimed for acceptance by CDE. Type of bridging study needed is determined depending on the analysis of the data within the clinical data package. In all sense, the policy that allows for the acceptance of foreign clinical data increase the conduct of bridging studies, allowing for an innovative drug to be marketed simultaneously in domestic and oversea market. For drugs targeting TAs that lack effective treatment (e.g. severe illness, rare disease and pediatric disease) and whose data is assessed as "partially accepted", it allows a conditional acceptance of foreign clinical data, which makes it possible for a drug to be marketed first, with post-market efficacy and safety data required later for a complete acceptance.

Assessment Results and Bridging Study Necessity

	Authentic and reliable data that aligns with ICH, GCP & registration requirement	Proved safety & efficacy in foreign data	Ethnicity sensitive factors affecting safety and efficacy	Extrapolatable to Chinese patients	Bridging Study
Completely Accepted	Yes	Yes	No	Yes	Not Needed
Partially Accepted	Yes	Yes	Yes	Uncertain	Needed
Not Accepted	No	No	Yes	NA	Apply as new drug

Determination on Type of Bridging Study

The applicant should discuss with CDE for detailed requirements on bridging study before implementation, but according to ICH, the following examples illustrate the types of bridging studies for consideration in different situations:

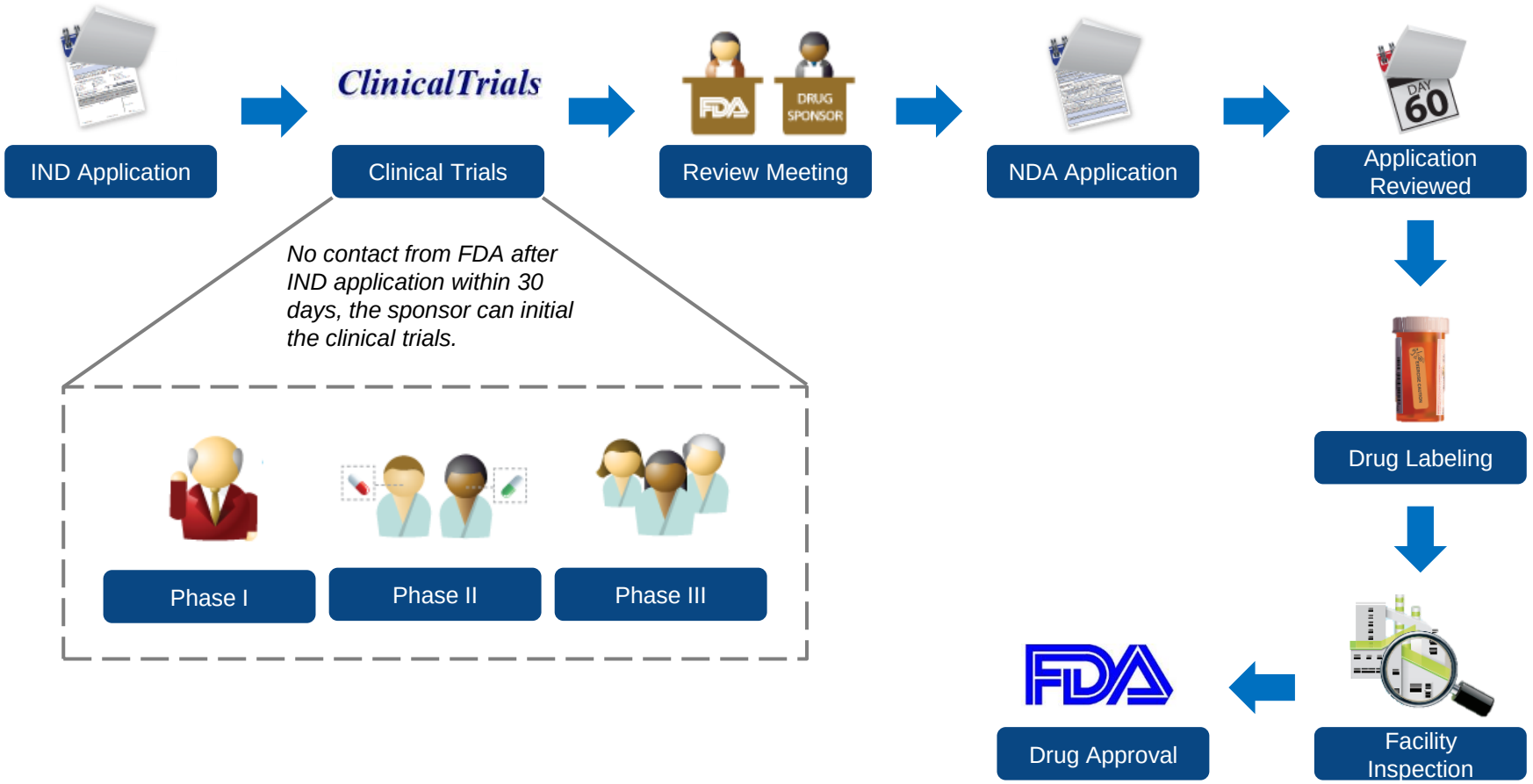
1) **Bridging Studies Using Pharmacologic Endpoints:** If the regions are ethnically dissimilar and the medicine is ethnically sensitive but extrinsic factors are generally similar (e.g., medical practice, design and conduct of clinical trials) and the drug class is a familiar one in the new region;
2) **Controlled Clinical Trials:** It will usually be necessary to carry out a controlled clinical trial, often a randomised, fixed dose, dose-response study, in the new region when:

- ◆ There are doubts about the choice of dose,
- ◆ There is little or no experience with acceptance of controlled clinical trials carried out in the foreign region,
- ◆ Clinical practice, e.g., use of concomitant medications and design and/or conduct of clinical trials are different,
- ◆ The drug class is not a familiar one in the new region.

Source: NMPA, ICH, Frost & Sullivan Analysis

Drug Registration Procedure in the US

- Drug registration in the US need comply with Federal Food, Drug and Cosmetic Act(FD&C Act), which stipulates the application filling and clinical trial requirements from IND application to drug approval.



Source: FDA, Frost & Sullivan analysis

FDA Expedited Programs for New Drug Approval

- FDA has developed four distinct and successful approaches to make innovative drugs or those with advantages over existing treatments as soon as possible. FDA expedited programs aims to help spur the development of new therapies for serious conditions.

1 Fast Track

Features

- Actions to expedite development and review
- Rolling review

Qualifying Criteria

- For serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need

2 Breakthrough Therapy

Features

- Intensive guidance on efficient drug development
- Organizational commitment
- Rolling review
- Other actions to expedite review

Qualifying Criteria

- For serious condition and preliminary clinical evidence indicates that the drug may be a substantial improvement over available therapies

3 Accelerated Approval

Features

- Approval based on an effect on a surrogate endpoint of an intermediate clinical endpoint that is reasonable likely to predict a drugs clinical benefit

Qualifying Criteria

- For serious condition and demonstrates an effect on a surrogate endpoint that is reasonable likely to predict clinical benefit or on a clinical endpoint that can be measured earlier

4 Priority Review

Features

- Shorter clock for review of marketing application(6 months compared with the 10-month standard review)

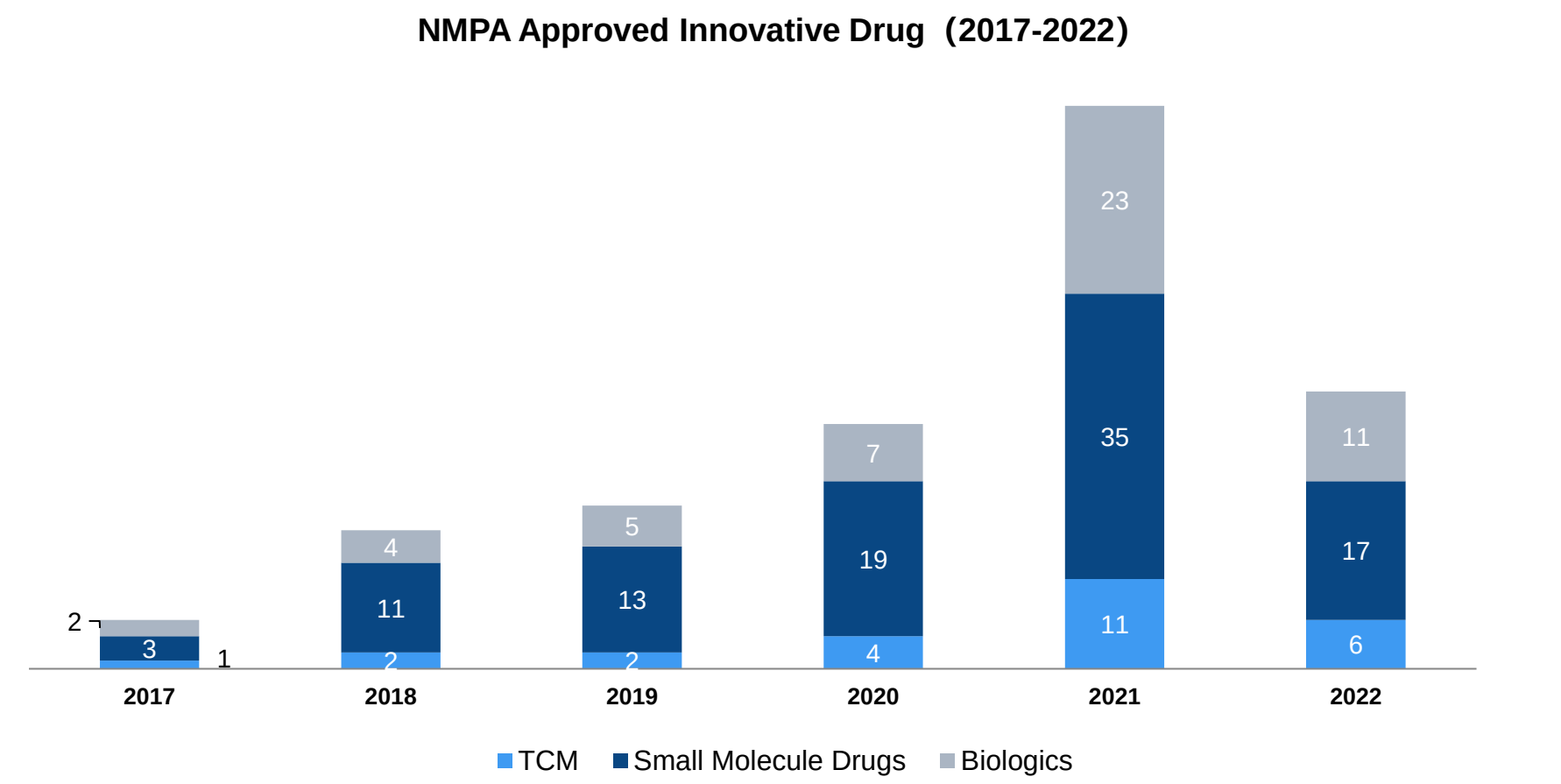
Qualifying Criteria

- For serious condition and, if approved, would provide a significant improvement in safety or effectiveness

Source: FDA, Frost & Sullivan analysis

NMPA Approved Innovative Drug (2017-2022)

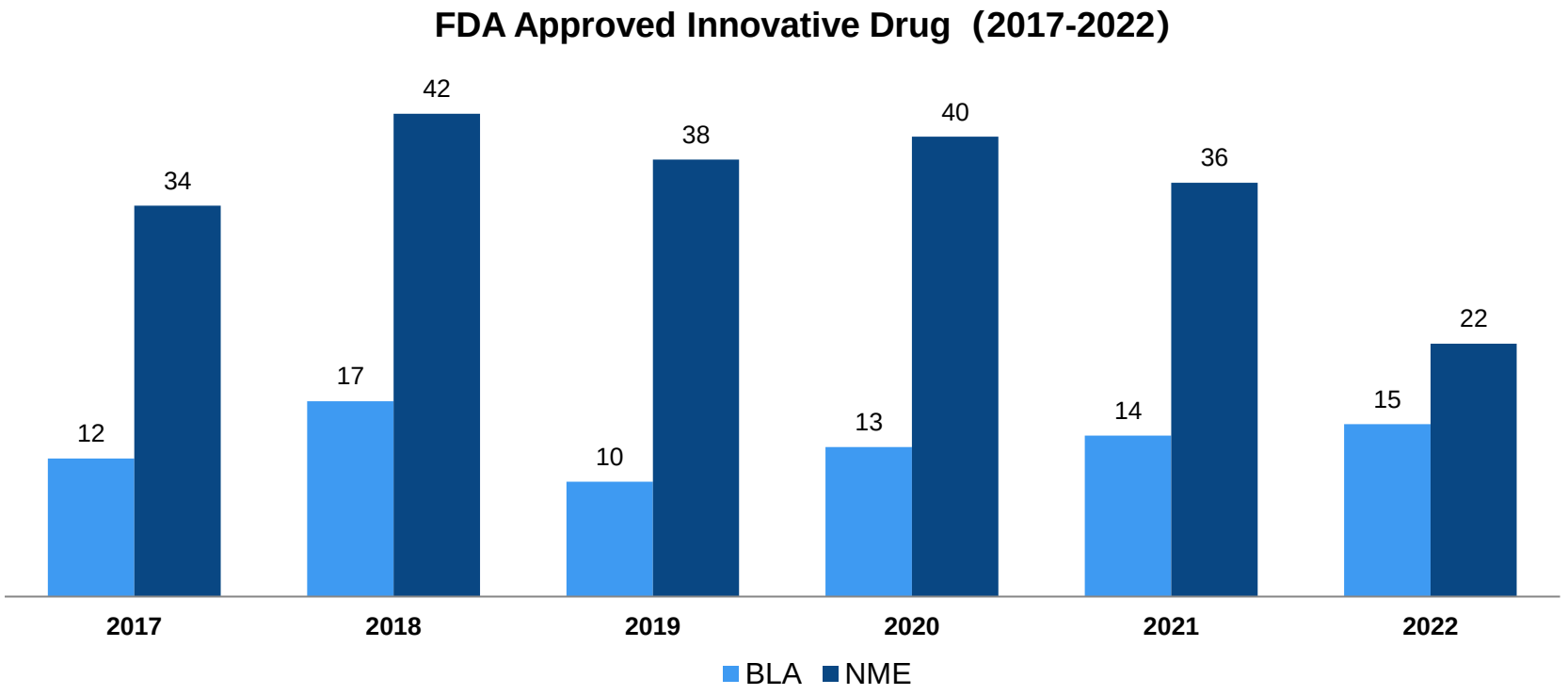
- The number of innovative drugs approved by NMPA have been increasing over years since 2017. In 2022, 17 small molecule drugs have been approved, representing 33.3% of total innovative drugs approved. The number of approved innovative drugs by NMPA decreased to 34 in 2022.



Source: CDE, Frost & Sullivan Analysis

FDA Approved Innovative Drug (2017-2022)

- The FDA's Center for Drug Evaluation and Research (CDER's) approves applications for a wide variety of drug treatments each year. A new drug is an innovative product that fills a previously unmet medical need or otherwise substantially helps to advance patient care. As defined by CDER, new drugs are either new molecular entities (NMEs) under New Drug Applications (NDAs) or new therapeutic biologics under Biologics License Applications (BLAs).
- In 2022, CDER approved 37 novel drugs.



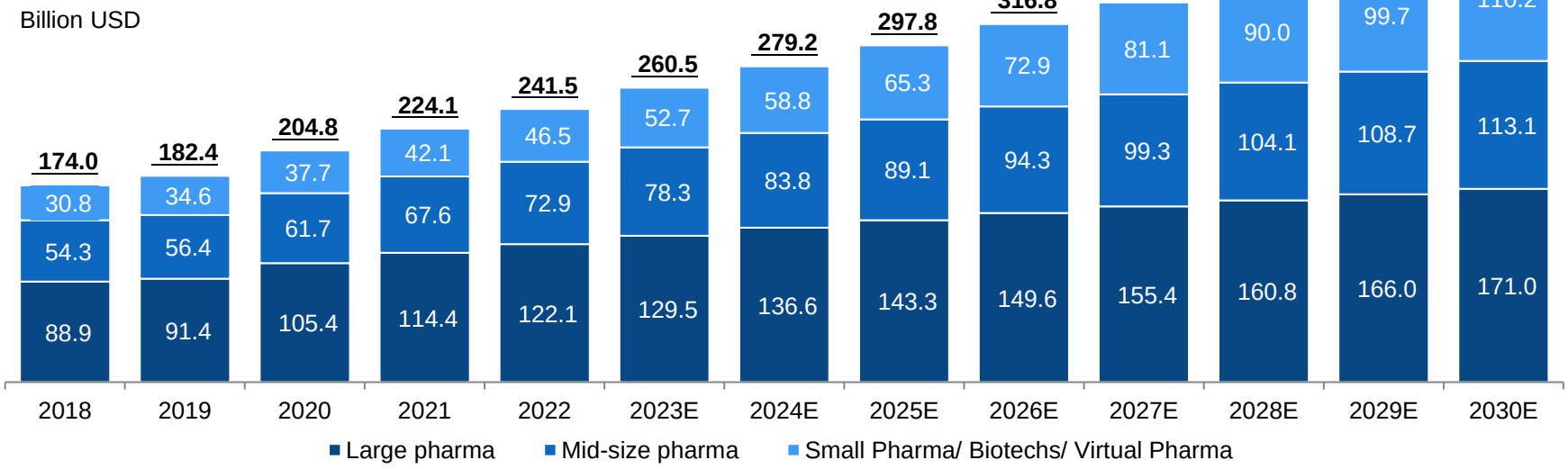
Source: FDA CBER report "New Molecular Entity (NME) Drug and New Biologic Approvals ", Frost & Sullivan Analysis

Global R&D Expenditure and Breakdown by Pharma Types, 2018-2030E

- The diagram reflects the global R&D expenditure breaking down by the different size of pharmas that are differentiated by the sales revenue.
- Global R&D expenditure increases from USD174.0 billion in 2018 to USD241.5 billion in 2022. In 2022, the spending from mid-sized and large pharma accounts for 80.7% of total expenditure. With the emerging of innovative drug R&D, small pharma, particularly those biotech companies, increases their R&D expenditure. The spending for small companies would increase form USD46.5 billion in 2022 to USD72.9 billion in 2026, with a CAGR of 11.9%, higher than that of mid-size and large pharma in the same period.

Global R&D Expenditure and Breakdown by Pharma Types, 2018-2030E

Period	Large Pharmaceutical Companies	Mid-sized Pharmaceutical Companies	Small Pharma/ Biotechs/ Virtual Pharma	Total
2018-2022	8.3%	7.6%	10.8%	8.5%
2022-2026E	5.2%	6.7%	11.9%	7.0%
2026E-2030E	3.4%	4.6%	10.9%	5.6%



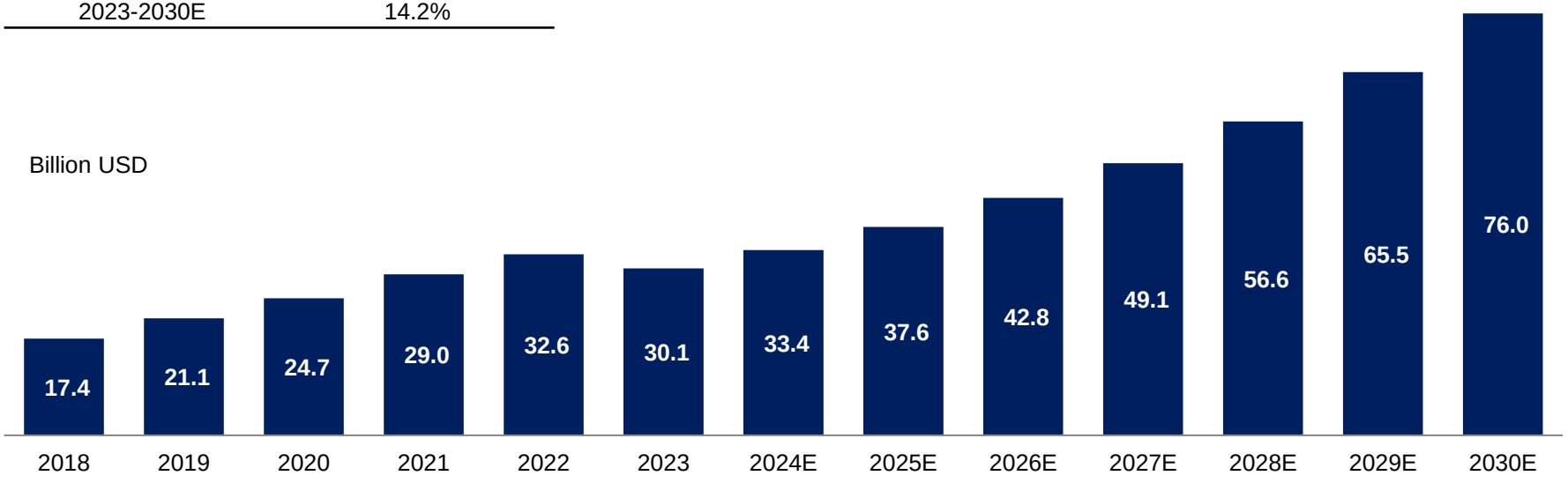
Source: Frost & Sullivan Analysis

China R&D Expenditure, 2018-2030E

- Since the encouragement from government, large pharmas in China has begun to strategize for new drug development. In addition, mid-size and small pharmas are devoting to drug innovation, expected to lead the trends of emerging biologics in China as well. The total R&D expenditure will rapidly grow in next few years.

China R&D Expenditure, 2018-2030E

Period	Total
2018-2023	11.5%
2023-2030E	14.2%



Notes: Large pharma refers to pharmaceutical companies with sales revenue over USD1 billion
Mid-sized pharma refers to pharmaceutical companies with sales revenue between USD100 million and USD1 billion.
Small Pharma including biotech companies and virtual pharmas refer to pharmaceutical companies with sales revenue lower than USD100 million.

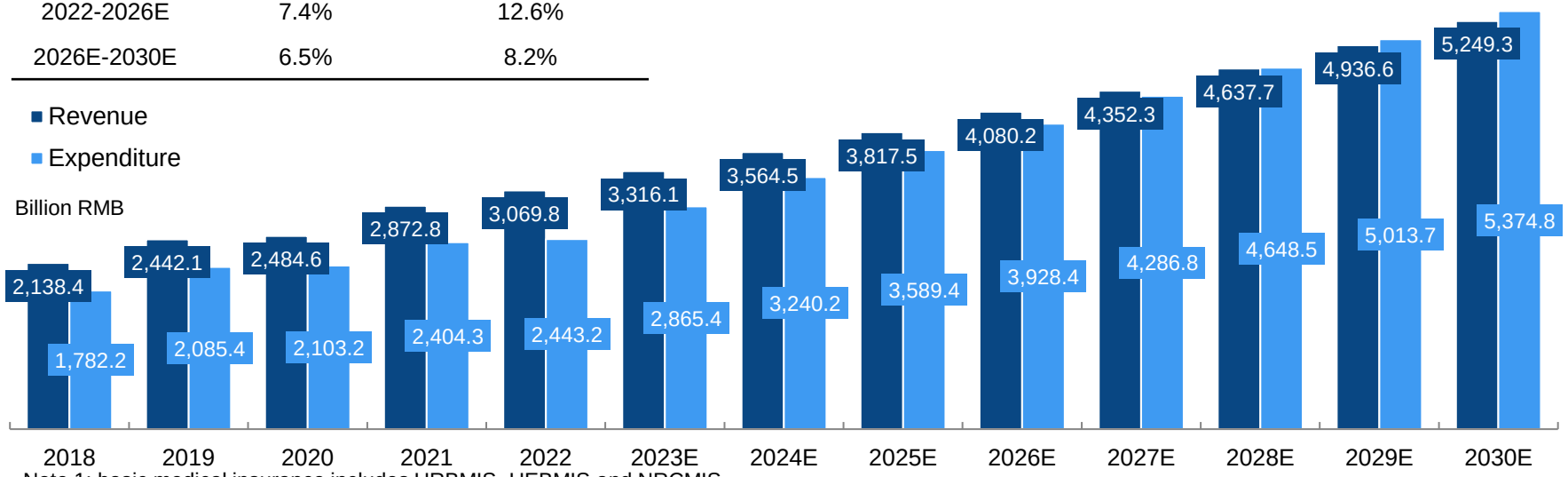
Source: Frost & Sullivan Analysis

Basic Medical Insurance Fund in China, 2018-2030E

- The revenue of basic medical insurance fund has increased from RMB2,138.4 billion in 2018 to RMB3,069.8 billion in 2022, with a CAGR of 9.5%, while the expenditure has increased from RMB1,782.2 billion in 2018 to RMB2,443.2 billion in 2022, representing a CAGR of 8.2% during the indicated period.
- The revenue is expected to continue its growth while the expenditure will experience a much higher growth if no intervention is implemented. The revenue and the expenditure is projected to reach RMB4,080.2 billion and RMB3,928.4 billion in 2026, respectively. The expenditure will surpass the revenue in 2028 and reach RMB5,374.8 billion in 2030. Therefore, there is a high willingness to control the expenditure of basic medical insurance fund, which can be achieved through digital technologies.

Revenue and Expenditure of Basic Medical Insurance Fund[1], 2018-2030E

Period	CAGR	
	Revenue	Expenditure
2018-2022	9.5%	8.2%
2022-2026E	7.4%	12.6%
2026E-2030E	6.5%	8.2%



Note 1: basic medical insurance includes URBMIS, UEBMIS and NRCMIS.

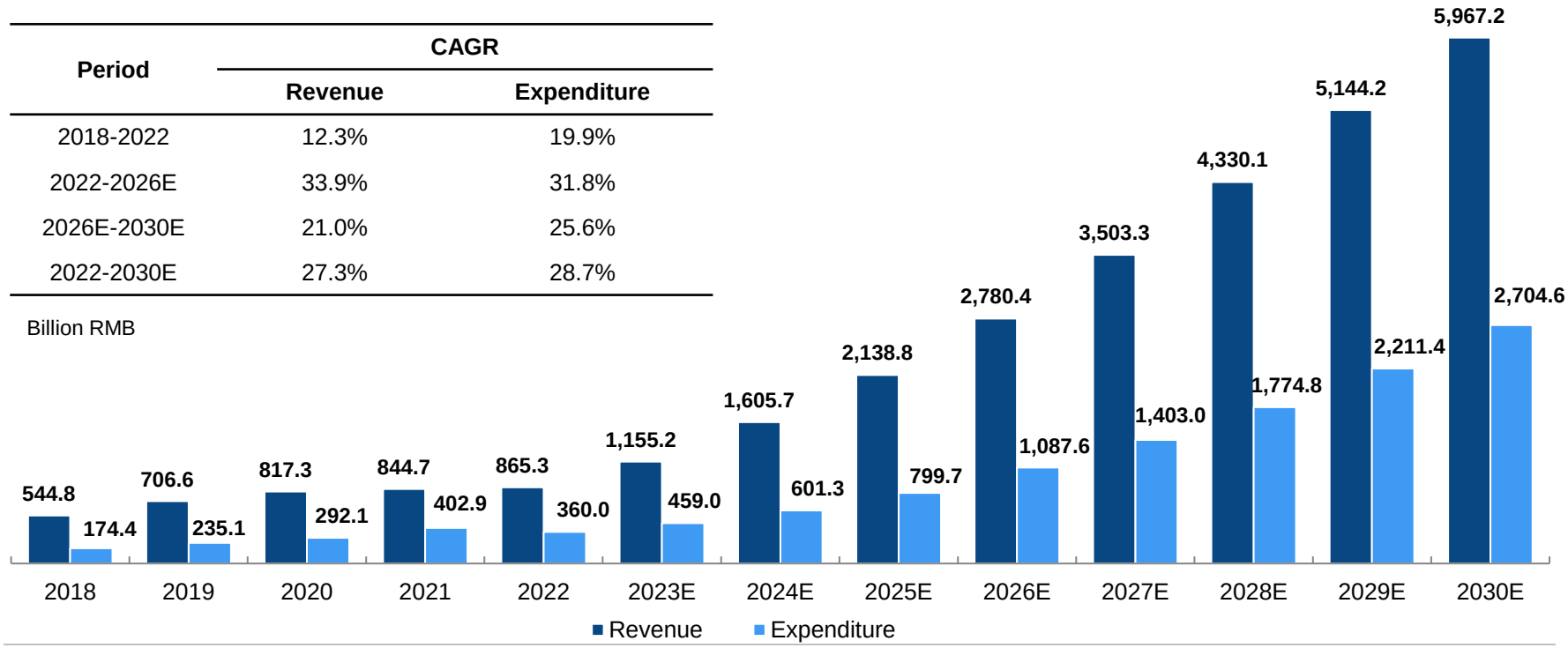
Source: NMPA, Frost & Sullivan Analysis

Commercial Health Insurance Fund in China, 2018-2030E

- According to China Insurance Regulatory Commission, the revenue of commercial health insurance fund has increased from RMB544.8 billion in 2018 to RMB865.3 billion in 2022, with a CAGR of 12.3%, while the expenditure has increased from RMB174.4 billion in 2018 to RMB360.0 billion in 2022, representing a CAGR of 19.9% during the indicated period.
- Commercial health insurance fund in China has shown explosive growth before 2017 due to the absence of regulation. After the introduction of a series of regulatory measures by China Insurance Regulatory Commission, commercial health insurance premiums began to reflect the real demand for health insurance. Along with demographic changes and increasing health awareness, the commercial health insurance is expected to continue its growth. The revenue and the expenditure is projected to reach RMB2,780.4 billion and RMB1,087.6 billion in 2026, respectively.

Revenue and Expenditure of Commercial Health Insurance Fund, 2018-2030E

Period	CAGR	
	Revenue	Expenditure
2018-2022	12.3%	19.9%
2022-2026E	33.9%	31.8%
2026E-2030E	21.0%	25.6%
2022-2030E	27.3%	28.7%

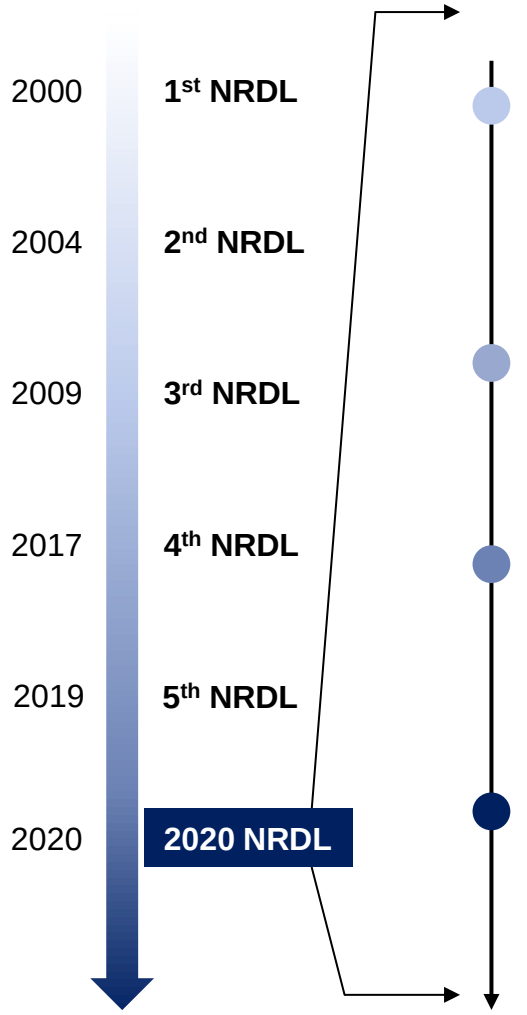


Source: CIRC, Frost & Sullivan Analysis

Analysis of Healthcare Reimbursement System in China

Recent Progress and Impact of the 2020 NRDL

Progression of NRDL



Recent Progression of 2020 NRDL

- On Dec 2020, NHSA and MOHRSS released the official work plan for the adjustment of the 2020 NRDL, enforced from Mar. 1st 2021. And it also clarified the organization form, working procedures and payment management issues.
- 162 kinds of drugs were involved in price negotiation, and 119 of them (including 96 exclusive drugs and 23 non-exclusive drugs) were smoothly negotiated. Among previous NRDL negotiations, drug prices have fallen furthest in 2020 NRDL negotiations, the average decline of drugs prices were 50.64%.
- Affected by fair competition in market, the drug list and payment standard should also be adjusted accordingly. Some drugs in previous NRDL occupied too much fund with relatively high price. In total 14 exclusive drugs, already involved in previous NRDLs, are held in latest NRDL negotiation for the first time, and the prices reduced by 43.36% on average. Additionally, 29 previous drugs were removed from the list due to substitutability and low clinical value.
- 17 new oncology drugs including 3 kinds of generics enter the List B of 2020 NRDL. 14 exclusive oncology drugs renewal the contract with price reduction of 14.95% on average. Individually, the price reduction even reach above 60%

Implication for Innovation

The inclusion of NRDL promoted the sales of innovative drugs significantly. At the same time, pharmaceutical companies need to embrace continuous innovation and accelerate the pace. Only those pharmaceutical companies that develop drugs with independent IP rights can win industrial competition and keep higher margin.

2020 NRDL restrict the price of drugs strictly by introducing economic competition among different drugs with same indication. The substitutability of drugs is now an important indicator, and only the most cost-effective drugs are expected to enter NRDL.

Numerous domestic innovative drugs were included by 2020 NRDL, marking the initiation of rapid increasing of sales and the rapid transformation of Chinese pharmaceutical industry towards innovation.

For the first time, the self-declaration system of pharmas was implemented. Only drugs that meet the conditions of 2020 NRDL plans can be included in the adjustment scope.

Source: Official Website Frost & Sullivan Analysis

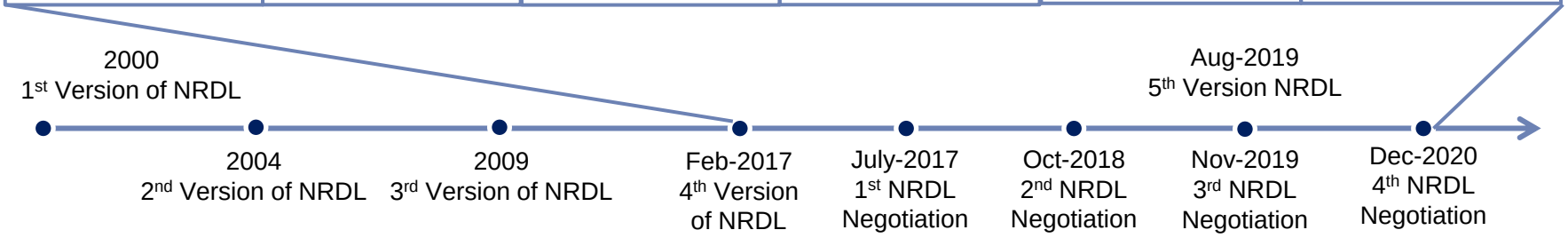
Analysis of Healthcare Reimbursement System in China

Impact of NRDL dynamic adjustment on oncology drug market

- Inclusion of oncology drugs into the National Reimbursement Drug List directly improves patient affordability and would benefit the manufacturer with sharp increase of the drug sales volume and revenue despite a reduction in the price.
- For example, after being included in the NRDL in July 2017, Avastin's sales revenue increased by 86.1% from 2017 to 2018. Tagrisso (Osimertinib) which was approved in March 2017 got included in the NRDL in October 2018, and its 2018 sales revenue increased by 325.4% in comparison with 2017 market performance.
- Dynamic adjustment of NRDL via price negotiation has been implemented in three successive year including 2017, 2018, 2019 and 2020 since its initial release. Such dynamic adjustments provide an additional way through which high value oncology drugs can be accessible to more patients, and simultaneously boost the sales of the pharmaceutical companies, motivating them to input more on R&D of new oncology drugs by making good use of their successful experience. In this way, the oncology drugs marketed is pushed forward.

Recent Progresses on NRDL Dynamic Adjustment Relevant to Oncology Drug

Sept, 2016	Feb, 2017	July, 2017	Oct, 2018	Nov, 2019	Dec, 2020
MoHRSS released measures to adjust RDL system, and the major contents are to add more **high clinical value new drugs** into new NRDL system.	The 4th version of NRDL has published. In which Icotinib was included into NRDL, as **the first targeted oncology drug**.	44 innovative drugs joined NRDL via the **1st NRDL negotiation**, and 36 drugs successfully entered into category B of NRDL, **with 18 oncology drugs.**	**17 oncology drugs** were included into NRDL through the **2nd negotiation**, with 12 drugs for solid tumors and 5 for hematologic tumor, with an average 56.7% price drop.	In the **3rd negotiation**, **22 oncology drugs** were included in NRDL, out of 97 of drugs that successfully joined NRDL (both numbers include renewal drugs).	In the **4th negotiation**, **17 oncology drugs** were included in NRDL, out of 119 of drugs that successfully joined NRDL, with an average 43.36% price drop.



Source: MOHRSS, Frost & Sullivan Analysis

Growth Drivers of Innovative Drugs Market (1/2)

Enlarging Patient Pool	• In China, disease spectrum is transforming from infectious diseases to chronic diseases among which include oncology are getting increasingly prevalent. Incidence of cancers has achieved 4.6 million in 2020 and is projected to reach 4.9 million in 2023. The cancer treatment features high cost and long-term medication demand. Since biologics have demonstrated the superior efficacy on such diseases with need of long-term medication, the increasing prevalence of chronic diseases especially for cancers is expected to spur the demands for biologics.
Increasing Capital Investment	• Pharmaceutical industry has the capital-intensive nature and require heavy investment on both research & development as well as manufacturing process. R&D expenditure on global pharmaceutical industry in 2020 has achieved USD204.8 billion, representing a CAGR of 6.9% from 2016 to 2020. The investment provide the abundant capital for innovative drugs R&D, investigations of emerging categories and the establishment of manufacturing facilities.
Technology Advancement	• The development of technology promotes the development of biologics. Biotechnology can create substances that cannot be found in nature, integrate two substances into one molecule to exploit benefits from both of them, and even utilize viruses for their unique features. • Multidisciplinary such as genome technology and information technology has promoted the development of precision medicine, so it is necessary to develop small molecule drugs with better targeting, which will increase the need for innovative chemical medicine.

Source: Frost & Sullivan Analysis

Growth Drivers of Innovative Drugs Market (2/2)

Promotion of Commercial Healthcare Insurance	• In addition to national medical insurance, lots of pharmaceutical companies are exploring new ways to solve the accessibility of innovative drugs through cooperation with commercial healthcare insurance platform. In addition to national medical insurance, many pharmaceutical companies are exploring new ways to solve the accessibility of innovative drugs through cooperation with commercial insurance companies or third-party insurance platforms. As the national medical insurance is characterized by "low guarantee and wide coverage", and the connection between pharmaceutical companies and commercial healthcare insurance undoubtedly provides a new payment method to increase the possibility of drug accessibility. • In recent years, the participation rate of commercial medical insurance is increasing year by year, such as Huihu Bao (惠沪保), Huirong Bao (惠蓉保), and Lecheng global special drug insurance (乐城全球特药险). In 2022, “Huhui Bao” expanded the number of domestic specific high-value drugs to 25, including car-t treatment drugs, PD-1 antibody products, ADCs and overseas special drugs, with the maximum total insured amount increasing to 3.1 million. In 2022, Huirong Bao expanded the list of special drugs to 58 as well.
Favorable Policy	• China government promulgated a series of policies to shorten the review and approval interval for innovative drugs. Also, priority review is implemented, which will accelerated getting to the market process for drugs with potential to address the urgently clinical need. Patent protection is greatly enhanced as well. All these reforms will attract MNC to market more global innovative drugs in China market and stimulate domestic players to invest more on research & development. Consequently, that available innovative drugs become increasingly diverse will boost consumption in the future.

Source: Frost & Sullivan Analysis

Future Trends of Innovative Drugs Market

Focusing on Chronic Diseases	• In China, disease spectrum is transforming from infectious diseases to chronic diseases, including cardiovascular diseases, cancer and chronic respiratory diseases. According to *China's Mid - and Long-term Plan for Chronic Diseases (2017-2025)*《中国防治慢性病中长期规划（2017-2025年）》issued by the State Council, Chronic diseases account for 86.6% of total deaths, and the disease burden has accounted for more than 70% of the total disease burden. Therefore, from the perspective of clinical demand, China's innovative drug research and development in the future will mainly focus on cancer, cardiovascular diseases, diabetes and other chronic diseases, while anti-infective drugs will still maintain a certain proportion.
Multi-disciplinary Integration	• After the two revolutions in life science caused by the development of molecular biology and genomics, the third revolution is characterized by the integration of multiple disciplines. It will be triggered by the convergence of disciplines such as life science, physics, engineering and information technology. The cross-fusion of gene editing technology, tumor immunotherapy, big data, artificial intelligence, 3D printing technology and other fields will promote the research and development of new drugs.
Cooperative Innovation	• Pharmaceutical enterprises can obtain resources from other entities to shorten the research and development time, reduce the research and production costs, and accelerate the entry of innovative drugs into the market. Pharmaceutical enterprises can entrust manufacturing enterprises with the production of innovative drugs, thus saving the capital and time of self-built factories and production lines. And pharmaceutical enterprises can cooperate with universities, research institutes CROs to do innovative drug research, which can reduce the cost and share the risk.
Improving Affordability	• The average disposable income of the Chinese population is expected to continue growing rapidly, increasing the willingness and ability of patients to pay for medications. In 2019, households with an annual disposable income of over US$30,000 accounted for 38.1% of the total households in China and are expected to increase to 56.5% of the total households in China by 2023. As more Chinese households increase their spending power, they can afford more expensive medical treatments, particularly for life-threatening diseases.

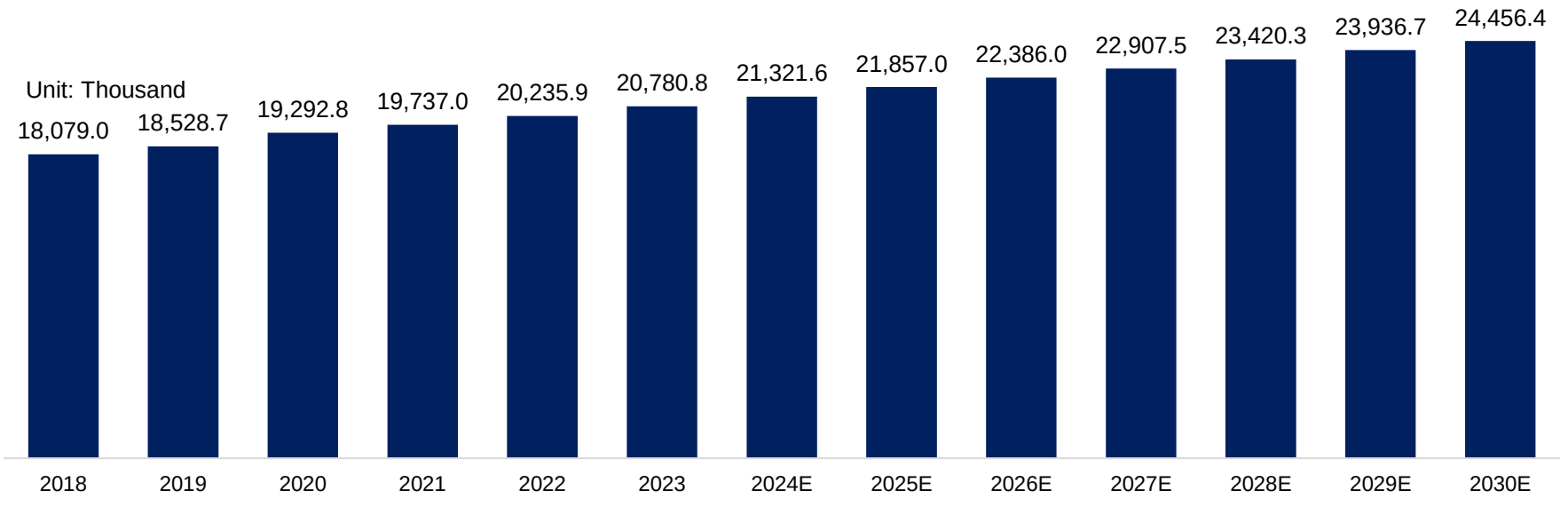
Source: Frost & Sullivan Analysis

Incidence of Total Cancer Globally, 2018-2030E

- The new cases of total cancer globally is growing to 20.8 million in 2023 from 18.1 million in 2018 with the CAGR of 2.8%. Due to the awareness and diagnosis for cancer, the number of new cases will increase to 24.5 million in 2030 with the CAGR of 2.4% from 2023 to 2030.

Total Cancer Incidence Globally, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2030E	2.4%



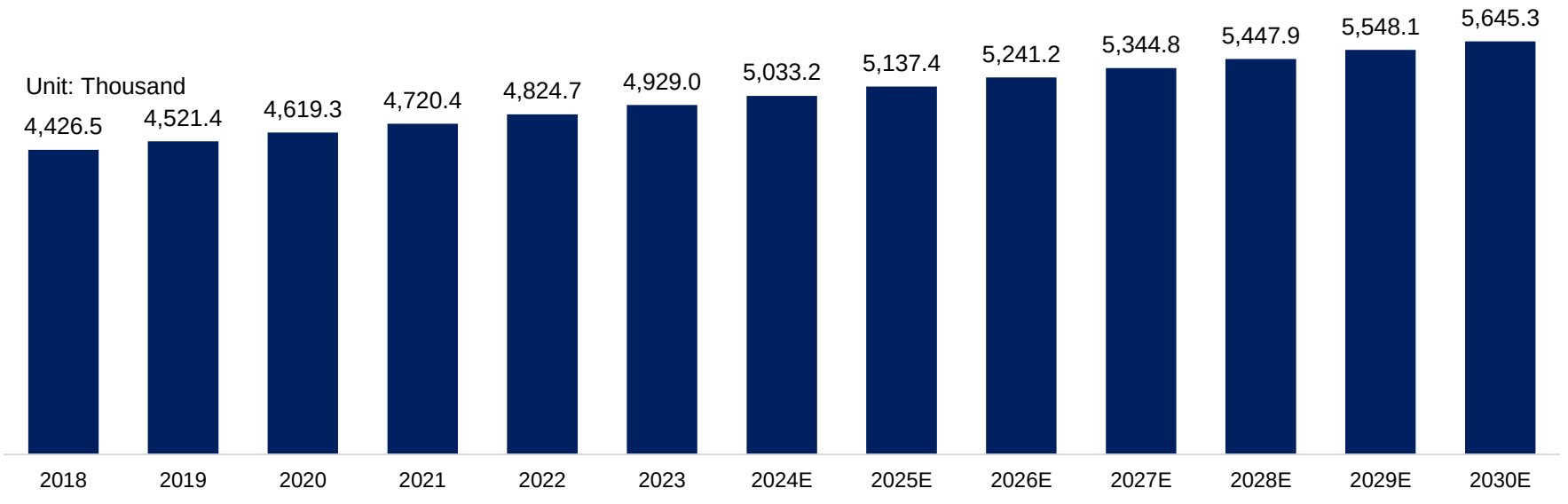
Source: Frost & Sullivan Analysis

Incidence of Total Cancer in China, 2018-2030E

- Cancer has been the second largest disease in China, the new cases is growing to 4.4 million in 2023 from 4.9 million in 2018 with the CAGR of 2.2%. Due to the awareness and diagnosis for cancer, the number of new cases will increase to 5.6 million in 2030 with the CAGR of 2.0%, from 2023 to 2030.

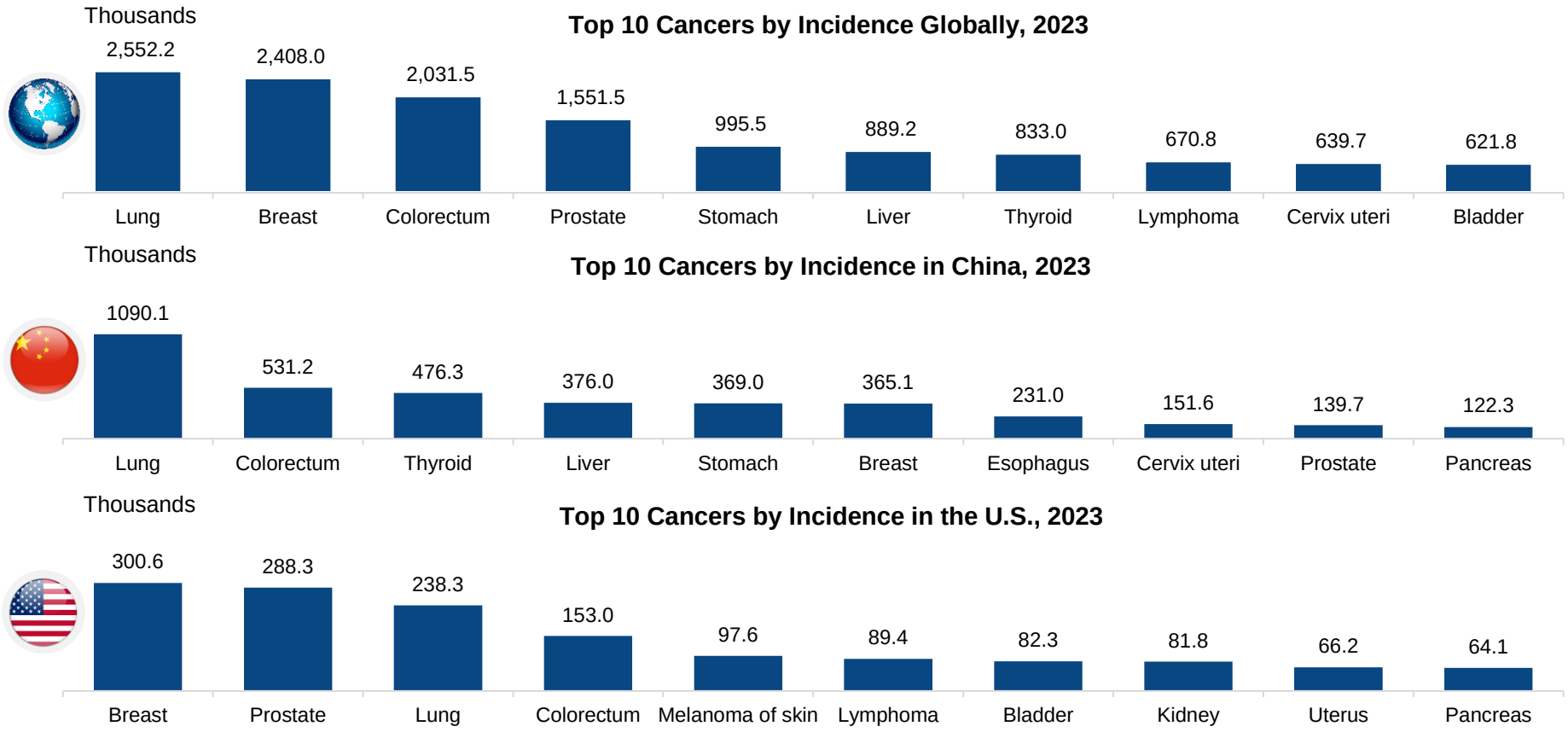
Total Cancer Incidence in China, 2018-2030E

Period	CAGR
2018-2023	2.2%
2023-2030E	2.0%



Source: Frost & Sullivan Analysis

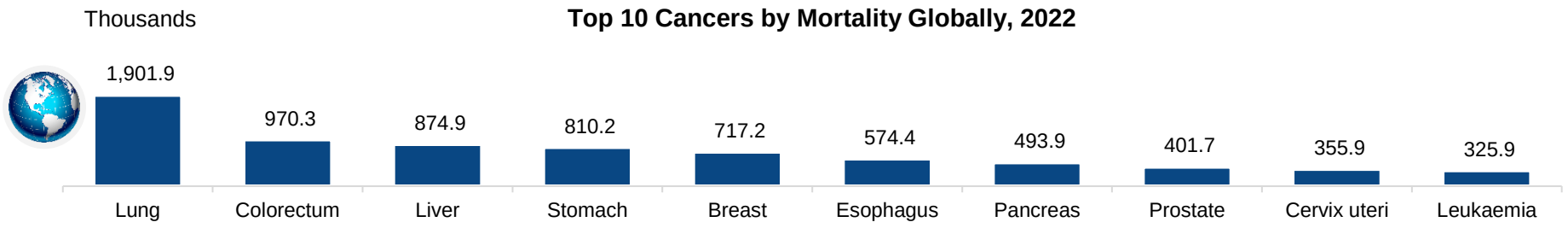
Global and China Top 10 Cancers by Incidence, 2023

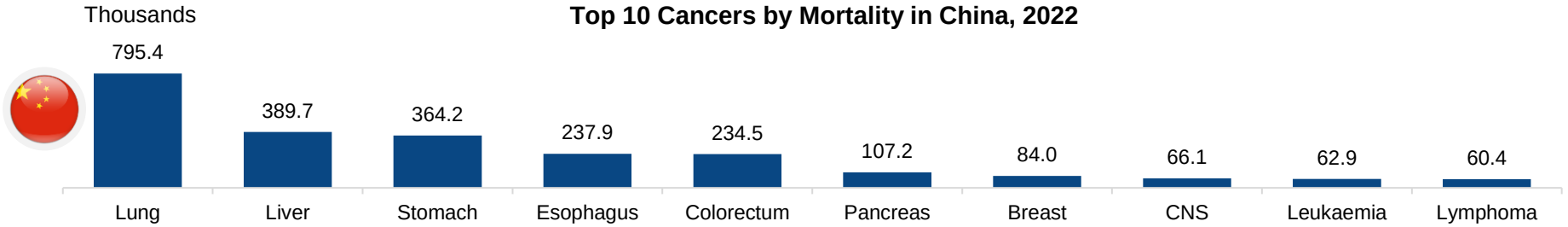


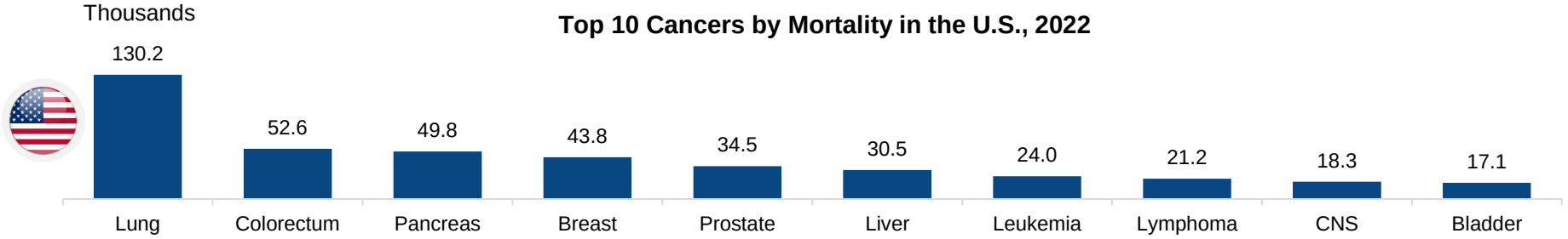
Source: Globocan, IARC, NCCR, Frost & Sullivan analysis

Global and China Top 10 Cancers by Mortality, 2022

- Different from top 10 cancers by incidence globally in 2022, there is a higher mortality of liver cancer, stomach cancer, and esophagus cancer in China.





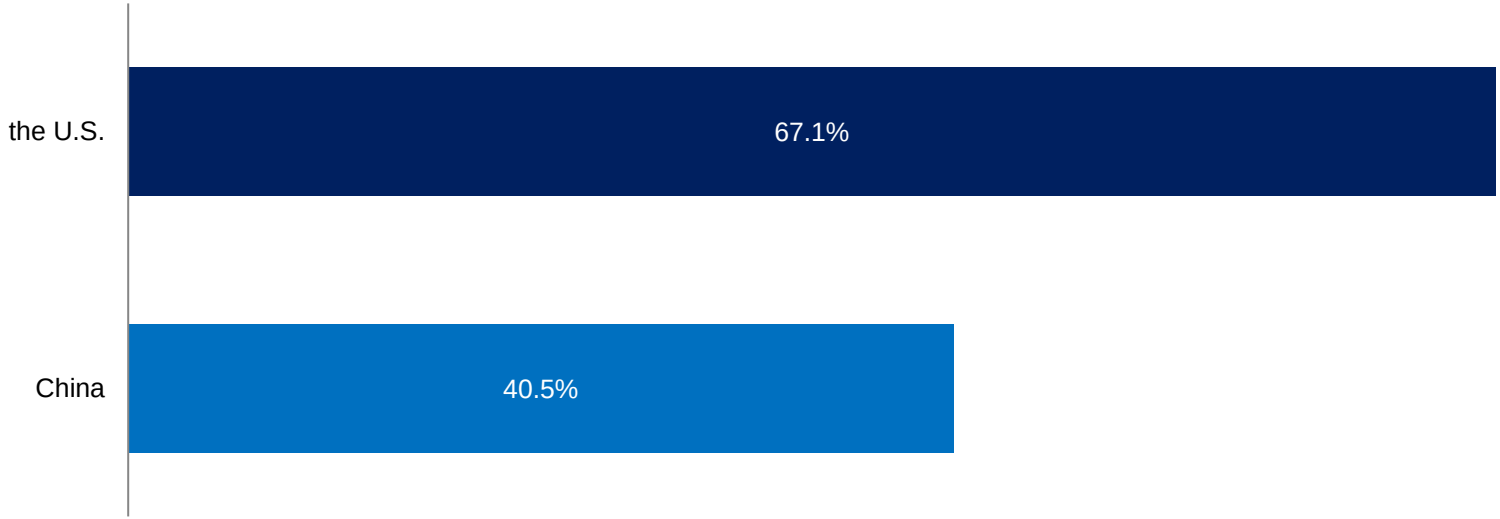


Source: ACS Cancer Statistics, IARC, NCCR, Frost & Sullivan analysis

Comparison of 5-year Survival Rate of Cancer in China and the U.S.

- The NCCR investigated the 5-year survival rate during 2003 to 2013 of a population pool from 17 cancer registries, and stratified survival estimates by calendar period (2003–05, 2006–08, 2009–11, and 2012–15). The latest 5-year survival rate is 40.5% in China.
- According to the SEER program (Sruveillance, Epidemiology and End Results Program) data based on NPCR registries from 2009-2015 and follow-up of patients through 2015, the latest 5-year survival rate is 67.1% in the U.S.
- Overall, the U.S. 5-year survival rate is around 26.4% higher that China due to the wide use of advanced therapies including targeted drugs and more scientific management of cancer patients.

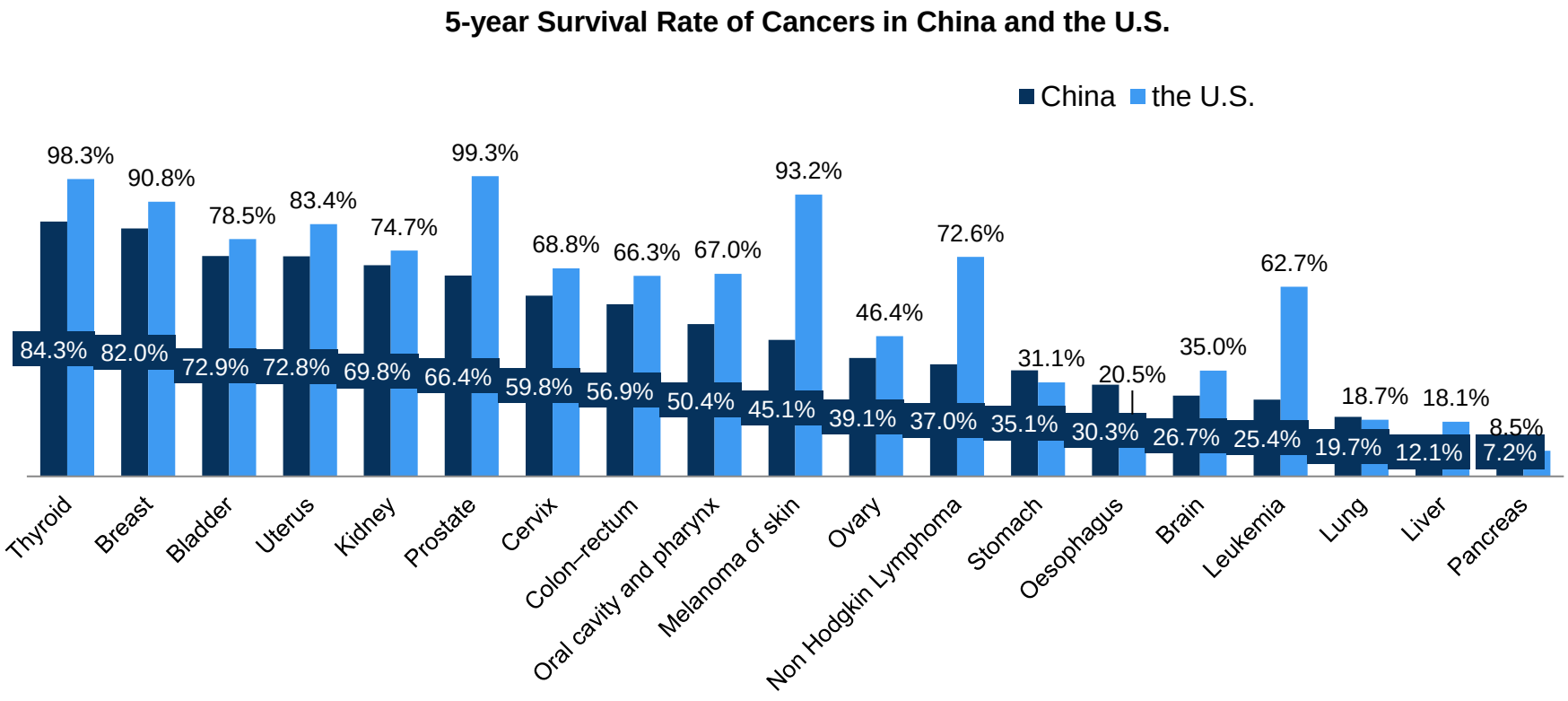
Overall 5-year Survival Rate of Cancers in China and the U.S.



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

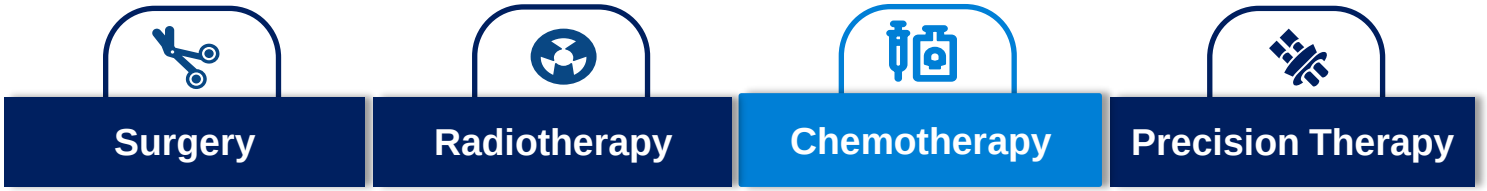
Comparison of 5-year Survival Rate of Cancers in China and the U.S.

- China's 5-year survival rate lags far behind the U.S. in prostate cancer, melanoma of skin, non Hodgkin lymphoma and leukemia.



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

Development Path of Cancer Treatment



	Surgery	Radiotherapy	Chemotherapy	Precision Therapy
Description	A procedure in which a surgeon removes cancer from a patient's body	High doses of radiation to kill cancer cells and shrink tumors	Use single or combinations of anti-cancer drugs to stop or slow tumor growth	Act on specific targets that are associated with cancer development
Features	Foundation of solid tumor treatment. More effective for early stage, limited for most late stage	Affects surrounding normal cells as well, causing side effects such as fatigue, hair loss	Targets all fast growing cells, can be used to treat many types of cancer alone or in combination with other treatments	Suppress tumor cells by regulating cell signaling pathways or relying on patient's own immune system. Includes small-molecule drug, mAb, ADC and CGT
Examples	Liver resection	3D-CRT, IMRT, SBRT	Taxanes, Cisplatin, Utidelone	TKI, PD-1 inhibitor

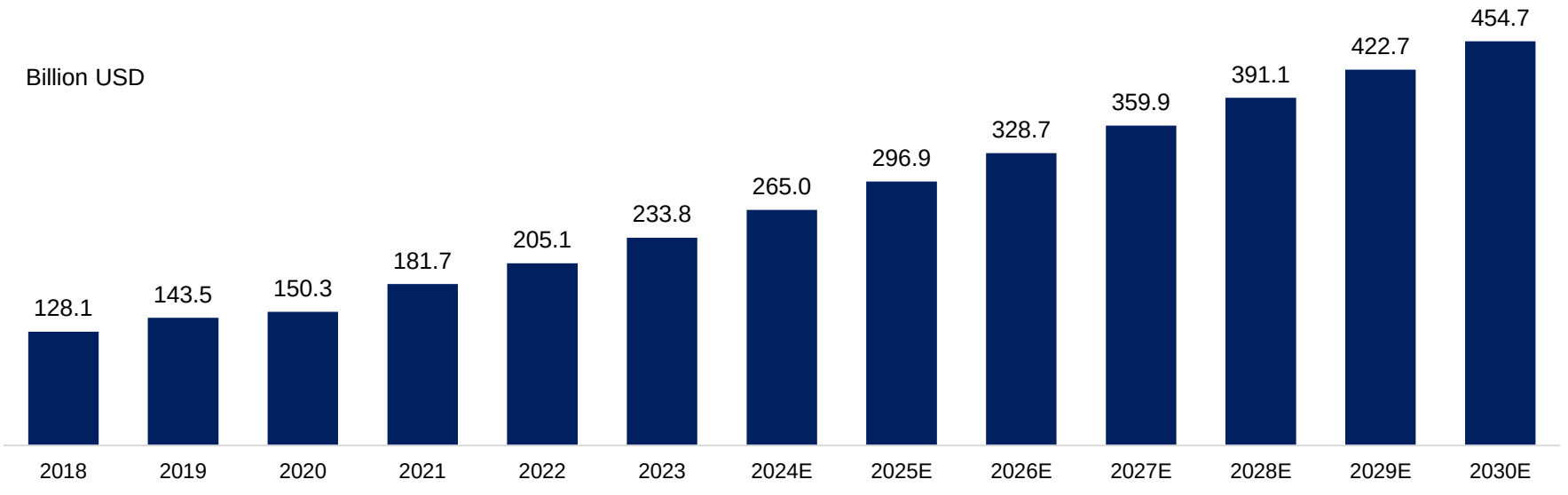
Source: Literature research, Frost & Sullivan Analysis

Global Oncology Drug Market, 2018-2030E

- The development of targeted therapies have shifted the treatment paradigm for many cancer types, leading to a fast expansion of the oncology market. From 2018 to 2023, global market of oncology drugs expanded from USD 128.1 billion to USD 233.8 billion, representing a CAGR of 12.8%, and is expected to reach USD 454.7billion by 2030, with a CAGR of 10.0% from 2023 to 2030.

Global oncology drug market, 2018-2030E

Period	CAGR
2018-2023	12.8%
2023-2030E	10.0%



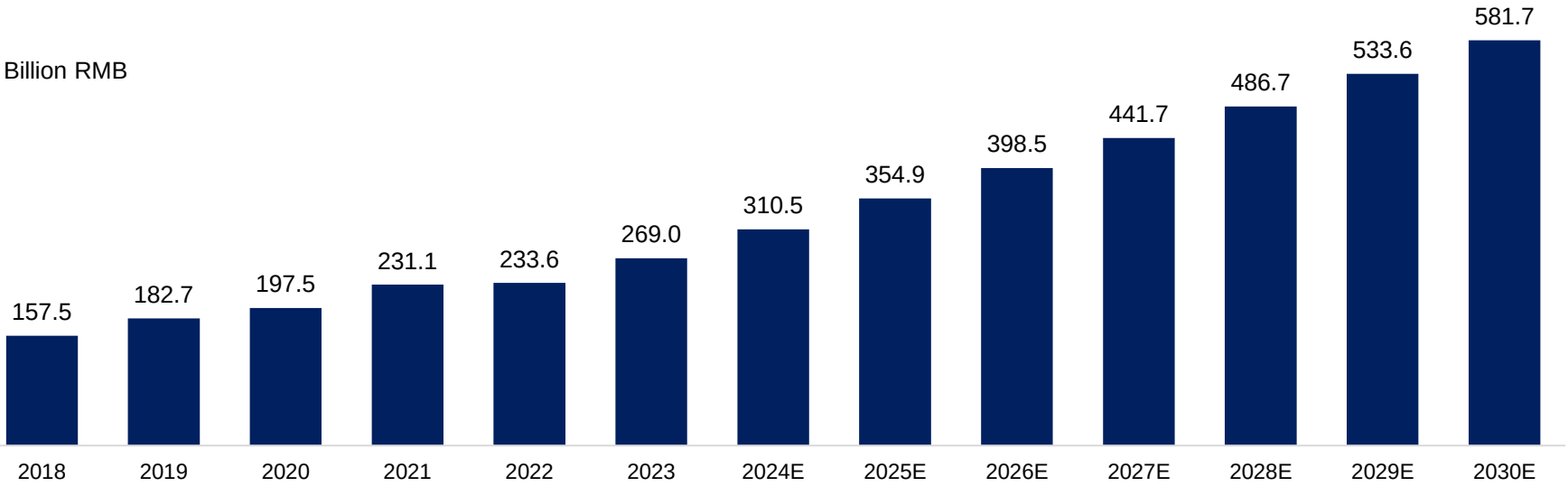
Source: Frost & Sullivan Analysis

Oncology Drug Market in China, 2018-2030E

- The oncology drug market in China grew from RMB157.5 billion in 2018 to RMB269.0 billion in 2023 at a CAGR of 11.3% and is forecasted to continue its strong growth, reaching RMB581.7 billion in 2030 at a CAGR of 11.6% from 2023.

Oncology drug market in China, 2018-2030E

Period	CAGR
2018-2023	11.3%
2023-2030E	11.6%



Source: Frost & Sullivan Analysis

NRDL Inclusion Impact on Oncology Drugs

2000 NRDL

The first version of NRDL.

2004 NRDL

2009 NRDL

Health Insurance Reform

2015 NRDL

- 1st Negotiation

The number of medicines increased during the period is considerable.

The renewal period is long and irregular.

2017 NRDL

2019 NRDL

2018 NRDL

2020 NRDL

2021NRDL

2022NRDL

Dynamic Adjustment

Increasing the total number of included drugs, with emphasis on drugs with high clinical value.

The indications include tumors, rare diseases, hepatitis, diabetes and other chronic diseases. The guarantee capability in key areas was further improved, and the guarantee capability of basic medical insurance reached a new height.

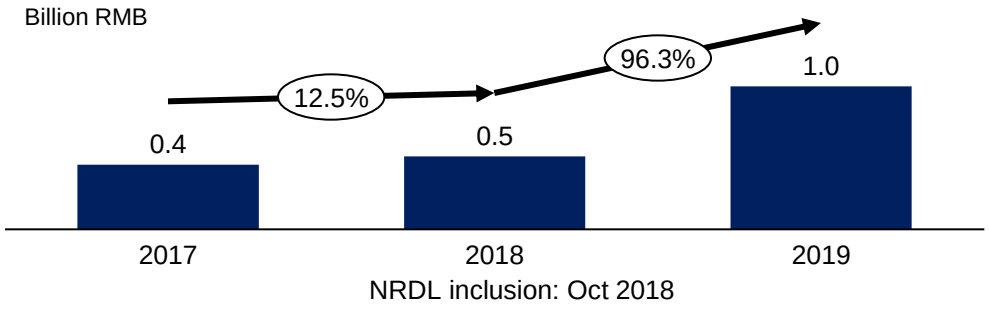
2023 NRDL

- Totally included 126 new
- drugs
- Average decrease percentage around 61.7%

- **Representative Oncology Drugs in China**

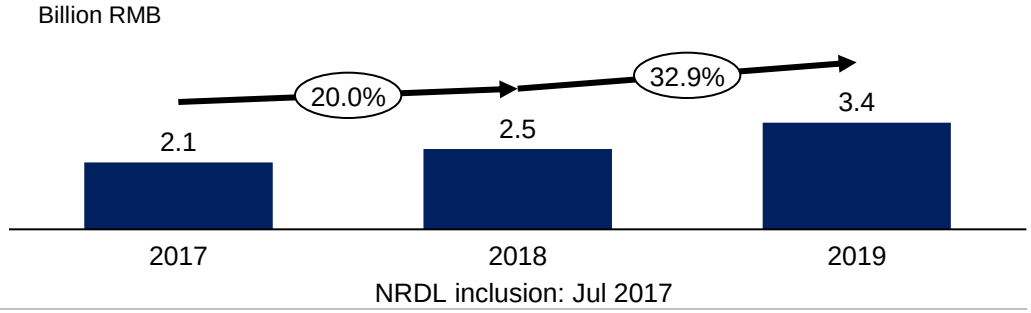
In general, the revenue of a drug would be impacted after it's listed in the NRDL. The boosted sales of the drug could be the main reason for this influence. This situation is especially obvious for oncology drugs, due to their original high prices and patients' reliance. This change is usually intensive during the first year of NRDL inclusion, as shown in the following Cetuximab graph. The increase in revenue would slow done after in the following years after a drug is listed in NRDL, as shown in the Rituximab graph.

Cetuximab Revenue in China



NRDL inclusion: Oct 2018

Rituximab Revenue in China



NRDL inclusion: Jul 2017

Source: Annual Reports, Frost & Sullivan Analysis

Growth Drivers of Oncology Drugs Market

Expanding Patient Pool with Significant Unmet Medical Needs	Together withpopulation growth and aging demographic, advances in early-stage diagnosis and improving survival rates have substantially increased the oncology patient pool, which has in turn driven the expansion of the oncology drug market globally. In China, the outcomes of oncology patients, despite the improvements witnessed in recent years, still lag behind those in developed countries. In part due to the relatively limited availability of targeted therapies and immunotherapies, the five-year survival rate of cancer patients in China (40.5%) was substantially lower compared to those in the U.S. (67.1%) in 2015, indicating a significant unmet medical need for more innovative therapies to improve cancer prognosis and outcome. As set out in its Healthy China Action (2019-2030) (《健康中國行動(2019-2030)》), China is committed to raising the overall five-year survival rate of cancer patients to 46.6% by 2030.
Increasing Medical Expenditure	The global economy experienced rapid growth in the past two decades. Higher disposable income per capita has made it easier for patients to afford treatments. In particular, healthcare expenditures per capita in China increased from approximately RMB4,237.0 in 2018 to RMB6,010.0 in 2022, having expanded at a CAGR of 9.1%. This factor is expected to continue enhancing Chinese patients' ability and willingness to pay for more advanced and expensive treatments options, especially for life-threatening diseases like cancers.
Improved Reimbursement Environment	In 2023, 126 new anti-cancer drugs were added to the NRDL, with an average price reduction of 61.7%, of which 14 new anti-cancer drugs were added. In the future, more innovative oncology drugs will be included in medical insurance through annual adjustments to the medical insurance catalog, significantly improving drug affordability and serving more patients. Chemotherapy drugs play an important role in current cancer treatment and are strongly supported by China's medical insurance policy. At the same time, according to the 2022 residents' income and consumption expenditures released by the Bureau of Statistics, the per capita disposable income of national residents was RMB36,883, an increase of 5.0% over the previous year. The income of Chinese residents continues to grow, and health awareness and investment have also increased, bringing greater market potential.
Favorable Government Policies Driving Innovation	Government support has driven andwill continue to drive oncology research and development. One of China's major goals is to reshape the industry from developing "me too" or "me better" drugs and relying on drug in-licensing to one that fosters and promotes end-to-end innovation. The "Fourteenth Five-Year Plan for National Economic and Social Development of the PRC and the Outline of Vision Goals for 2035 (《中華人民共和國國民經濟和社會發展第十四個五年規劃和2035年遠景目標綱要》)" released in 2021 continues to emphasize the central role of innovation in China's modernization progress, and the significance of R&D breakthrough in medical science. After launching its priority review mechanism in 2016, the NMPA has further streamlined NDA review procedures, which contributed to a significant growth in NDAs granted for Class 1 innovative drugs. For more details on China's recent healthcare reform, see "Regulatory Overview – Laws and Regulations in Relation to New Drugs."

Source: Frost & Sullivan Analysis

Future Trends of Oncology Drugs Market

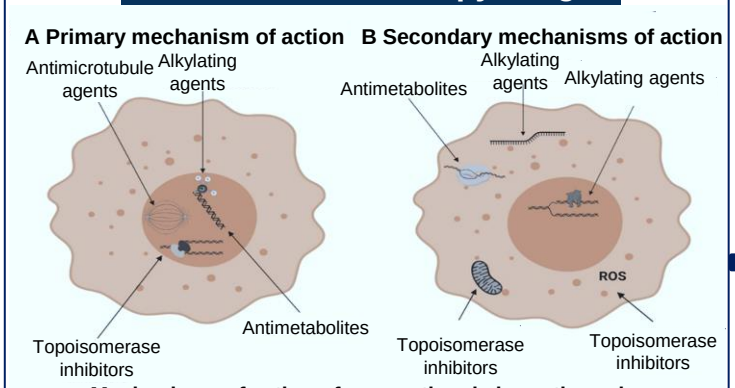
Shifting Treatment Paradigm and Emergence of New Modalities	As a global trend, targeted therapy and immunotherapy drugs with improved clinical efficacy and safety are increasingly used as standard treatments alongside chemotherapy, improving the clinical efficacy and safety of more traditional therapies. These emerging treatment modalities have the potential to change the treatment paradigm for many cancer indications. On the other hand, with the innovation of the structure or dosage form of chemotherapy drugs themselves, emerging chemotherapy drugs gradually replace traditional chemotherapy drugs and become the main treatment drugs for oncology in the future.
Increasing Use of Combination Therapy.	Combination therapy, which uses two or more therapies with distinct mechanisms of actions, has become increasingly common as it can target cancers from multiple approaches simultaneously with potentially superior efficacy relative to monotherapies. The development of novel treatment modalities is expected to result in a greater number and variety of combination treatments.
Precision Medicine	Due to tumor heterogeneity, precision medicine tailored to each patient is critical for effective cancer treatment. Advances in genomic profiling have enabled more accurate characterization of a patient's tumor. This, combined with a deeper understanding of disease biology, has empowered the development of precision oncology treatments, highlighted by an increasing number of targeted therapy and immunotherapy based on targetable biomarkers. Some of these biomarker-driven therapies have demonstrated robust clinical benefits across multiple tumor types that share the same genomic alterations, leading to broad indication approvals, such as PD-(L)1 inhibitors that target patients with certain immunotherapy biomarkers. Rapidly evolving genomic technologies are expected to accelerate the translation of biomarker discoveries into novel targeted therapy and immunotherapy that may continue to transform treatment paradigm.
Managing Cancer as a Chronic Disease	With therapeutic advances over the years, many cancers can now be controlled with treatments for months or even years. Patients previously without effective treatments, especially those diagnosed at an advanced stage, are now more likely to benefit from increasing treatment options. The need for managing cancer as a chronic disease effectively calls for innovative therapies with optimized balance between safety and efficacy, as well as differentiated mechanisms of action that may overcome drug resistance to existing treatments to prolong disease control.

Source: Frost & Sullivan Analysis

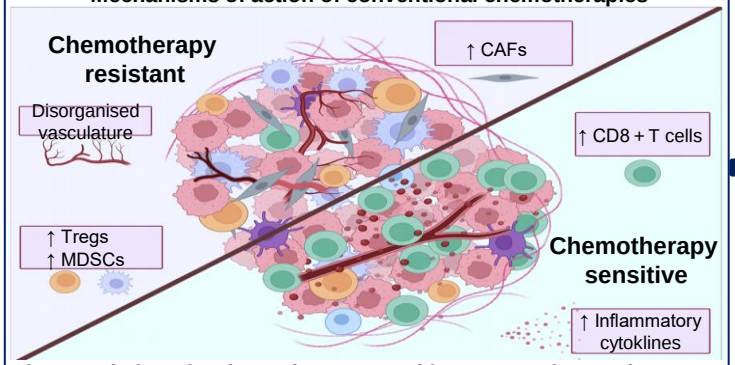
Overview of Chemotherapy Drug

- Chemotherapy is the core method of current cancer treatment and is a systemic treatment method that is different from surgery and radiotherapy. Chemotherapy drugs use their own cytotoxicity to inhibit actively dividing tumor cells, thereby inhibiting tumor growth and killing some tumor cells. Regardless of the route of administration, chemotherapy drugs will spread to most organs and tissues throughout the body through blood circulation, inhibiting or killing tumor cells. In many localized cancers, chemotherapy before or after surgery and/or combined with radiotherapy can provide durable, long-term survival benefits for many patients. Besides, the intracellular (factors at the individual cell level) and cell extrinsic (factors within the tumor microenvironment) are drivers of chemotherapy sensitivity or resistance, and the immune system is a critical determinant of chemotherapy response.

MOA of Chemotherapy Drugs



Mechanisms of action of conventional chemotherapies



Characteristics of a chemotherapy sensitive tumor microenvironment

Development of Chemotherapy Drugs

1910s
Development of the first rodent transplantable tumor system

1940s
Discovery of actinomycin D, cyclophosphamide, nitrogen mustard and methotrexate

1

2

3

4

5

1900s
Treatment of syphilis with a rabbit model

1930s
Establishment of NCI; Birth of hormone therapy

1950s
Discovery of thioguanine, 5-FU, and 6-mercaptopurine; Cure of choriocarcinoma and testicular cancer; Establishment of CCNSC;

1960s
Discovery of vinca alkaloids and natulane; Cure of acute childhood leukemia and hodgkin's disease

1990s
Synthesized new drugs, such as taxanes, etc.

2020s to present
Development of epothilones, Utidelone got approved by NMPA; Decline in cancer mortality

6

7

8

9

10

1970s
Cure of DLBCL; Pass of The National Cancer Act; Exploration of adjuvant chemotherapy; Development of drug screening system

2010s
Exploration of PD-1, PD-L1 and ADC Drugs in combination with chemotherapy drugs; Exploration of administration of chemo drugs

Source: Frost & Sullivan Analysis

Classification of Chemotherapy Drugs

- Chemotherapy drugs are broad-spectrum anti-tumor drugs. They can be divided into five categories according to their principles of action. They inhibit cell division in different ways, thereby killing tumor cells.

Drug Type	MOA	Main Drugs & Approved date	Main Indications
microtubule Inhibitors	By inhibiting the polymerization or depolymerization of microtubules, causing them to be unable to perform their normal functions, thereby inhibiting the division of tumor cells.	Paclitaxel(1992), docetaxel(1995), utidelone(2021), eribulin(2010), ixabepilone(2007), vinorelbine(1994)	Breast cancer, non-small cell lung cancer, gastric cancer, esophageal cancer, prostate cancer
Alkylating agent	By destroying DNA molecules, cross-linking occurs between bases, thereby preventing tumor cells from dividing.	Cisplatin(1978), carboplatin(1989), oxaliplatin(1996), cyclophosphamide(1959), nitrogen mustard(1960s), carmustine(1977)	Non-small cell lung cancer, esophageal cancer, ovarian cancer, cervical cancer
Antimetabolites	Prevent tumor cells from dividing by inducing DNA depletion, or causing DNA structural abnormalities by inserting DNA.	Fluouracil(1962), capecitabine(1998), gemcitabine(1995), pemetrexed(2004)	Gastric cancer, colorectal cancer, breast cancer, ovarian cancer, lung cancer, cervical cancer
Anti-tumor Antibiotics	Affects DNA synthesis and replication by inserting DNA strands or producing superoxide, causing DNA strand breaks and preventing tumor cells from dividing.	Doxorubicin(1974), epirubicin(1999), pirarubicin(1988), mitomycin(1974)	Breast cancer, lung cancer, stomach cancer, colorectal cancer, esophageal cancer, liver cancer
Topoisomerase Inhibitor	By inhibiting the activity of topoisomerase, it prevents the unwinding and supercoiling of DNA, preventing the normal transcription and replication of tumor cell DNA.	Hydroxycamptothecin(1998), irinotecan(1996), topotecan(2007), etoposide(1983)	Non-small cell lung cancer, gastric cancer, esophageal cancer, small cell lung cancer, ovarian cancer

Source: Literature Review, Frost & Sullivan Analysis

Dosage Form Iteration of Chemotherapy Drugs

- In the research and development of pharmaceutical preparations, the same drug often has different dosage forms, or different excipients and preparation processes, and its clinical effects or toxic and side effects will be significantly different. Therefore, selecting appropriate dosage forms, designing reasonable prescriptions and processes, effectively improving clinical efficacy and bioavailability, and reducing side effects are important tasks in the research and development of new drugs. Dosage form optimization can change the properties of the drug in many aspects, such as changing the drug's action properties, speed of action, reducing toxic and side effects, etc.
- The above problems are particularly prominent in chemotherapy drugs, so a variety of different dosage forms of chemotherapy drugs have been produced, which not only facilitate the clinical use of chemotherapy drugs, but also meet different clinical needs. While it is convenient for storage, transportation and use, it can also reduce toxic and side effects to a certain extent.

Development of Paclitaxel Drug Dosage Forms

Liposomal paclitaxel was approved by the NMPA for marketing in China in 2003.

- The drug uses a phospholipid bilayer structure composed of phospholipids, cholesterol, etc. to wrap paclitaxel to improve water solubility without adding polyoxyethylene castor oil. This dosage form solves the solubility problem of paclitaxel.
- Although liposomal paclitaxel significantly reduces the toxic and side effects compared with paclitaxel injection, it still does not completely solve the allergic problem, and cumbersome pretreatment is still required in clinical practice.

Liporaxel, the only oral paclitaxel in the world, was developed by South Korea's Dahua and was approved for marketing in South Korea in 2016.

- Oral paclitaxel does not require anti-allergic treatment before administration and is the latest dosage form of paclitaxel. Oral dosage forms have the advantages of convenient and painless clinical use, and are widely used clinically. Compared with injections, oral chemotherapy drugs have shown excellent convenience and high acceptance in clinical practice. They are suitable for the treatment of many cancers and have great potential to be widely used around the world.

High Bioavailability & High Safety

Injectable paclitaxel (albumin-bound) was approved in China in 2013 for the treatment of metastatic breast cancer.

- It uses patented nanotechnology to combine paclitaxel and nano-albumin particles, which greatly reduces side effects and prolongs the action time. It is a new generation of paclitaxel preparation and has great advantages in clinical application. Human albumin not only serves as a carrier for paclitaxel but also plays a stabilizing role, increasing its water solubility. Nano-albumin-paclitaxel does not contain polyoxyethylene castor oil and does not require hormone pretreatment at all. Its in vivo pharmacokinetic characteristics are also different from traditional paclitaxel, the tolerated dose is greatly increased, and the therapeutic effect is significantly improved.

Paclitaxel polymer micelles were approved in 2021.

- It is a new dosage form of paclitaxel that can effectively avoid the sensitization problem of ordinary paclitaxel. There is no need for any anti-allergic and antiemetic pretreatment before clinical infusion, and it is highly safe. And compared with ordinary paclitaxel injection combined with cisplatin, paclitaxel micelles combined with cisplatin achieved significant clinical benefits in objective response rate and progression-free survival. In addition, when the clinical dosage is significantly increased, paclitaxel polymer micelles have a relatively better safety profile.

Source: Frost & Sullivan Analysis

Growth Drivers and Future Trends of Chemotherapy Drugs Market-I

Expanding Patient Pool	The incidence of overall cancers in China continues to increase. The incidence in China was 4.81 million in 2022, with a CAGR of 2.9% from 2018 to 2022. It is expected that the incidence of overall cancers in China will reach 5.79 million in 2030.
Significant Unmet Medical Needs	It became evident that there is a substantial demand for chemotherapy drugs, as other therapies often require combination with them to achieve optimal therapeutic effects. For example, a majority of China's PD-(L)1 antibodies are approved for the combination uses with chemotherapy drugs to be effective.
Increasing R&D Investments	Domestic pharmaceutical R&D expenses maintain steady and sustained growth. From the statistical domestic R&D expenses of pharmaceutical companies, the cumulative R&D investment of Chinese pharmaceutical companies in 2022 is 32.6 billion US dollars. It is expected that the cumulative R&D investment of Chinese pharmaceutical companies will reach 67.5 billion RMB in 2030, with a CAGR of 9.5%. The stable R&D investment of domestic pharmaceutical companies reflects the market's expectations for the industry.

Source: Frost & Sullivan Analysis

Growth Drivers and Future Trends of Chemotherapy Drugs Market-II

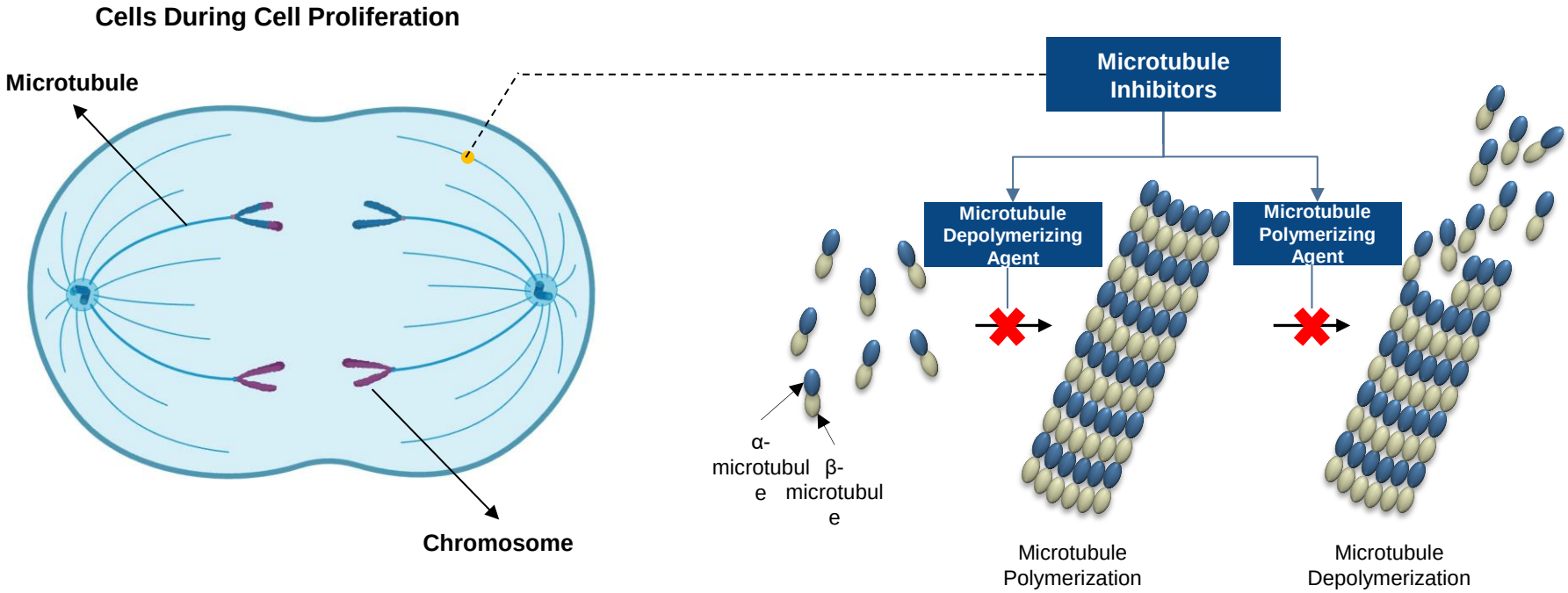
Regulatory Reform and Favorable Government Policies	In 2023, China issued a number of policies to benefit the development of innovative medicines. The "Action Plan for the High-Quality Development of the Pharmaceutical Industry (2023-2025)" （《医药工业高质量发展行动计划（2023-2025年）》） highlights the need to concentrate on the challenging, time-consuming, and expensive aspects of pharmaceutical R&D and innovation. It also calls for full-chain support, encouragement and guidance for leading pharmaceutical companies to expand and thrive, and an improvement in the degree of industry concentration and market competitiveness. With the release of the "Working Procedures for Review and Approval of Drug Conditional Approval for Marketing Applications (Trial) (Revised Draft for Comments)" 《药品附条件批准上市申请审评审批工作程序（试行）（修订稿征求意见稿）》by the NMPA, a fresh avenue for restructuring the supply side of innovative medicines was also established. The NMPA issued a notice on the "Center for Drug Evaluation to Accelerate the Review of Innovative Drug Marketing License Applications (Trial)" 《药审中心加快创新药上市许可申请审评工作规范（试行）》, which will accelerate innovation through early intervention, research and review linkage, rolling submission, and proactive verification and inspection work. Review of drug marketing applications. On the policy front, policies supporting innovative drugs are still positive. These policies aim to encourage innovative approaches to research and development for children's and rare disease drugs, as well as help speed up the review and approval of innovative drug varieties.
Increasing Affordability and Healthcare Awareness	China’s per capita disposable income increased from RMB28,228 in 2018 to RMB36,883 in 2022. It is projected to reach RMB64,745 by 2030, with a CAGR of 7.3% from 2022. This increase, along with growing health awareness, is expected to enhance residents’ ability to pay for healthcare.

Source: Frost & Sullivan Analysis

Overview of Microtubule

- Microtubules are the basic tissue components of eukaryotic cells and are mainly composed of α-microtubule and β-microtubule. These structures primarily exist as cytoplasmic microtubules within the cell's cytoplasm, where they are arranged in a network or bundled formation. Microtubules can adapt to cell changes through the assembly and disassembly of their subunits, assemble with other proteins into structures such as spindles, centrioles, and flagella, and participate in the maintenance of cell morphology, intracellular movement, and cell division.
- Mitosis is the process by which eukaryotic cells divide the chromosomes in their nucleus into two daughter nuclei. Microtubules polymerize into spindles in the early stages of cell division, and the spindles pull chromosomes to move to two levels during mitosis and enter the two daughter cells to complete cell proliferation. At the end of mitosis, spindle microtubules depolymerize and reassemble into cytoplasmic microtubules. The dynamic changes (polymerization and depolymerization) between microtubule and microtubules play an important role in normal cell mitosis.

Mechanism of Action of Microtubule Inhibitors



Source: Literature Review, Frost & Sullivan Analysis

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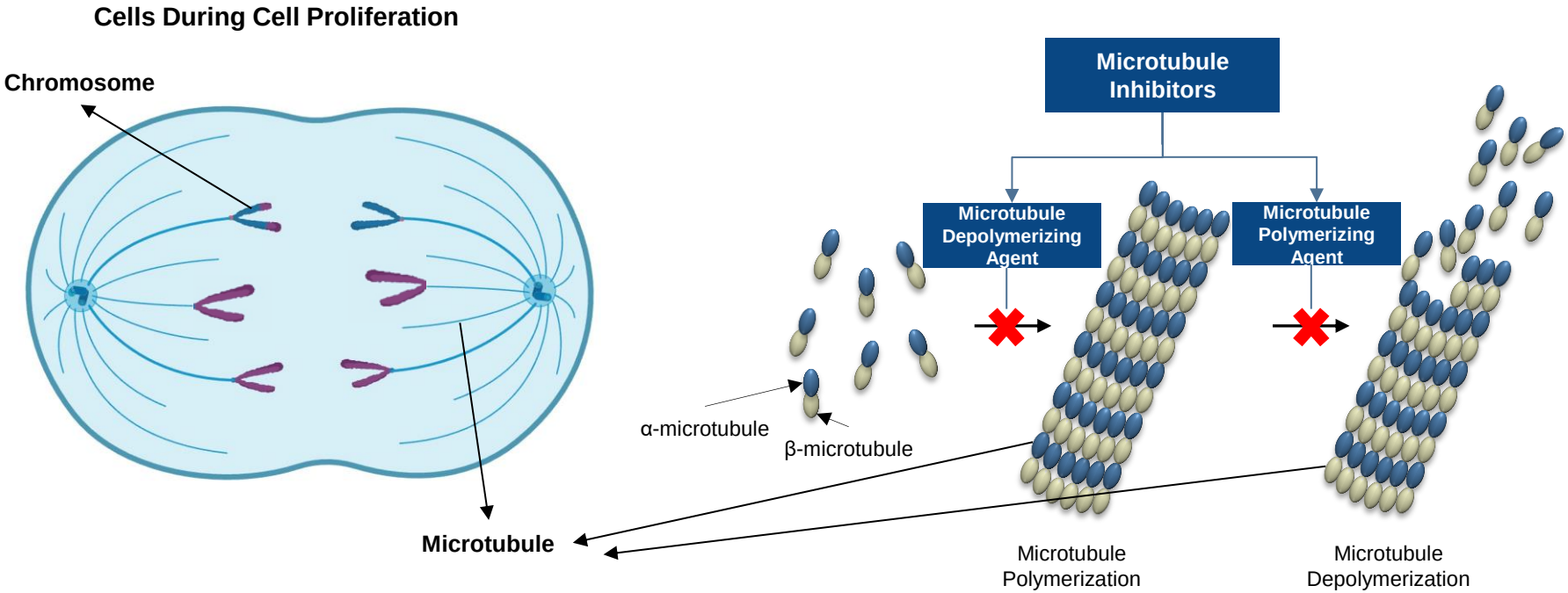

Source: Literature Review, Frost & Sullivan Analysis

Overview of microtubule Inhibitors

- microtubule inhibitors are a class of anti-tumor chemotherapy drugs that can inhibit tumor proliferation by inhibiting cell mitosis. microtubule inhibitors have a wide range of clinical applications and currently play a central role in the treatment of various cancers, such as ovarian cancer, breast cancer, and lung cancer.
- According to different mechanisms of action, microtubule inhibitors can be divided into (1) Microtubule depolymerizing agent, which promote microtubule polymerization, mainly including taxanes, epothilones, etc. (2) Microtubule polymerizing agent, which inhibit microtubule polymerization, mainly include eribulin, etc.

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- microtubule inhibitors can effectively inhibit cell mitosis by inhibiting the polymerization of microtubule or inducing microtubule to form a hyperstable state, ultimately arresting the cell cycle and leading to apoptosis. They have a strong effect on rapidly dividing tumor cells. inhibitory effect. Among them, taxanes are an important category of microtubule inhibitors. They have strong anti-tumor effects and are commonly used clinical chemotherapy drugs. Epothilones not only bind to the same site as paclitaxel, but also bind to other sites, further inhibiting microtubule formation. Epothilones are more active than taxanes, and clinical studies have shown that they are still effective in taxane-resistant advanced cancers.

Source: Literature Review, Frost & Sullivan Analysis

Overview of microtubule Inhibitors - Epothilone Drug

Compared with Other Chemotherapy Drugs

- **Anti-tumor Mechanism:** microtubule inhibitors affect all rapidly dividing cells by disrupting the formation and depolymerization of microtubules. Therefore, it exerts anti-tumor effects by inhibiting the proliferation of cancer cells that proliferate faster than most normal cells.
- **Indications:** As an important class of chemotherapy drugs, microtubule inhibitors are widely used to comba various cancer diseases such as non-small cell lung cancer, ovarian cancer, breast cancer, esophageal cancer, head and neck cancer, and have shown good efficacy.
- **Main Categories:** Representative microtubule inhibitors include paclitaxel, epothilones, etc. Paclitaxel is considered to be one of the most effective naturally derived anti-tumor chemotherapy drugs currently known. It can inhibit most solid tumors, and is especially effective against breast cancer, ovarian cancer, non-small cell lung cancer and other cancers.

Epothilone Drug

- **Anti-tumor Mechanism:** The mechanism of action of epothilone drugs is similar to that of paclitaxel, but it has a stronger inhibitory effect on cancer cells, and tumor cells that are resistant to paclitaxel still have high activity.
- **Clinical Performance:** In clinical trials, epothilone drugs still show good clinical effects on many tumors that have developed drug resistance. For example, the new microtubule inhibitor Utidelone has better clinical efficacy than previous second-line chemotherapy drugs. It can significantly prolong the survival of anthracycline- and taxane-resistant breast cancer patients with good safety, providing a new treatment option for patients with advanced cancer. Compared with capecitabine monotherapy, Utidelone combined with capecitabine extended the progression-free survival (PFS) from 4.1 months to 8.4 months and the overall survival (OS) from 15.7 months to 20.9 months, showing great clinical potential.

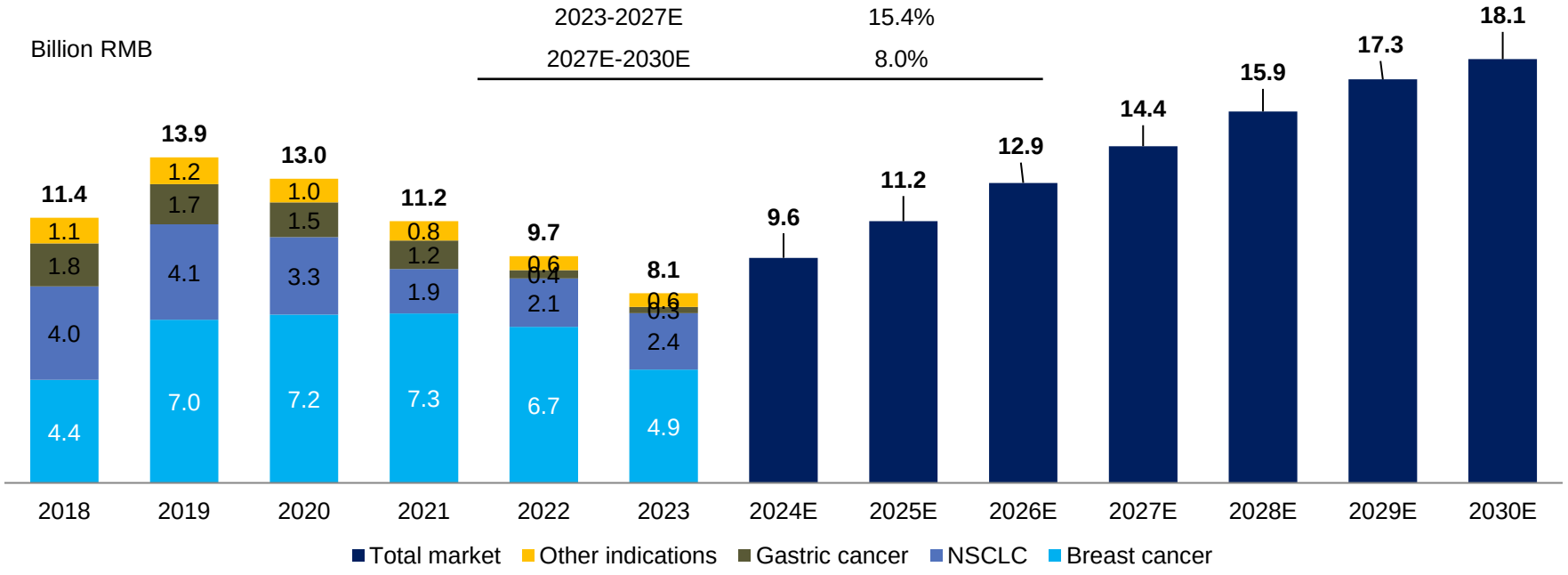
Source: Literature Review, Frost & Sullivan Analysis

microtubule Inhibitor Drug Market in China, 2018-2030E

- From 2018 to 2019, China's microtubule inhibitor market has grown steadily, reaching RMB 13.9 billion in 2019. With the implementation of the VBP policy on microtubule inhibitor drugs, especially taxane drugs, in 2020, the prices of related drugs have dropped significantly, and the market size has begun to gradually decline, reaching 8.1 billion RMB in 2023. With the gradual stabilization of the microtubule inhibitor market for drugs included in VBP, and the launch of new microtubule inhibitors such as Utidelone and new dosage forms of drugs, China's microtubule inhibitor market will gradually grow. It is expected to reach RMB 18.1 billion by 2030, with a CAGR of 8.0% from 2027 to 2030.

microtubule inhibitor drug market in China, 2018-2030E

Period	CAGR
2018-2023	-6.5%
2023-2027E	15.4%
2027E-2030E	8.0%



Source: Frost & Sullivan Analysis

Unmet Needs for Approved microtubule Inhibitor Chemotherapy Drugs

Drug Resistance	Chemotherapy drugs are generally more effective in the early stages of cancer. However, as time goes by, tumors continue to adapt to the drugs and will gradually develop drug resistance and sensitivity to the drugs. As a result, the efficacy of chemotherapy drugs is reduced or even ineffective. For the treatment of advanced cancer, when tumor resistance appears, multiple chemotherapy drugs are often used in clinical practice, but the efficacy is generally unsatisfactory.
Serious Side Effects	Chemotherapy drugs are not targeted and act on cells throughout the body. While killing cancer cells, they also impose a greater burden on patients and can cause a variety of serious side effects. Cancer patients in advanced stages of treatment are often forced to reduce the dose of treatment because they cannot accept the severe side effects, which affects the treatment effect.
Single Dosage Form	Currently, the main microtubule inhibitors are taxanes. The formulation of polyoxyethylated castor oil (Cremophor EL) and absolute ethanol for paclitaxel injection has been used clinically. However, there are side effects such as peripheral neuropathy, hypotension, and hypersensitivity, which limit the clinical application of paclitaxel. The emergence of new dosage forms such as paclitaxel albumin and paclitaxel liposomes has alleviated allergic reactions to a certain extent, but safety issues still exist and the response rate still needs to be improved. At present, microtubule inhibitors are mainly injections, and the injection time is generally long. For example, paclitaxel drugs are infused intravenously for at least 3 hours. Prolonged injections are inconvenient for clinical use and put a strain on the medical system.

Source: Frost & Sullivan Analysis

Classification and Comparison of Approved microtubule Inhibitor Chemotherapy Drugs in China – I

microtubule inhibitors are important chemotherapy drugs, among which taxanes are an important category of microtubule inhibitors. Due to its strong anti-cancer effect, it is widely used in the treatment of many cancers, such as breast cancer, lung cancer, gastric cancer, esophageal cancer, etc. It occupies an extremely important position among microtubule inhibitors. Utidelone is the first and only national Class 1 innovative drug for microtubule inhibitors independently developed by a domestic company. Except for Utidelone, no other microtubule inhibitors with new molecular structures have been successfully approved in China, the United States, Japan, Europe and Australia in the past 10 years (eribulin was approved by the FDA in 2010 and NMPA in 2019, so its The approval of NMPA does not constitute the approval of a new molecular structure microtubule inhibitor).

Approved microtubule Inhibitor Chemotherapy Drugs in China - I

Category	Generic Name	Company[2]	Approval Date	Main Indications	NRDL Inclusion	2023 Reven Billion RM
Taxanes	Paclitaxel	BMS	1996	Ovarian cancer, breast cancer, non-small cell lung cancer, Kaposi sarcoma	Class A	7.0
	Docetaxel	Sanofi	1997	Breast cancer, non-small cell lung cancer, gastric cancer, prostate cancer	Class B	
	Paclitaxel liposomes	Luye pharma	2003	Ovarian cancer, breast cancer, non-small cell lung cancer	Class B	
	Paclitaxel (albumin-bound)	Celgene/Beigene	2008	Breast cancer	Class B	
	Paclitaxel polymer micelles	Yizhong Pharmaceutical	2021	Non-small cell lung cancer	NA	

Source: NMPA, Frost & Sullivan Analysis

Classification and Comparison of Approved microtubule Inhibitor Chemotherapy Drugs in China – II

Approved microtubule Inhibitor Chemotherapy Drugs in China - II

Category	Generic Name	Company[2]	Approval Date	Main Indications	NRDL Inclusion	2022 Reve Billion R
Epothilones	Utidelone	Biostar Pharmaceutical	2021	Breast cancer	Class B	0.1
Halichondrin B	Eribulin	Eisai	2019	Breast cancer	Class B	0.1
Vinca Alkaloids	Vinblastine	Eli Lilly	1996[3]	Hematological and solid tumors	NA	1.0
	Vincristine	Eli Lilly	1982[3]	Hematological and solid tumors	Class A	
	Vindesine	Sanofi	1995[3]	Malignant tumors	Class B	
	Vinorelbine	Pierre Fabre	1999[3]	Breast cancer, non-small cell lung cancer	Class B	
	Vinorelbine (soft capsules)	Pierre Fabre	2014[4]	Breast cancer, non-small cell lung cancer	Class B	

Note: 1. As of Dec 31, 2023

2. Only original companies are included

3. Some products have been on the market for a long time, and only the earliest traceable approval time is marked.

4. The generic drug of vinorelbine soft capsules was approved in 2006 before the original drug, and the original drug was approved in China in 2014.

Source: NMPA, Frost & Sullivan Analysis

Classification and Comparison of Approved microtubule Inhibitors

Category	Binding Site & MOA	Raw material & manufacture method	Indication	Water Solubility	Others
Utidelone	Both in taxane pocket of the subunit of β-microtubule m-loop, but their binding sites with microtubule are different. Prevent the depolymerization of microtubules and thus prevent the progression of cells through the m-phase of the cell cycle.	• Raw material：soy peptone, sugar, inorganic salt, and buffer • Manufacture method：biosynthesis, a more efficient and environmentally friendly method than other current manufacture methods	• breast cancer	• water solubility problem has been solved through formulation technology, and the oral capsule that has shown good bioavailability is in the clinical development stage	• not p-glycoprotein substrate drugs, meaning less likelihood of developing resistance during treatment • has the ability to cross blood-brain barrier, showing potential efficacy in brain metastases of solid tumors and brain tumors that currently lack treatment options
Other Epothilones (Ixabepilone)		• Raw material：chemical raw materials, and metabolism of the cellulose-degrading myxobacterium, Sorangium cellulosum • Manufacture method：semi-synthesis	(Only approved in US) • breast cancer	• very slight water solubility but not yet developed as an oral formulation	• not p-glycoprotein substrate drugs, showed potent cytotoxic activity toward paclitaxel-sensitive and paclitaxel-resistant cells expressing P-glycoprotein or mutant tubulin • may have potential to cross blood-brain barrier • abandoned the tedious process, and the production cost is reduced
Taxanes (Paclitaxel, docetaxel)		• Raw material：natural yew • Manufacture method：direct extraction from natural yew or semi-synthesis based on intermediates in natural yew	• breast cancer • non-small cell lung cancer • gastric cancer • prostate cancer • ovarian cancer • kaposi sarcoma • prostate cancer	• poor water solubility makes it difficult to be formulated into oral dosage forms, with poor bioavailability of marketed oral liquid	• p-glycoprotein substrate drugs, and drug resistance is likely to develop during treatment • poorly penetrate the blood-brain barrier, showing little efficacy against brain metastases and brain tumors • the most widely approved microtubule inhibitors with multiple innovative dosage forms, among which paclitaxel liposomes have rare allergic reactions and have good safety
Vinca Alkaloids (Vinblastine, Vincristine, Vindesine, Vinorelbine)	The vinca site is at the interface between α and β heterodimers in a head-to-tail arrangement. Prevent the polymerization of microtubules and thus prevent mitosis.	• Raw material：Catharanthus roseus • Manufacture method：direct extraction from natural Catharanthus roseus or semi-synthesis based on intermediates in natural Catharanthus roseus	• hematological • malignant tumors • breast cancer • non-small cell lung cancer	• some drugs are water soluble but poor bioavailability of marketed oral soft capsule	• p-glycoprotein substrate drugs, and drug resistance is likely to develop during treatment • poorly penetrate the blood-brain barrier, showing little efficacy against brain metastases and brain tumors • variety of drugs have been approved, some of which are effective against blood tumors
Halichondrin B (Eribulin)	Halichondrin B binds microtubule at a site close to the vinca site altering depolymerization. Prevent the polymerization of microtubules and thus prevent mitosis.	• Raw material：chemical raw materials and intermediates • Manufacture method：chemical synthesis	• breast cancer	• water soluble but has not yet been developed into an oral dosage form	• p-glycoprotein substrate drugs, and drug resistance is likely to develop during treatment • poorly penetrate the blood-brain barrier, showing little efficacy against brain metastases and brain tumors • inhibits tumor cells with beta-tubulin mutations, which help overcome drug resistance of taxanes caused by genetic alterations

Note: 1.Only anti-oncology approved microtubule Inhibitors are included

2. Chemotherapy drugs usually require 6-8 cycles of treatment. Annual Cost is estimated as 2023 median treatment cost for breast cancer in China, with basis on original drug's price.

The median treatment cost was estimated based on an assumed average body surface area of 1.6 square meters and eight treatment cycles per year, without consideration to medical insurance and free medication.

Vinblastine, Vincristine, and Vindesine listed in China are not produced by the original manufacturer. Therefore, their annual costs are not available.

The import, sale and use of Celgene/Beigene's paclitaxel for injection (albumin bound) were suspended by NMPA until 2024.

Source: Literature Review, Frost & Sullivan Analysis

Classification and Comparison of Approved microtubule Inhibitor Chemotherapy Drugs in US - I

The microtubule inhibitor drugs marketed in the United States are mainly taxanes, epothilones, spongiolides and vinca alkaloids, all of which have been on the market for a long time. Taxane drugs are widely used in clinical applications and are suitable for various cancers including breast cancer, non-small cell lung cancer, and gastric cancer.

Approved microtubule Inhibitor Chemotherapy Drugs in US - I

Category	Generic Name	Company[2]	Approval Date	Main Indications
Taxanes	Paclitaxel	BMS	1992	Breast cancer, ovarian cancer
	Docetaxel	Sanofi	1996	Breast cancer, non-small cell lung cancer, gastric cancer, prostate cancer
	Paclitaxel (albumin-bound)	Celgene	2005	Breast cancer, non-small cell lung cancer, pancreatic cancer
	Cabazitaxel	Sanofi	2010	Prostate cancer
Epothilones	Ixabepilone	BMS	2007	Breast cancer

Source: FDA, Frost & Sullivan Analysis

Classification and Comparison of Approved microtubule Inhibitor Chemotherapy Drugs in US - II

Approved microtubule Inhibitor Chemotherapy Drugs in US - II

Category	Generic Name	Company[2]	Approval Date	Main Indications
Halichondrin B	Eribulin	Eisai	2010	Breast cancer, liposarcoma
Vinca Alkaloids	Vinblastine	Eli Lilly	1965[3]	Hematological and solid tumors
	Vincristine	Eli Lilly	1963[3]	Hematological and solid tumors
	Vindesine	Sanofi	1995[3]	Malignant tumors
	Vinorelbine	Pierre Fabre	1994[3]	Non-small cell lung cancer

Note: 1. As of Dec 31, 2023

2. Only original companies are included

3. Some products have been on the market for a long time, and only the earliest traceable approval time is marked.

Source: FDA, Frost & Sullivan Analysis

microtubule Inhibitor Chemotherapy Drugs Under Phase III Development in China

Molecular screening of new chemotherapy drugs is difficult, and it is extremely difficult to control side effects while ensuring clinical effects. Therefore, the development cycle of chemotherapy drugs is long. Paclitaxel has been developed for nearly 30 years since its discovery. Chemotherapy drugs under research in China in the past 10 years have mainly been improved dosage forms of already marketed molecules, and very few Chinese pharmaceutical companies have successfully developed new chemotherapeutic molecules.

microtubule Inhibitor Chemotherapy Drugs Under Phase III Development in China

Drug name	Company	Indication	Dosage Form	Clinical Stage	First Post Date
Cabazitaxel	Sanofi	Prostate cancer	Injection	Phase III	2016-03-18

Note: 1. As of Dec 31, 2023
2. Only innovative molecules are included.
3. DHP107 (Liporaxol) was only approved for marketing in South Korea in 2016.
Source: CDE, Frost & Sullivan Analysis

microtubule Inhibitor Chemotherapy Drugs Under Phase III Development Globally

Currently, the global microtubule chemotherapy drugs under development are mainly improved dosage forms of already marketed molecules, while there are fewer new microtubule inhibitors with innovative molecules.

microtubule Inhibitor Chemotherapy Drugs Under Phase III Development Globally

Drug name	Company	Indication	Dosage Form	Clinical Stage	First Post Date
There are currently no microtubule inhibitor chemotherapy drugs are actively under phase III development globally.					

Note: 1. As of Dec 31, 2023

2. Only innovative molecules are included.

Source: Clinical Trials, Frost & Sullivan Analysis

Future Opportunities and Challenges of microtubule Inhibitor Chemotherapy Drugs

Policy Support

China has promulgated a number of industrial policies to support and encourage innovative drug research and development in recent years, including the Pharmaceutical Industry Development Planning Guidelines, Healthy China 2030, and the "14th Five-Year Plan" National Drug Safety and Promotion of High-Quality Development Plan. It provides support to biopharmaceutical companies from various aspects such as systems, finance, taxation, technology, approval and talent, and helps the innovative drug market achieve further development. For innovative biopharmaceutical companies that focus on major treatment areas such as tumors, relevant industrial policies are opportunities for R&D innovation and business development.

Growing Number of Cancer Patients

In recent years, China's population is aging at a rate higher than the global level due to multiple factors such as the increase in life expectancy, the decrease in the birth rate, and the improvement of residents' medical and health awareness. As the population ages, the prevalence of cancer in China has gradually increased. In 2022, the number of new cancer cases in China will reach 4.8 million. It is expected that the number of new cancer cases in China will reach 5.8 million by 2030, representing a huge patient population. Therefore, the demand for anti-tumor drugs will continue to increase in the future.

Improved Accessibility

In the field of innovative anti-tumor drugs, including microtubule inhibitors, due to their high research and development costs, drug prices are high and few people can afford them. In recent years, the country has continued to increase medical insurance, and more and more innovative drugs have entered medical insurance, which has greatly improved the accessibility of innovative anti-tumor drugs. With the normalization of national medical insurance negotiations, the speed of China's innovative anti-tumor drugs being included in medical insurance has further increased. The average time from approval to inclusion in medical insurance will gradually decrease, which will better help pharmaceutical companies increase sales after new drugs are launched, allowing companies to recover costs faster and expand other innovative drug pipelines.

Opportunities

Competition Between New Treatment Modalities and Traditional Chemotherapy

Chemotherapy has always been one of the classic methods of tumor treatment due to its wide adaptability to the population and stable therapeutic effect. However, in recent years, with the development of the biomedical industry, many innovative drugs have emerged, which have shown good clinical effects in many cancers. For example, in breast cancer: HER-2, CDK4/6 targeting drugs; in non-small cell lung cancer: EGFR, ALK targeting drugs; and PD-1/L1 monoclonal antibodies and ADC drugs, etc. In the future, with the continuous optimization of these new drugs, competition for chemotherapy will gradually intensify. However, many new therapeutic drugs are mainly targeted at patients with relevant target expression. However, broad-spectrum chemotherapy drugs are still used clinically for patients without relevant targets or those who are resistant to targeted therapy. At the same time, new anti-tumor drugs still need to be combined with chemotherapy drugs in clinical practice to further improve the therapeutic effect. Therefore, the basic status of chemotherapy drugs remains unshakable in a short period of time.

NRDL Price Reduction

After the NRDL adjustment in 2023, a total of 126 new drugs will be included in the NRDL, including 14 anti-tumor drugs, and the average price reduction of drugs will also reach 60%. After their products are launched on the market, innovative drug companies can quickly achieve mass sales of their products by including them in medical insurance. However, they also face price reduction pressure during medical insurance negotiations and bear the risk of declining return on R&D investment. In the United States, the treatment prices of ixabepilone and eribulin are relatively high, with annual treatment costs for patients ranging from $105,000 to $155,000.

Challenges

Source: Frost & Sullivan analysis

Overview on Oral microtubule Inhibitor Chemotherapy Drugs – I

Deficiencies in chemotherapy drug injections

- Low patient compliance
- Safety issues such as serious allergic reactions
- Complicated pre-treatment process

Advantages of oral chemotherapy drugs

Improvement in patient compliance

✓ Oral chemotherapy has the unique advantage of allowing them to take their medication directly at home, with a marked improvement in patient comfort and QoL

Convenience for healthcare workers

✓ For healthcare workers, this means fewer patients to care for, optimization of resources (bed turnover, time allocation, equipment and drugs for IV infusion, etc.), which means more optimal allocation of healthcare resources

Flexibility in dosage adjustment

✓ Oral chemotherapy can be used in combination or as a single agent, offers the convenience of being able to be flexibly adapted to the patient's specific case

Marketed Oral microtubule inhibitor product

marketed product – Liporaxel®

- an oral paclitaxel developed by DAEHWA Pharmaceutical based on the DaeHwa-Lipid bAsed Self-Emulsifying Drug delivery system (DH-LASED), it has been approved for the second-line treatment of advanced and metastatic or local recurrent gastric cancer by the South Korean Ministry of Food and Drug Safety (MFDS)

marketed product – Navelbine®

- an orally available vinca alkaloid developed by Pierre Fabre. It has been approved for the treatment of metastatic breast cancer in China. Pharmacokinetic studies of this agent indicate that it has a large volume of distribution, a long terminal half-life, and a high clearance rate. Navelbine is an effective and well-tolerated agent which can be used in first-line and subsequent metastatic breast cancer settings.

Source: Literature review, Frost& Sullivan Analysis

Overview on Oral microtubule Inhibitor Chemotherapy Drugs – II

Oral microtubule inhibitor drug under development

Oral paclitaxel developed by Athenex rejected by FDA

- Athenex was established in 2003 and listed on Nasdaq in June 2017 with the stock code ATNX. The company is mainly committed to the research, development and commercialization of new anti-cancer drugs.
- 2020.9, Athenex submitted an NDA for oral paclitaxel capsules for the treatment of metastatic breast cancer to the US FDA, and the FDA granted the application priority review.
- 2021.3, the FDA issued a complete response letter (CRL) to the new drug application (NDA) of Athenex's metastatic breast cancer therapy-oral paclitaxel + Encequidar, rejecting the marketing of the therapy. The reason is that the FDA is concerned that oral paclitaxel may increase the safety risk of neutropenia-related sequelae compared with intravenous paclitaxel.
- 2023.5, Athenex filed for voluntary bankruptcy proceedings.

Other Drugs under development (examples)

Drug Code	Company	Explanation
UTD2	Biostar Pharmaceutical	Utidelone has the property of non-P-glycoprotein substrate, which does not bind to P-glycoprotein on the cancer cell membrane, resulting in higher bioavailability, with natural advantage of oral administration
Veru-111	Veru Inc.	At oral doses, VERU-111 had a favorable safety profile as it did not cause neutropenia or myelosuppression, common dose limiting side effects of other classes of commercially available antimicrotubules

Source: Literature review, Frost& Sullivan Analysis

Entry Barriers for microtubule Inhibitor Chemotherapy Drugs

Chemotherapeutic drugs can only be discovered from natural organisms, lacking a standardized screening platform. The current main microtubule inhibitor chemotherapeutic drugs like paclitaxel are extracted from yew, and eribulin is separated from the marine organism sponge.

Entry Barriers for microtubule Inhibitor Chemotherapy Drugs R&D

Chemotherapeutic drugs as a kind of non-targeted therapy can inhibit or kill any rapidly replicating cells in the body such as tumor cells, but at the same time, they can also harm normal cells. The screening and design of chemotherapeutic drugs need to take into account both safety and effectiveness if the treatment window is narrow. In other words, it is difficult to control the patient's blood drug concentration within a safe dose range during treatment. If the concentration is too high, it will cause adverse events. If the concentration is too low, the treatment purpose cannot be achieved. The therapeutic index of most anti-tumor chemotherapy drugs is low, the toxicity is high, the effective concentration is close to the toxic dose, and it is difficult for doctors to control the patient's medication within the effective concentration range. In the process of practice, it is necessary to regularly carry out therapeutic drug monitoring to judge the toxic side effects and effectiveness of the medication and adjust the patient's medication amount. Therefore, screening out a chemotherapeutic drug with excellent anti-tumor efficacy and a suitable treatment window is very difficult. Over the years, only a few microtubule inhibitor drugs have been successfully marketed.

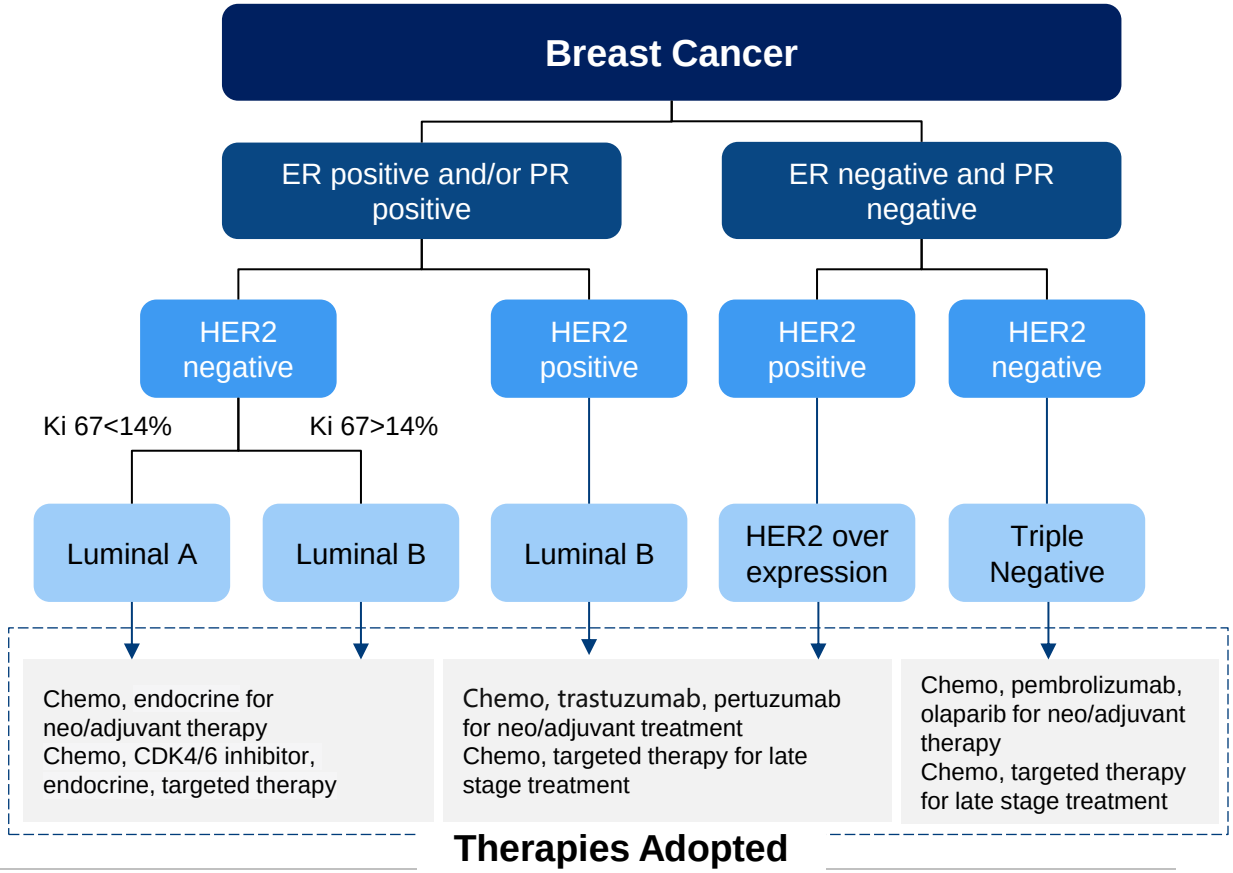
Source: Frost & Sullivan Analysis

Overview of Breast Cancer

- Breast cancer is the most common cancers in women, and the incidence increases year by year. Breast cancer mostly happens in women aged 50. Developing from breast tissue, breast cancer may present as a lump in the breast, a change in breast shape, dimpling of the skin, fluid coming from the nipple, a newly inverted nipple, or a red or scaly patch of skin.
- Besides, breast cancer can be classified into four genotypes based on the expression level of hormone receptors(Estrogen Receptor, Progesterone Receptor) and HER-2.

Risk Factors

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



Source: Literature Review, Frost & Sullivan analysis

Overview of Breast Cancer

Breast Cancer Stages		Stage at diagnosis in China*
Stage 0	• Non-invasive breast cancers such as Ductal Carcinoma In Situ • No evidence of cancer cells or non-cancerous abnormal cells breaking out of the part of the breast in which they started • No invasion of neighboring normal tissue	
Stage 1	• Invasive breast cancers, breaking through to normal surrounding breast tissue, divided into two subcategories • Stage IA: tumor measures up to 2 cm and no spread outside the breast, no lymph nodes involved • Stage IB: small groups of cancer cells found in lymph nodes instead of tumor in the breast or tumor measures larger than 0.2 mm but no larger than 2 mm in the lymph nodes	15.7%
Stage 2	• Invasive breast cancers, divided into two subcategories • Stage IIA: no tumor found in the breast but cancer found in 1-3 axillary lymph nodes, or tumor measures up to 2 cm spread to the axillary lymph nodes, or tumor measures 2-5 cm not spread to the axillary lymph nodes • Stage IIB: tumor measures 2-5 cm and small groups of cancer cells found in the lymph nodes, or cancer cells spread to 1 to 3 axillary lymph nodes or to lymph nodes near the breastbone	44.9%
Stage 3	• Invasive breast cancers, divided into three subcategories, known as Stage IIIA, IIIB and IIIC • Based on the criteria of stage 2, breast cancers of stage III have more axillary lymph nodes affected and the tumor size may measure larger than 5 cm	18.7%
Stage 4	• Invasive breast cancer spread beyond the breast and nearby lymph nodes to other organs of the body, such as lungsm distant lymph nodes, skin, bones, liver or brain	2.4%

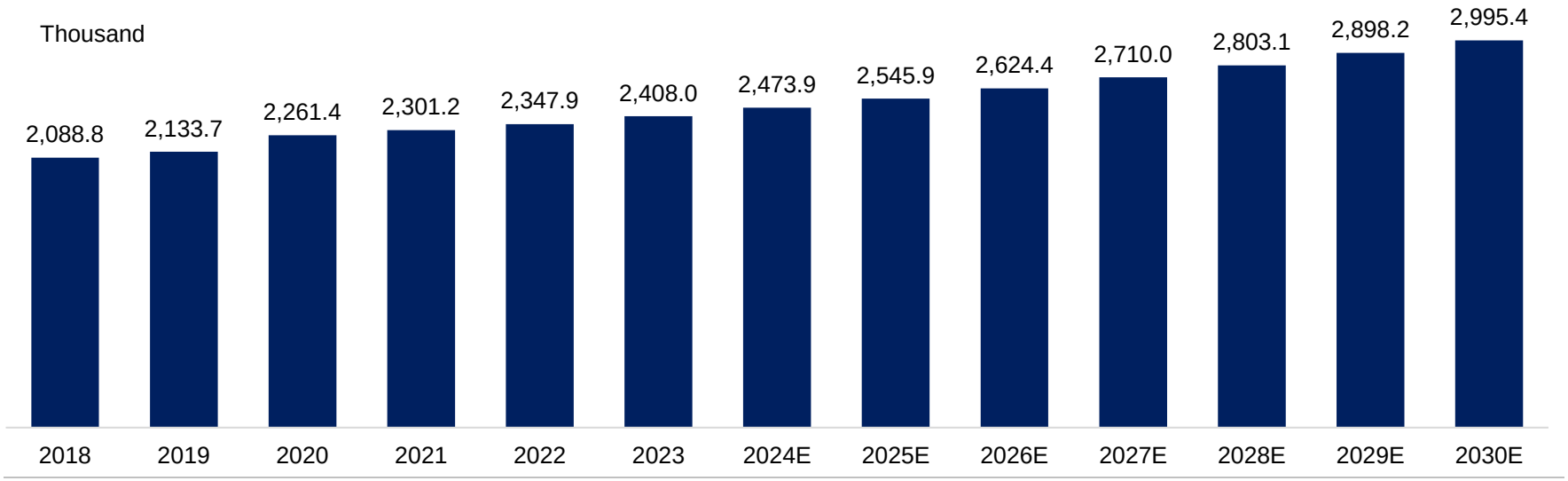
*Source: *Initial diagnosis only, Fan, Lei, et al. "Breast cancer in China." The lancet oncology15.7 (2014): e279-e289 , Frost & Sullivan analysis*

Global Incidence of Breast Cancer, 2018-2030E

- In 2023, 2,408.0 thousand new cases of breast cancer have occurred worldwide. The number is set to grow to 2,995.4 thousand by 2030 with a CAGR of 3.2% from 2023 to 2030. Studies have shown that the proportion of patients who have HR+/HER2- BC and TNBC is around 55% and 15% of the total breast cancer patients globally, with a five-year survival rate of about 12% and 30% for advanced TNBC and advanced HR+/HER2- BC respectively.

Incidence of Breast Cancer Globally, 2018-2030E

Period	CAGR
2018-2023	2.9%
2023-2027E	3.0%
2027E-2030E	3.4%



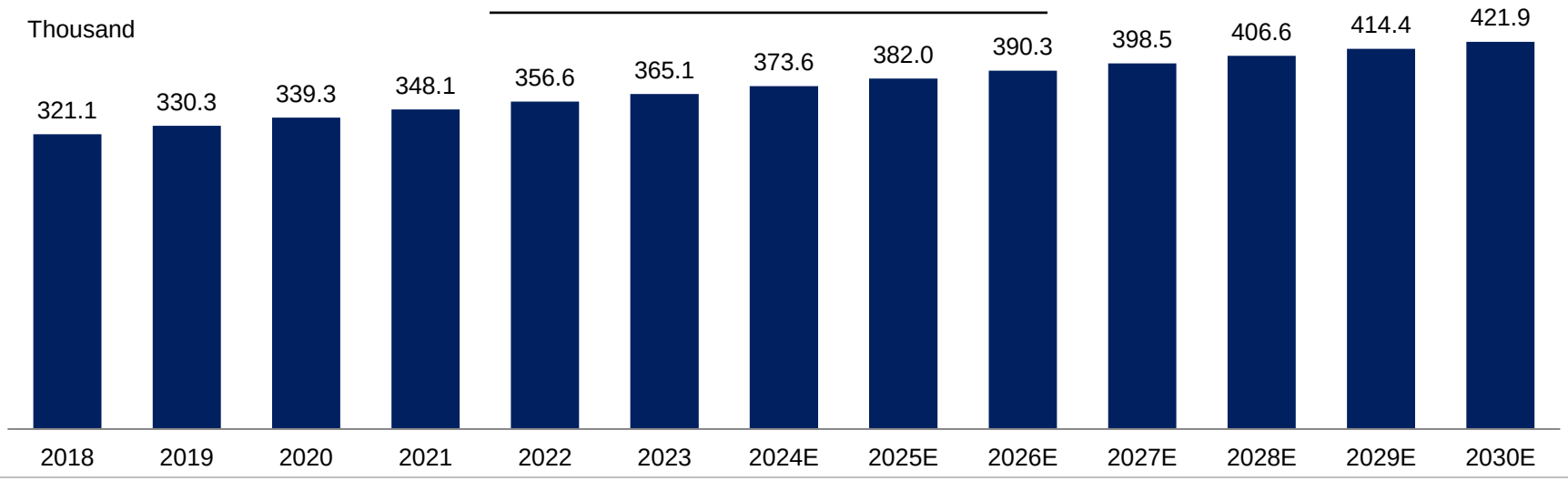
Source: Frost & Sullivan analysis

Incidence of Breast Cancer in China, 2018-2030E

- Breast cancer places as one of the top 10 cancer types ranking by incidence both in China and America. In 2023, 365.1 thousand new cases of breast cancer have occurred in China. The number is set to grow to 421.9 thousand by 2030 with a CAGR of 2.1% from 2023 to 2030.
- Patients with HR+/HER2- BC and TNBC take account around 55% and 15% of the total breast cancer patients in China.
- The growth rate of incidence is slower year by year, which is associated with the raising awareness on cancer management. In addition, the system on controlling the risk factors of breast cancer will be more thorough, which is useful on controlling cancer incidence.

Incidence of Breast Cancer in China, 2018-2030E

Period	CAGR
2018-2023	2.6%
2023-2027E	2.2%
2027E-2030E	1.9%

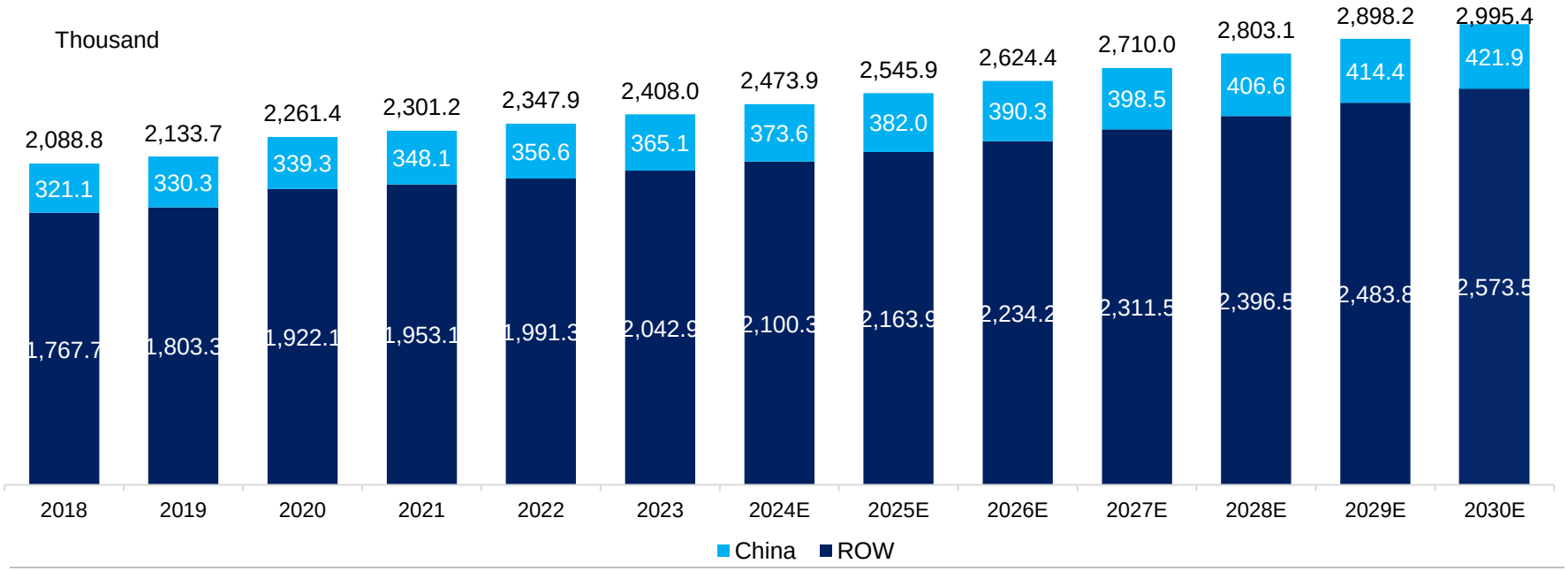


Source: NCCR, Frost & Sullivan analysis

China and Global Incidence of Breast Cancer, 2018-2030E

China and Global Incidence of Breast Cancer, 2018-2030E

CAGR	China	ROW	Total
2018-2023	2.6%	2.9%	2.9%
2023-2027E	2.2%	3.1%	3.0%
2027E-2030E	1.9%	3.6%	3.4%

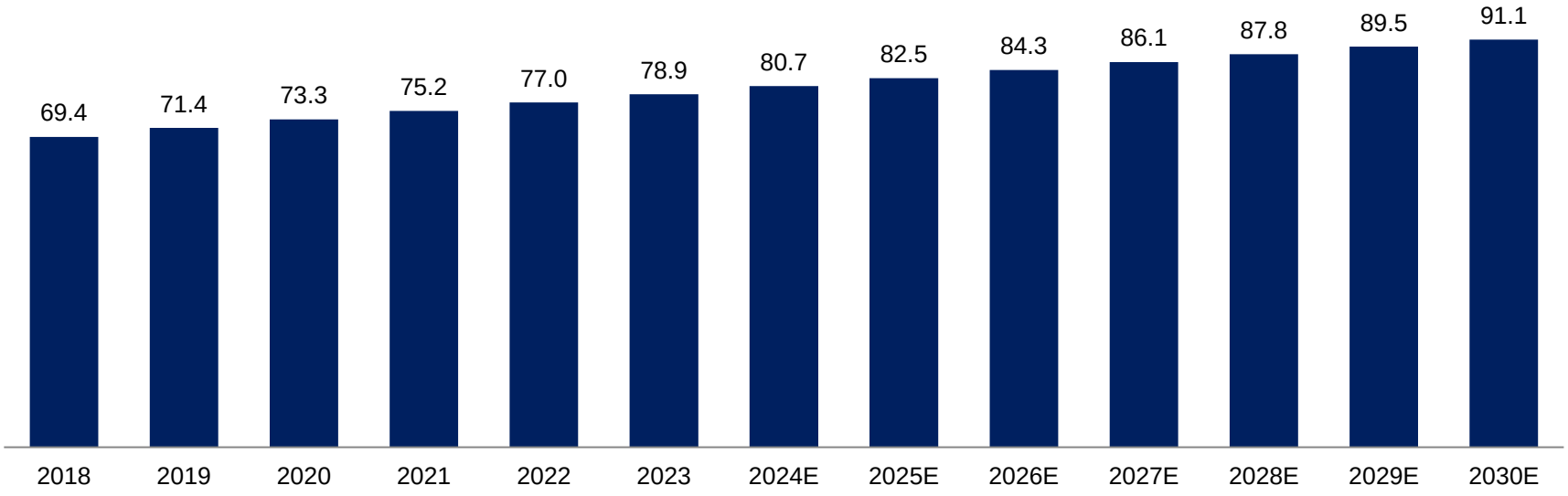


Source: Frost & Sullivan Analysis

Incidence of Advanced Breast Cancer in China, 2018-2030E

Incidence of Advanced Breast Cancer in China, 2018-2030E

Period	CAGR
2018-2023	2.6%
2023-2027E	2.2%
2027E-2030E	1.9%

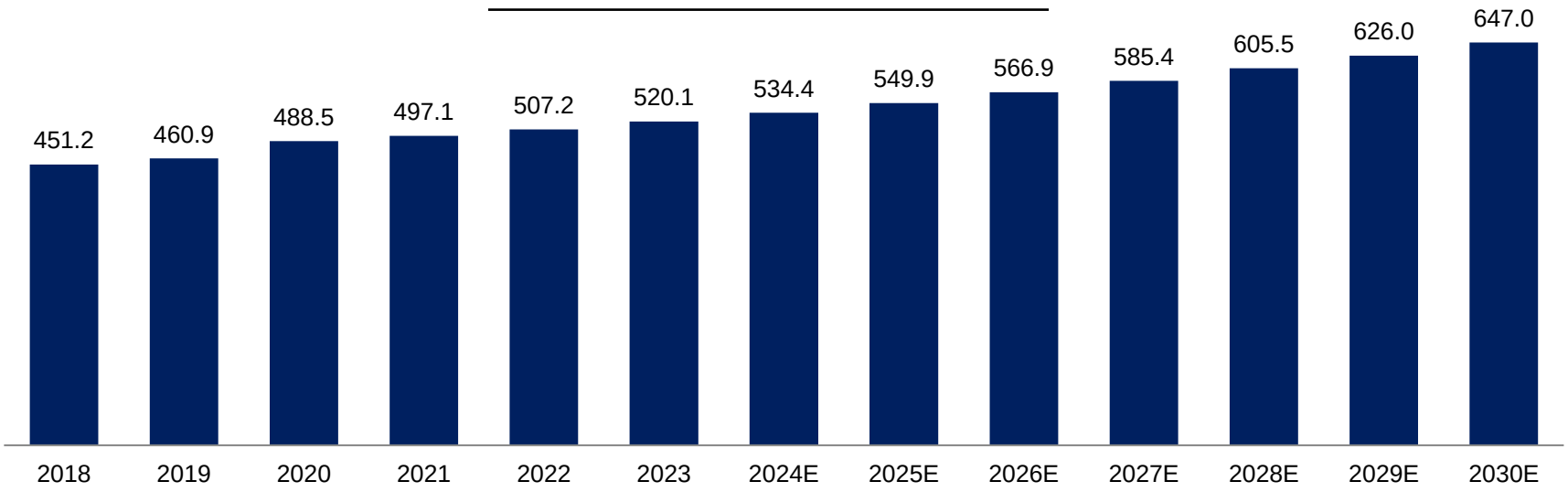


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Advanced Breast Cancer, 2018-2030E

Global Incidence of Advanced Breast Cancer, 2018-2030E

Period	CAGR
2018-2023	2.9%
2023-2027E	3.0%
2027E-2030E	3.4%

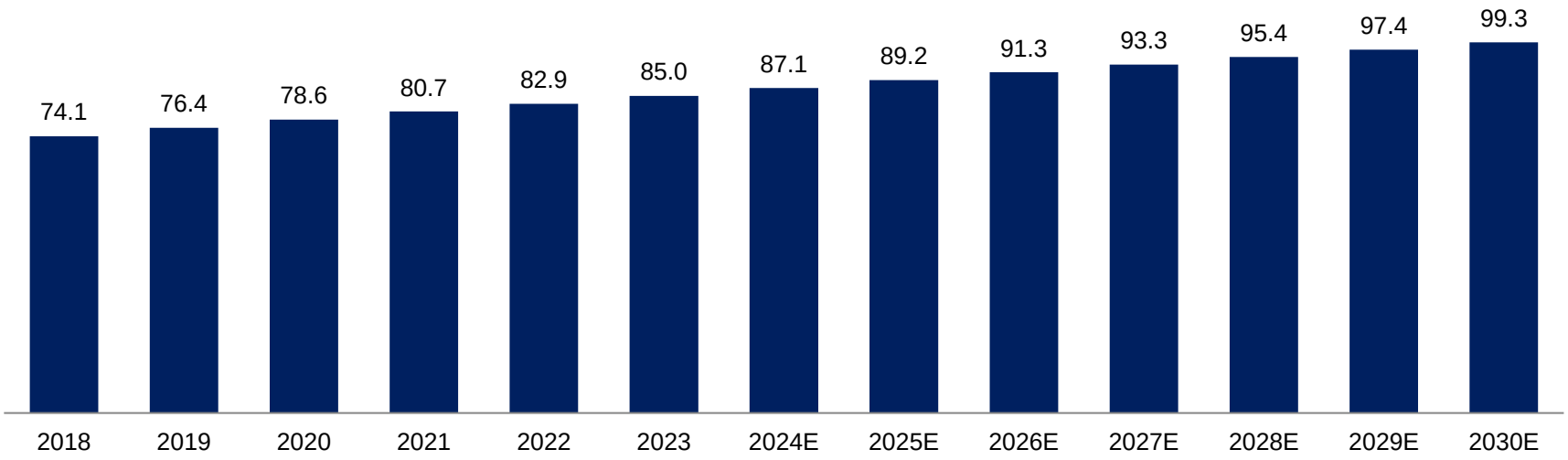


Source: NCCR, Frost & Sullivan analysis

Incidence of Relapsed or Metastatic Breast Cancer Patients Who Have Received at Least One Anthracycline- or Taxane-containing Chemotherapy Regimen in China, 2018-2030E

Incidence of Relapsed or Metastatic Breast Cancer Patients Who Have Received at Least One Anthracycline- or Taxane-containing Chemotherapy Regimen in China, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.4%
2027E-2030E	2.1%

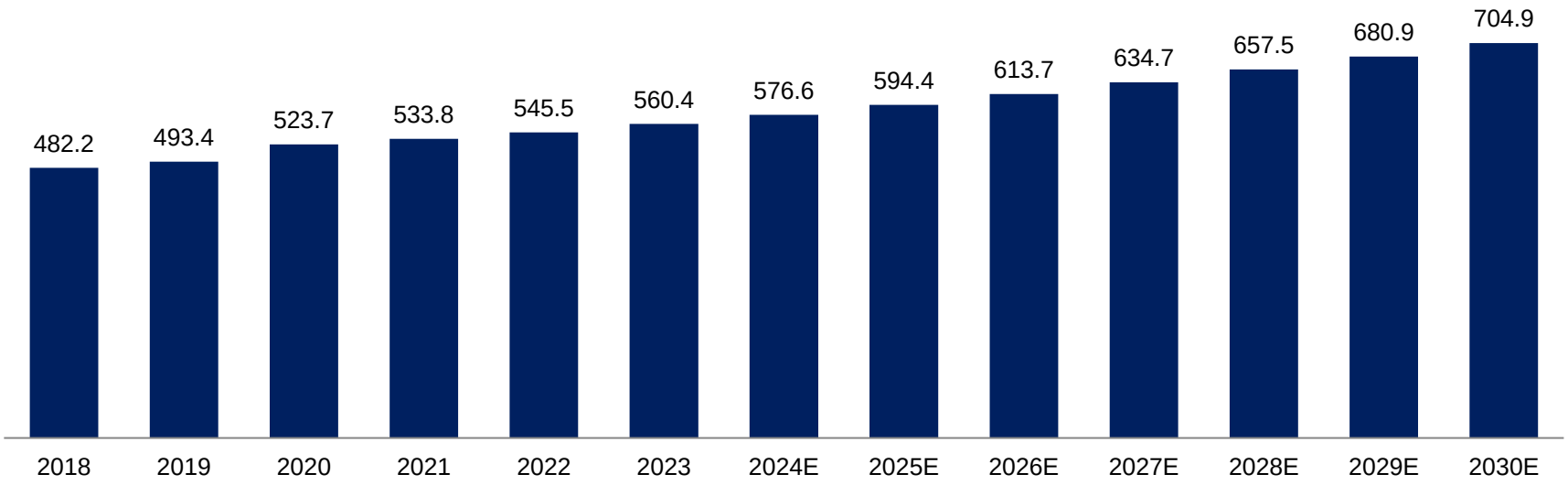


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Relapsed or Metastatic Breast Cancer Patients Who Have Received at Least One Anthracycline- or Taxane-containing Chemotherapy Regimen, 2018-2030E

Global Incidence of Relapsed or Metastatic Breast Cancer Patients Who Have Received at Least One Anthracycline- or Taxane-containing Chemotherapy Regimen, 2018-2030E

Period	CAGR
2018-2023	3.0%
2023-2027E	3.2%
2027E-2030E	3.6%

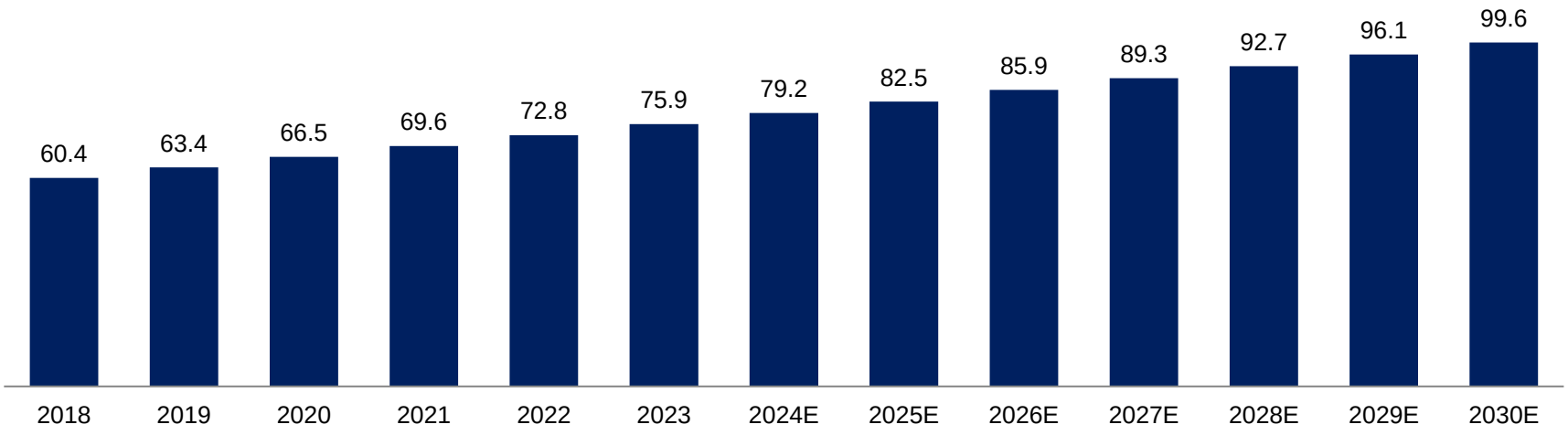


Source: NCCR, Frost & Sullivan analysis

Incidence of Breast Cancer suitable for Neoadjuvant Therapy in China, 2018-2030E

Incidence of Breast Cancer suitable for Neoadjuvant Therapy in China, 2018-2030E

Period	CAGR
2018-2023	4.7%
2023-2027E	4.1%
2027E-2030E	3.7%

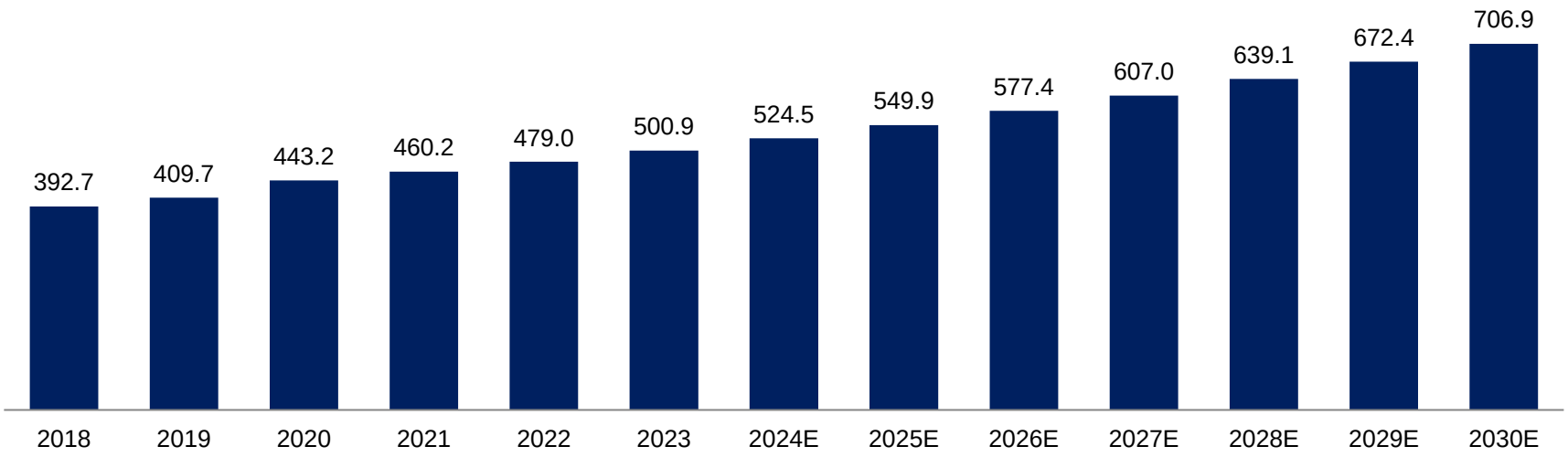


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Breast Cancer suitable for Neoadjuvant Therapy, 2018-2030E

Global Incidence of Breast Cancer suitable for Neoadjuvant Therapy, 2018-2030E

Period	CAGR
2018-2023	5.0%
2023-2027E	4.9%
2027E-2030E	5.2%

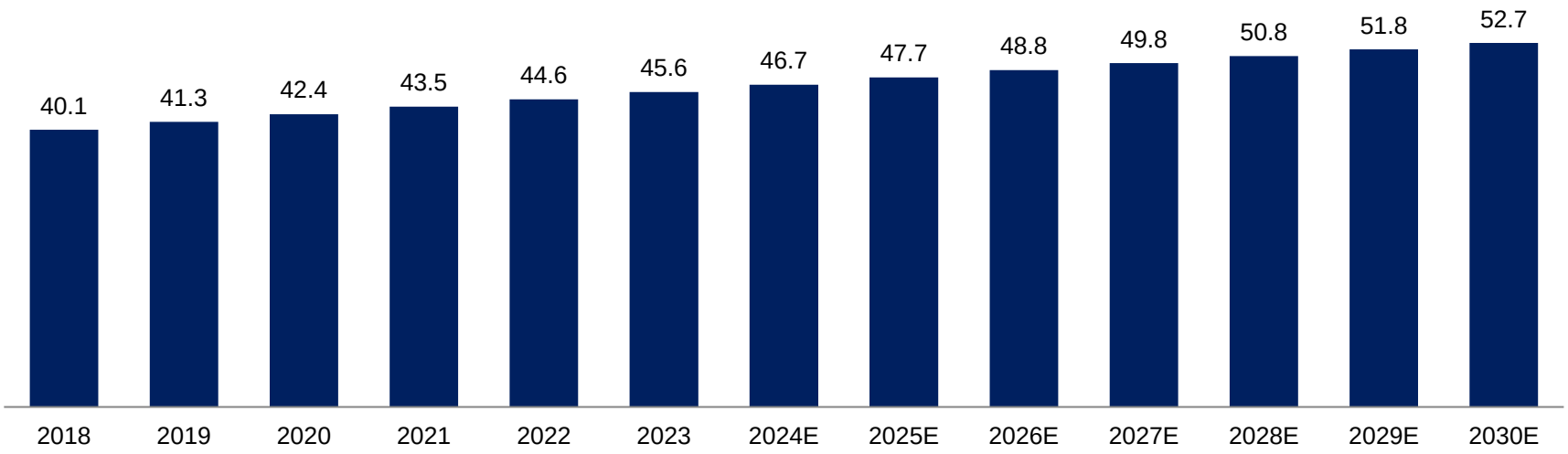


Source: NCCR, Frost & Sullivan analysis

Incidence of Breast Cancer Brian Metastasis in China, 2018-2030E

Incidence of Breast Cancer Brian Metastasis in China, 2018-2030E

Period	CAGR
2018-2023	2.6%
2023-2027E	2.2%
2027E-2030E	1.9%

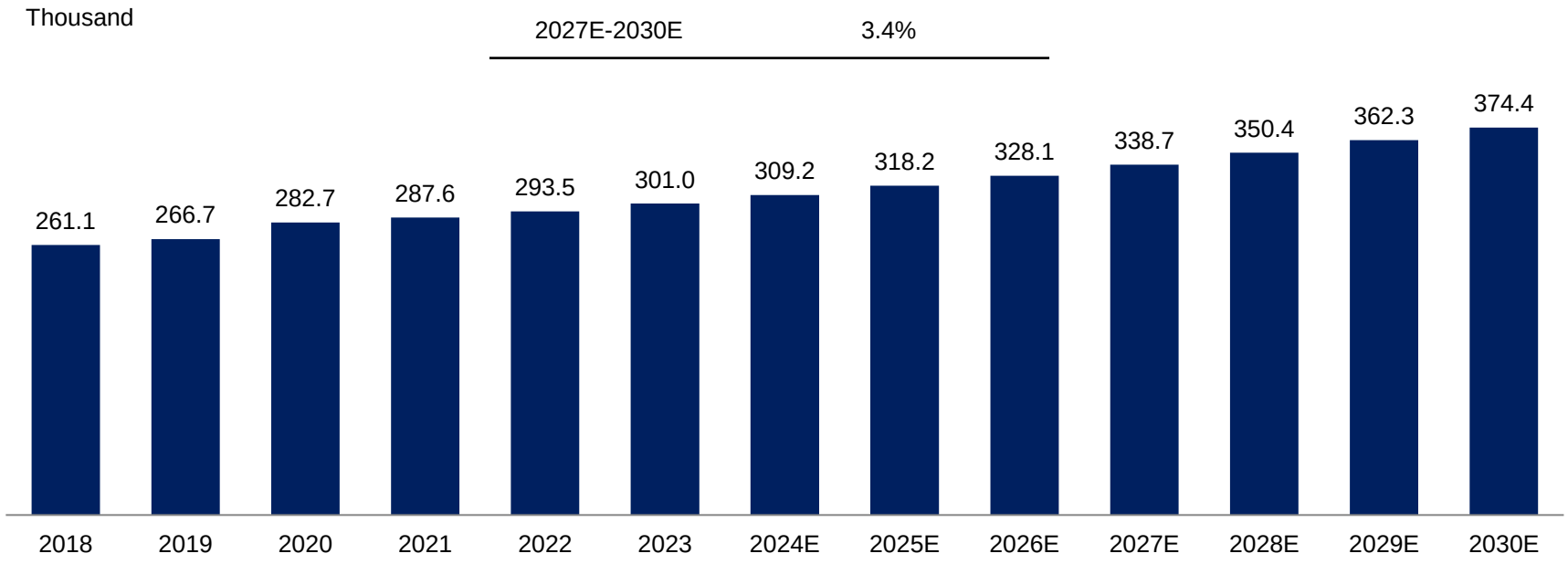


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Breast Cancer Brian Metastasis, 2018-2030E

Global Incidence of Breast Cancer Brian Metastasis, 2018-2030E

Period	CAGR
2018-2023	2.9%
2023-2027E	3.0%
2027E-2030E	3.4%



Source: NCCR, Frost & Sullivan analysis

Recommended Therapy Regimens of Breast Cancer from CSCO

Treatment of Recurrent or Stage IV Disease

- Treatment for TNBC is not clearly stated in the CSCO Guideline. However, salvage chemotherapy is recommended as the first-line treatment for recurrent or metastatic breast cancer. Endocrine therapy is recommended for hormone receptor-positive breast cancer. For TNBC, patients are lack of treatment options, especially novel therapies, representing large unmet clinical needs.

Indication	Treatment		
HER2+	Sensitive to H therapy	• THP • TH+ Pyrotinib	• TXH • H+ Chemo • Pyrotinib+ X • HP+ Chemo
	After the treatment failure of H	• Pyrotinib+ X • T-DM1 • T-Dxd	• Nerlynx+ X • Margetuximab + Chemo • Lapatinib+ X • TKI+ Chemo • HP+ Chemo
	After the treatment failure of TKI	• T-Dxd • HP+ Chemo	• T-DMI • Clinical research • Another TKI + Chemo
HER2-	After First Line Treatment Systemic therapies	Sensitive to taxane therapy	• Paclitaxel-albumin/docetaxel/paclitaxel • TX • GT • TPt • X • N • G • Etoposide • Paclitaxel-albumin+ PD-1 inhibitor • T+Bevacizumab • LD • Paclitaxel Liposome • Olaparib • Chemo+ PD-1 inhibitor
		After the treatment failure of taxane	• Alibrin/X/N/G • NPt • GPt • NX • UTD1+X • Sacituzumab govitecan-hziy/ Paclitaxel-albumin/Etoposide • Bevacizumab +X • Paclitaxel-albumin + Chemotherapeutic drug • LD • Paclitaxel Liposome • Olaparib • Chemo+ PD-1 inhibitor
ER+ and/or PR+	Without prior endocrine therapy	• AI+ Abemaciclib/Palbociclib • AI+ Ribociclib	• AI • F • F+CDK4/6 inhibitor • TAM
	After the treatment failure of TAM	• AI+ Abemaciclib/Palbociclib • AI	• AI+ Chidamide/ Ribociclib/ Dalpicilib/ Everolimus • F
	After the treatment failure of NSAI	• F+Abemaciclib/Palbociclib/Dalpicilib	• SAI+Chidamide/Everolimus • F+ Ribociclib • F/SAI • TAM/toremifene • Progestogen
	After the treatment failure of SAI	• F+Abemaciclib/Dalpicilib/Palbociclib • F+ Ribociclib/Everolimus	• F/NSAI • NSAI+CDK4/6 inhibitor • TAM/toremifene • Progestogen
	After the treatment failure of CDK4/6i	• Chidamide/ Everolimus /Alpelisib+Endocrine therapy	• Another CDK4/6 inhibitor+ Endocrine therapy • Toremifene • Progestogen
	Salvage chemotherapy	• Paclitaxel-albumin/docetaxel/paclitaxel/	• liposomal paclitaxel • X/G/LD/Vinorelbine • Cb/UTD1/Eribulin

Source: CSCO 2023, Frost & Sullivan Analysis

Notes:

Chemotherapy: T=docetaxel, paclitaxel and albumin-bound paclitaxel; A= Anthracyclines, including Epirubicin, Doxorubicin, Pirarubicin; E= Epirubicin; X=capecitabine; N=navelbi

Recommended Therapy Regimens of Breast Cancer from CSCO

Neoadjuvant Treatment and Adjuvant Treatment of BC (for II-III stage and Patients with locally advanced breast cancer who are inoperable)

- Neoadjuvant therapy refers to the systemic treatment of breast cancer prior to definitive surgical therapy. The purpose of treatment prior to surgery is to downstage the extent of disease in the breast and/or regional lymph nodes and provide information regarding treatment response to direct adjuvant therapies.
- Adjuvant therapy is cancer treatment that's given after primary treatments, such as surgery. Even if all visible cancer is removed during surgery, there still may be some remaining in the body that can't be seen. The goal of adjuvant therapy is to lower the chance of recurrent cancer and advanced cancer.

Indication	Neoadjuvant Treatment			
HER2+	• TCbHP • THP×6 • THP×4	• TH+ Pyrotinib • AC-THP • H+TKI	• ADC drugs	
HER2-	• TAC • AT	• TPt • Pembrolizumab + TPt	• AC-T • AC-TPt	
ER+ and/or PR+	Chemotherapy	• TAC	• AT	• AC-T
	Endocrine therapy – After Menopause	• AI	• AI + CDK4/6i	• F
	Endocrine therapy – Before Menopause	• OFS + AI	• OFS + AI + CDK4/6i	

Indication	Adjuvant Treatment			
HER2+	• AC-THP • TCbHP • AC-TH	• TCbH • TC+H • wTH	• H + Endocrine therapy • Neratinib	
HER2-	• AC-T • ddAC-ddT • TAC • TPt	• AC-TPt • FEC-T • TC×4 • AC	• TC×6 • Oraparib	
ER+ and/or PR+	Chemotherapy	• AC-T • ddAC-ddT • TAC	• FEC-T • TC×4 • AC	• TC×6
	Endocrine therapy – After Menopause	• AI +Abemaciclib • AI	• TAM + Abemaciclib • TAM + AI	• TAM
	Endocrine therapy – Before Menopause	• OFS + AI + Abemaciclib • OFS + AI	• OFS +TAM • TAM	• OFS + TAM + Abemaciclib

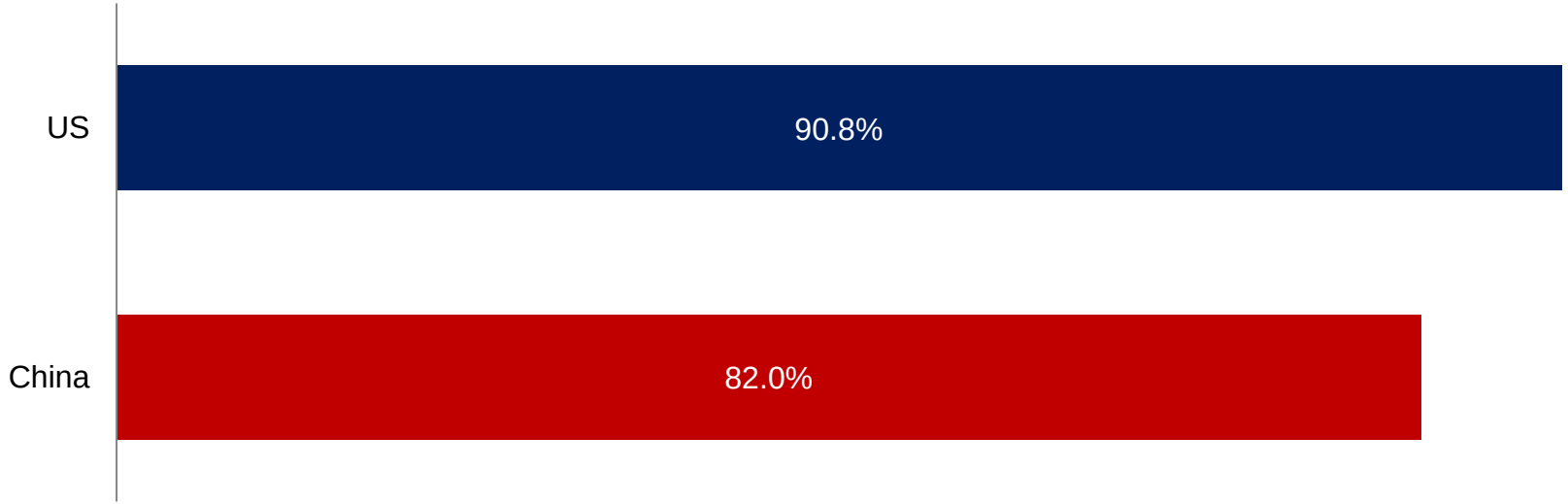
Source: CSCO 2023, Frost & Sullivan Analysis

Notes:

Comparison of 5-year Survival Rate of Breast Cancer in China and the US

- Breast cancer has a high incidence rate worldwide and seriously threatens women's lives and health. With the continuous enhancement of modern people's health awareness and the continuous development of science and technology, the diagnosis and treatment technology of breast cancer has also continued to improve. In recent years, with the widespread use of new therapies such as new chemotherapy drugs in breast cancer patients, the five-year survival rate of breast cancer in China and the United States has exceeded 80%.

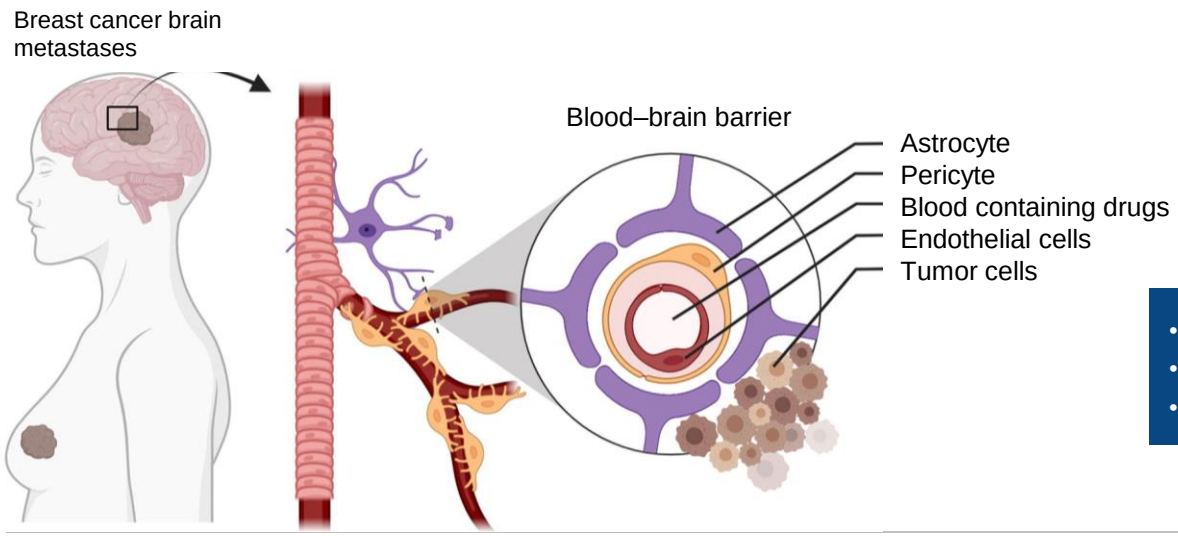
Overall 5-year Survival Rate of Breast caner in China and the US



Source: Literature Review, Frost & Sullivan analysis

Overview of Breast Cancer Brain Metastasis

- Breast cancer is the second most common origin of brain metastasis after lung cancer. Among breast cancer patients, the probability of developing brain metastases is approximately 5%. For people with more aggressive breast cancer subtypes, such as HER2-positive or triple-negative breast cancer, the risk of brain metastases is generally higher, ranging from 14% to 38%.
- Brain metastasis in breast cancer is commonly found in patients with advanced course disease and has a poor prognosis because the blood–brain barrier is thought to be a major obstacle to the delivery of many drugs in the central nervous system. In the past, it was believed that macromolecular drugs such as trastuzumab cannot penetrate the blood-brain barrier, and the intracranial drug concentration is low, so the therapeutic effect is effective. Therefore, local treatments including surgery, stereotactic radiation therapy, and whole-brain radiation therapy are currently considered the gold standard treatments.
- However, the current survival time of patients with breast cancer brain metastases is still limited. The median survival time after diagnosis of breast cancer brain metastases is only about 7.2 months, and even the median survival time of patients with TNBC brain metastases is only 3.5 months. Therefore, effective treatments are urgently needed for patients with breast cancer brain metastases.



Treatment Paradigm of Breast Cancer Brain Metastasis

Breast Cancer Brain Metastasis

- Radiotherapy
- Surgery
- HER2 drug treatment

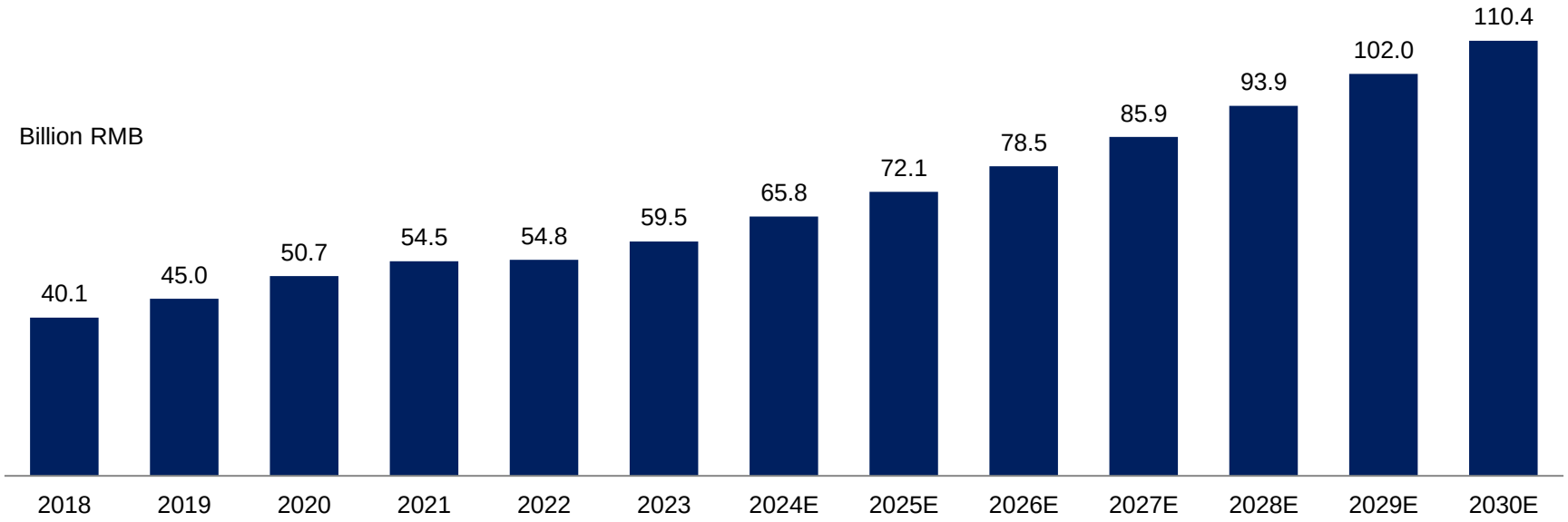
Source: Literature Review, CSCO, Frost & Sullivan analysis

Breast Cancer Drug Market in China, 2018-2030E

- China's breast cancer drug market size will reach RMB59.5 billion in 2023, with a CAGR of 8.2% from 2018 to 2023. Due to the large number of patients in China and the continuous expansion of medical insurance coverage, the market size will climb to RMB85.9 billion and RMB110.4 billion in 2027 and 2030 respectively.

Breast Cancer Drug Market in China, 2018-2030E

Period	CAGR
2018-2023	8.2%
2023-2027E	9.6%
2027E-2030E	8.7%



Source: Note: Market size calculations already take clinical trial success rates into account.

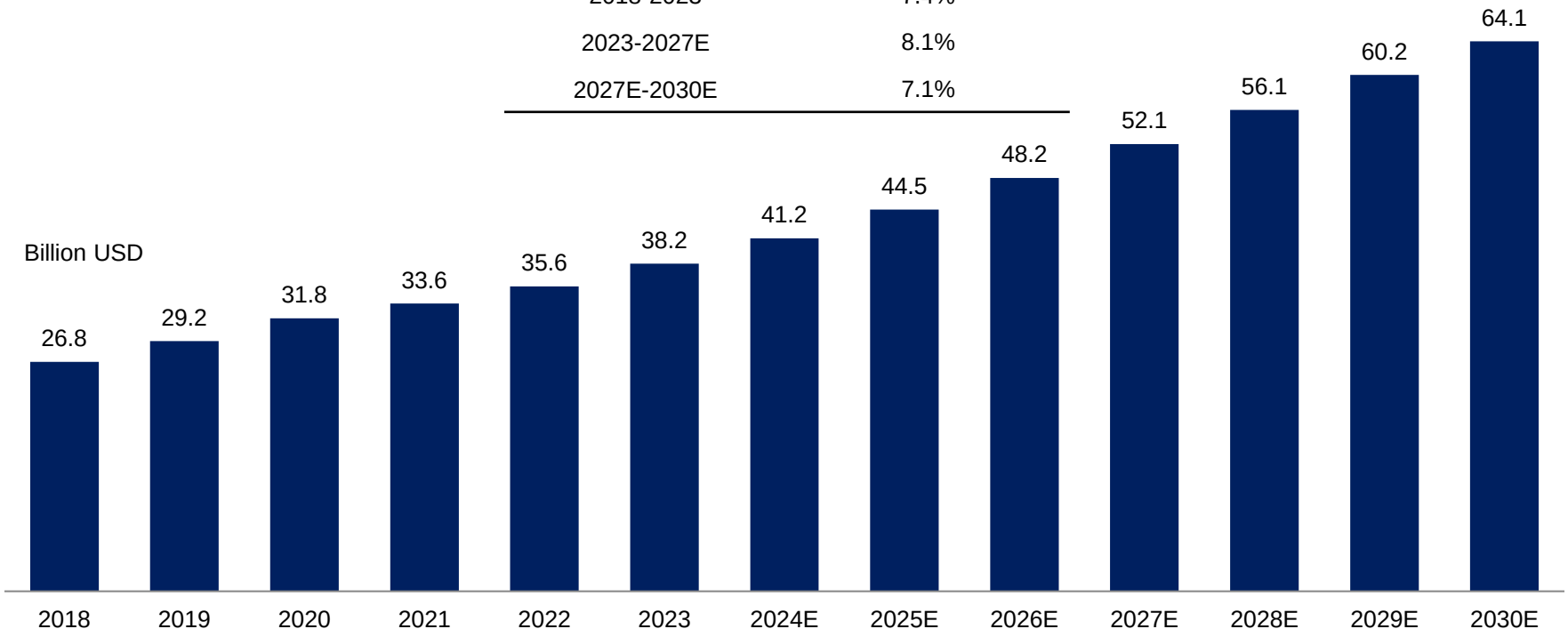
Source: Frost & Sullivan Analysis

Global Breast Cancer Drug Market, 2018-2030E

- The global breast cancer drug market size will reach USD38.2 billion in 2023, with a CAGR of 7.4% from 2018 to 2023. The market size is expected to reach USD51.2 billion in 2027, with a CAGR of 8.1% from 2023 to 2027. The market will further grow to USD64.1 billion in 2030, with a CAGR of 7.1% from 2027 to 2030.

Global Breast Cancer Drug Market, 2018-2030E

Period	CAGR
2018-2023	7.4%
2023-2027E	8.1%
2027E-2030E	7.1%



Source: Note: Market size calculations already take clinical trial success rates into account.

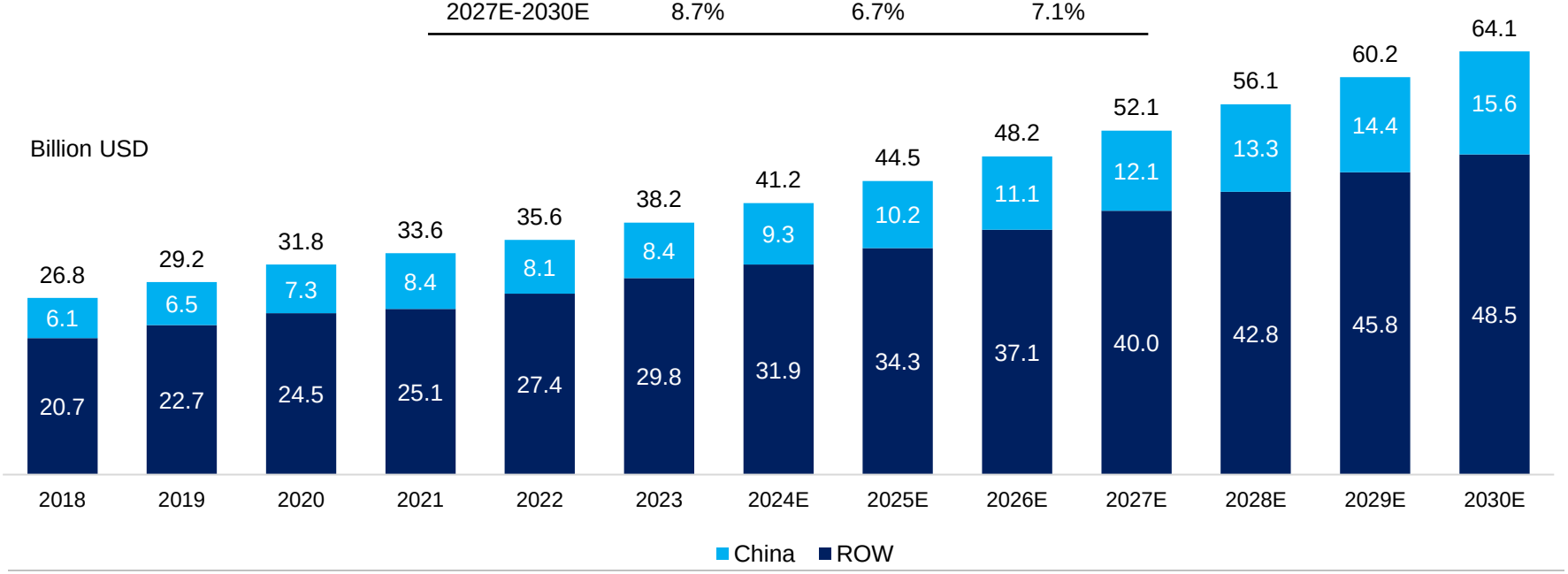
Source: Frost & Sullivan Analysis

Breakdown of Global Breast Cancer Drug Market, 2018-2030E

- The global breast cancer drug market size will reach USD38.2 billion in 2023, with a CAGR of 7.4% from 2018 to 2023. The market size is expected to reach USD52.1 billion in 2027, with a CAGR of 8.1% from 2023 to 2027. The market will further grow to USD64.1 billion in 2030, with a CAGR of 7.1% from 2027 to 2030.

Breakdown of global breast cancer drug market, 2018-2030E

CAGR	China	ROW	Total
2018-2023	6.8%	7.6%	7.4%
2023-2027E	9.6%	7.6%	8.1%
2027E-2030E	8.7%	6.7%	7.1%



Source: Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Breast Cancer in China

- NMPA has approved the marketing of a total of 8 microtubule inhibitors for the treatment of breast cancer. Most microtubule inhibitor drugs have been approved for a long time, and it is difficult to develop new drugs. In recent years, only two innovative drugs, eribulin and utidelone, have been launched. The microtubule inhibitor chemotherapy drugs for advanced breast cancer in China mainly use utidelone, paclitaxel, paclitaxel liposome, paclitaxel (albumin-bound), vinorelbine, and eribulin.

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Breast Cancer in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Rou admini
Docetaxel	TAXOTERE	Sanofi	1997	Class B	910 (0.5ml:20mg)	43,680	Inje
Paclitaxel	TAXOL	BMS	1999	Class A	489 (5ml:30mg)	39,146	Inje
Vinorelbine	NAVELBINE	Pierre Fabre	2000	Class B	283 (1ml:10mg)	34,020	Inje
Paclitaxel liposome	LIPUSU	Luye pharma	2003	Class B	228 (30mg)	16,416	Inje
Paclitaxel (albumin-bound)	ABRAXANE	Celgene/Beigene	2008	Class B	NA	NA	Inje
Vinorelbine (soft capsules)	NAVELBINE	Pierre Fabre	2014	Class B	780 (20mg)	131,070	O
Eribulin	HALAVEN	Eisai	2019	Class B	726 (2ml:1mg)	33,594	Inje
Utidelone	YOUTIDI	Biostar pharmaceutical	2021	Class B	908 (5ml:50mg)	36,320	Inje

Source: NMPA, Company Website, Frost & Sullivan Analysis

Analysis of other Representative Approved Drugs for the Treatment of Breast Cancer in China

Analysis of other Representative Approved Drugs for the Treatment of Breast Cancer in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Route of administration	
Capecitabine	Xeloda	Roche	2007	Class B	264(0.5g)	19,731	Oral	
Gemcitabine	Gemzar	Eli Lilly	1999	Class B	272(0.2g)	43,592	Injection	Unr
Fulvestrant	Faslodex	AstraZeneca	2010	Class B	2,306(0.25g)	32,284	Injection	ER
Trastuzumab	Herceptin	Roche	2002	Class B	7,600(0.44g)	83,600	Injection	M
Pertuzumab	Perjeta	Roche	2018	Class B	4,955(0.42g)	94,145	Injection	Cor H
Palbociclib	Ibrance	Pfizer	2018	Class B	440(0.075g)	200,277	Oral	HR
fam-trastuzumab deruxtecan-nxki	Enhertu	AstraZeneca /Daiichi	2023	NA	8,860(0.1g)	567,040	Injection	HER

Note: 1. As of May 31, 2024, only the brand name, company and treatment cost of the original drug are included.

2. The annual treatment cost is estimated based on an average body surface area of 1.6m2 and 8 treatment cycles per year, or the recommended medication cycle in the ins

The unit price is calculated based on the pre-medical insurance price of the original drug, and free drugs are not considered.

Source: NMPA, Company Website, Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Breast Cancer in the US

- A total of 6 microtubule inhibitors have been approved by the US FDA for the treatment of breast cancer. The microtubule inhibitor chemotherapy drugs for advanced breast cancer in the US mainly use paclitaxel, paclitaxel (albumin-bound), docetaxel, vinorelbine, eribulin, and ixabepilone.

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Breast Cancer in the US

Generic Name	Brand Name	Company	Approval Date
Vinorelbine	NAVELBINE	Pierre Fabre	1994
Docetaxel	TAXOTERE	Sanofi	1996
Paclitaxel	TAXOL	BMS	1992
Paclitaxel (albumin-bound)	ABRAXANE	Celgene	2005
Ixabepilone	IXEMPRA	BMS	2007
Eribulin	HALAVEN	Eisai	2010

Note: As of May 31, 2024, only the brand name and company of the original drug are included.

Source: FDA, Company Website, Frost & Sullivan Analysis

Pipeline of microtubule Inhibitor Drugs under Clinical Development in China for the Treatment of Breast Cancer

- The microtubule inhibitors currently being developed in China for the treatment of breast cancer are mainly new dosage forms of original drugs, such as micelles, liposomes or oral dosage forms. Among them, the oral dosage form has great potential in clinical use because it greatly improves the convenience of administration.

Pipeline of microtubule Inhibitor Drugs under Clinical Development in China for the Treatment of Breast Cancer

Dosage Form	Drug Name	Company	Clinical Stage	First Post Date
Injection	Docetaxel albumin-bound for injection/HB1801	CSPC Zhongqi Pharmaceutical	Phase III	2023-05-12
Injection	Vinflunine tartrate concentrated solution for injection	Tigermed	Phase III	2013-11-15
Oral	RMX3001/DHP107	Daehwa Pharmaceutical/Haihe Biopharm	Phase III	2019-03-12
Injection	Paclitaxtide for injection	Yuansheng Biopharm	Phase II	2014-02-21
Injection	Paclitaxel polymer micelles for injection	Main Luck Skywing Pharmatech	Phase II	2015-05-11
Injection	Docetaxel Injection Concentrate (SEDDS)	Beijing Deliinje Pharmaceutical	Phase I	2023-08-16
Injection	Docetaxel liposome for injection	Jinyuan Pharmaceutical	Phase I	2018-10-17
Injection	Docetaxel polymer micelles for injection	Chemo Wanbang Biophama	Phase I	2019-03-25
Injection	Vinorelbine tartrate micelles for injection	Topfond Pharmaceutical	Phase I	2020-07-02

Note: As of May 31, 2024.

Source: CDE, Frost & Sullivan Analysis

Pipeline of microtubule Inhibitor Drugs under Clinical Development Globally for the Treatment of Breast Cancer

- The microtubule inhibitors currently being developed in China for the treatment of breast cancer are mainly new dosage forms of original drugs, such as micelles, liposomes or oral dosage forms. Among them, the oral dosage form has great potential in clinical use because it greatly improves the convenience of administration.

Pipeline of microtubule Inhibitor Drugs under Clinical Development Globally for the Treatment of Breast Cancer

Dosage Form	Drug Name	Company	Clinical Stage	First Post Date

There are currently no microtubule inhibitor chemotherapy drugs are actively under phase III development globally.

Note: As of May 31, 2024.

Source: Clinical Trials, Frost & Sullivan Analysis

Comparison of Competing Chemotherapy Drugs for Advanced Breast Cancer - I

- Compared with other new anti-microtubule drugs, such as eribulin and ixabepilone, utidelone has greater advantages in effectiveness and safety in the second-line treatment of recurrent and metastatic breast cancer. Effectiveness is generally better than other competing products. In terms of side effects, utidelone has hematological toxicity, low liver function damage, and mild gastrointestinal reactions. The main side effect is peripheral nervous system toxicity, and the median response time is about 3.1 weeks. Overall, utidelone shows good efficacy and safety data and has great market potential.

Comparison of Clinical Data on Combined Drug Therapies

Drug Name	Utidelone		Ixabepilone		Ixabepilone		Docetaxel[1]	
Trial Protocol	UTD1+CAP	CAP	IXA+CAP	CAP	IXA+CAP	CAP	CAP+DOC	DOC
Trial Code	BG01-1323L		CA163046		CA163048		NA	
Number of Patients Enrolled	270	135	375	377	609	612	255	256
ORR/%	49.8	26.7	34.7	14.3	43.3	28.8	42.0	30.0
PFS(TTP)/Month	8.6	4.1	5.8	4.2	6.2	4.4	6.1	4.2
HR/p	0.46,p<0.0001		0.75，p=0.0003		0.79,p=0.0005		0.65,p=0.0001	
OS/Month	20.9	15.7	12.9	11.1	16.4	15.6	14.5	11.5
HR/p	0.69,p=0.003		0.9,p=0.19		0.90,p=0.11		0.775,p=0.0126	

Note: 1.The enrolled patients have not received taxane drug treatment in the past.
2.UTD1 is utidelone; CAP is capecitabine; IXA is ixabepilone; DOC is docetaxel.

Source: FDA, NMPA, Literature Review, Frost & Sullivan Analysis

Comparison of Competing Chemotherapy Drugs for Advanced Breast Cancer - II

Comparison of Clinical Data on Single Drug Therapies				
Drug Name	**Utidelone**	**Ixabepilone**	**Eribulin**	**Albumin Paclitaxel**
Trial Protocol	Single drug	Single drug	Single drug	Single drug
Trial Code	BG01-1222D	CA163081	NA	CA012-01
Number of Patients Enrolled	70	126	103	186
ORR/%	31.8	11.5	11.5	21.4
PFS/Month	4.6	3.1	2.6	5.6
OS/Month	17.5	8.6	9.0	15.1

Note: 1.The enrolled patients have not received taxane drug treatment in the past.

Source: FDA, NMPA, Literature Review, Frost & Sullivan Analysis

Comparison of Competing Chemotherapy Drugs for Advanced Breast Cancer - III

Safety Comparison of Combination Therapy (Incidence Of Major Adverse Events (Grade 3-4))								
Drug Name	**Utidelone**		**Ixabepilone**		**Ixabepilone**		**Docetaxel[1]**	
Trial Protocol	UTD1+CAP	CAP	IXA+CAP	CAP	IXA+CAP	CAP	CAP+DOC	DOC
Trial Code	BG01-1323L		CA163046		CA163048		NA	
Number of Patients Enrolled	270	135	369	368	595	603	251	255
Neutropenia	11.6%	10.0%	68.0%	11.0%	73.0%	9.0%	16.0%2	15.0%2
Febrile Neutropenia	0.0%	0.0%	4.8%	0.5%	7.0%	0.6%	16.0%	21.0%
Leukopenia	5.6%	5.4%	57.0%	6.0%	63.0%	7.0%	NA	NA
Thrombocytopenia	0.0%	3.1%	8.0%	4.0%	6.0%	2.8%	NA	NA
Peripheral Neurotoxicity	25.1%	0.8%	22.8%	0.0%	24.7%	1.2%	NA	NA
Median Recovery Time from Peripheral Neurotoxicity/ Month	3.1	NA	6.0	NA	6.2	NA	NA	NA
Hand-foot Syndrome	7.1%	7.7%	18.0%	17.0%	21.0%	20.0%	24.0%	1.0%

Note: 1.The enrolled patients have not received taxane drug treatment in the past.

2. Only patients with grade III/IV neutropenia who require medical intervention are included. These patients cannot recover spontaneously and require medical intervention (s

3. UTD1 is utidelone; CAP is capecitabine; IXA is ixabepilone; DOC is docetaxel.

Source: FDA, NMPA, Literature Review, Frost & Sullivan Analysis

Overview of Neoadjuvant Treatment of Breast Cancer

- Neoadjuvant treatment for breast cancer can help patients in reducing distant recurrence, allowing patients to start systemic treatment earlier and reducing their tumor stages.
- Pre-treatment examinations should be conducted before neoadjuvant treatment, thus patients with the right indications can be treated with rational and suitable treatment schemes.

Neoadjuvant Treatment of Breast Cancer

- Neoadjuvant treatment is a systemic treatment for breast cancer used prior to curative surgical treatment (preoperative treatment)

- Neoadjuvant therapy of breast cancer is helpful in
  - allowing patients at higher risk of distant recurrence to start systemic therapy earlier
  - reducing patient's tumor stage, thus may reduce the surgical area of the breast and/or axilla, avoiding mastectomy for patients who are able to undergo breast-conserving surgery, thereby avoiding the risk of breast reconstruction, improving cosmetic outcomes, and reducing postoperative complications such as lymphoedema

Pre-treatment examination

Tumor-related assessments	• Clinical tumor staging • Tumor pathological type, histological grading, molecular features (HER-2, ER, PR, Ki-67) • Tumor localization • …
Other assessments	• Disease history • Physical examination • General haematological examination • Major organ function assessment (e.g. liver, kidney, heart) • …

Indications for treatment

Neoadjuvant medication is an option for patients who meet one of the following criteria

- Large lumps (If primary lump is >5cm, neoadjuvant therapy can be considered; if primary lump is 2-5cm, other biological indicators should be taken into account to choose whether or not to start the therapy)
- Axillary lymph node metastasis
- HER-2 positive
- Triple-negative
- Breast-conserving, but tumor size is too large in proportion to breast size for breast conservation

Source: Breast Cancer Treatment Guidelines(CSCO 2023), Literature Review, Frost & Sullivan analysis

Neoadjuvant Treatment options for Breast Cancer

- Neoadjuvant treatment primarily includes chemotherapy, targeted therapy and endocrine therapy. CSCO guideline for breast cancer recommends standard neoadjuvant treatment options, while many companies also started developing new neoadjuvant drugs for breast cancer patients.
- Currently, except for utidelone, no microtubule inhibitors are in clinical development for neoadjuvant treatment of breast cancer in China.

Neoadjuvant Treatment options of Breast Cancer

- Neoadjuvant treatment includes chemotherapy, targeted therapy and endocrine therapy
- Chemotherapy is largely considered as the standard neoadjuvant treatment for most patients
- Dual-targeted therapy is recommended in CSCO guideline for all patients who are eligible for single-targeted neoadjuvant treatment, as clinical studies showed that the neoadjuvant treatment of HER-2-positive patients with trastuzumab in combination with chemotherapy significantly improves the pCR rate compared with chemotherapy alone

CSCO recommended treatment options

1st line

1A：TCbHP
2A：THPx6
3A：THPx4

2nd line

1. TH + Vidonatinib
2. Anti-HER-2 monoclonal antibody combined with other paclitaxel-based regimens e.g. AC-THP
3. Scientifically designed clinical studies e.g. H+TKI, anti-HER2 ADC, etc.

Note:

T. Paclitaxel, including docetaxel, albumin paclitaxel, taxol

A. Anthracyclines, including epirubicin, pirarubicin, doxorubicin

C. Cyclophosphamide

Cb. Carboplatin

H. Trastuzumab

P. Pertuzumab

TKI. Tyrosine kinase inhibitor

Neoadjuvant treatment options under development

BIOSTAR

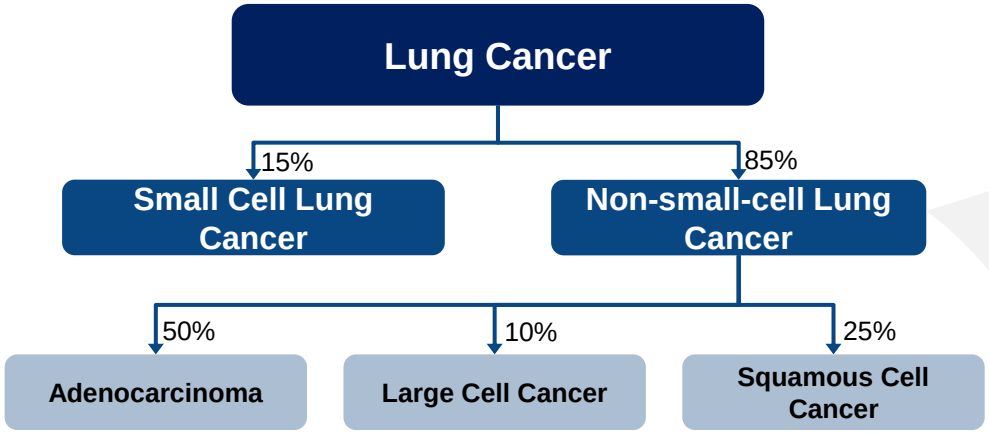
"Study of Utidelone in combination with Doxorubicin(A) and Cyclophosphamide(C) vs. Docetaxel + AC for Neoadjuvant Chemotherapy in HER2- Early High-Risk or Locally Advanced Breast Cancer"

BG01-2102 Study

- A Phase III, open, randomized controlled clinical study
- **Primary endpoint**: pathological complete remission rate (tpCR)
- **Secondary endpoint**: breast pathological remission rate (bpCR), objective response rate(ORR), 3-year event-free survival (EFS) rate, and safety
- Addressing the suboptimal efficacy of existing anthracycline-paclitaxel combination therapies, such as the tpCR rate

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

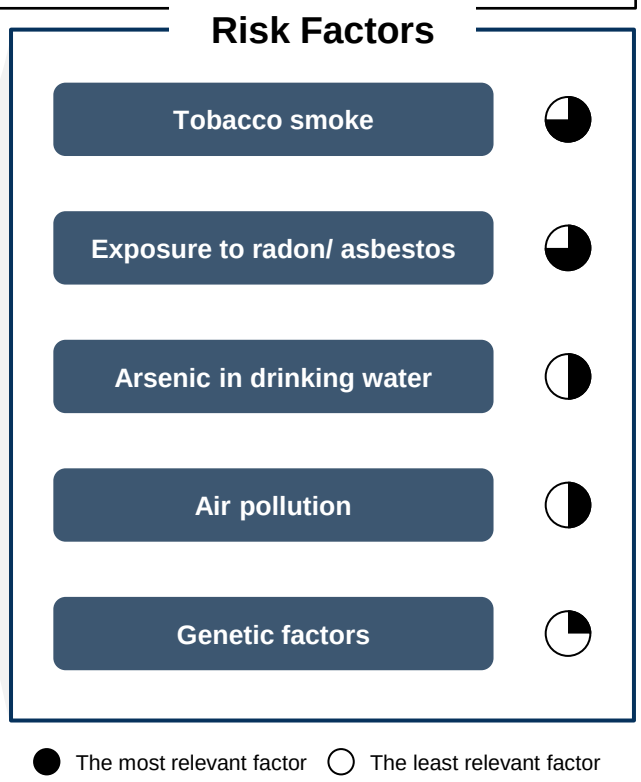
- Non-small-cell lung cancer (NSCLC) is any type of epithelial lung cancer other than small cell lung cancer (SCLC). NSCLC accounts for over 85% of LC, which is the second most common cancer and the leading cause of cancer death globally. The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. All types can occur in unusual histologic variants and developed as mixed cell-type combinations.
- RET+ NSCLC amounts to approximately 1 to 2% of total NSCLC cases. According to Frost & Sullivan, the incidence of RET+ NSCLC in China grew from 13,100 in 2017 to 15,400 in 2021 and is expected to reach 20,100 in 2030.
- Symptoms of more advanced NSCLC cases include bone pain, headache, weakness and vomiting.



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

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

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



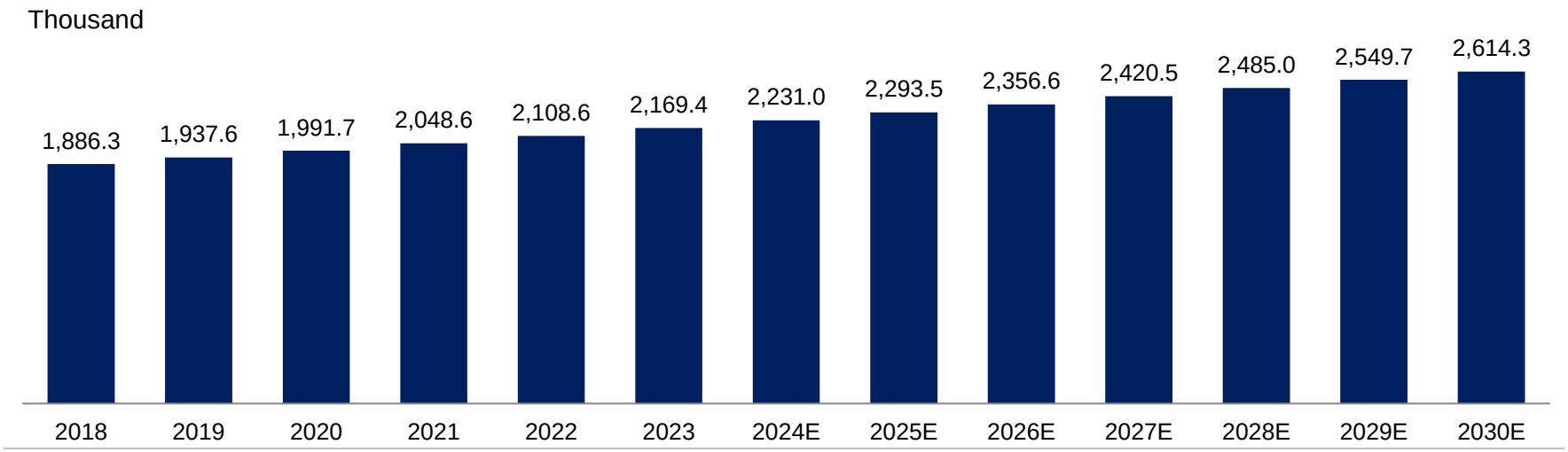
Source: Literature Review, Frost & Sullivan Analysis

Global Incidence of NSCLC, 2018-2030E

- In 2023, the number of global NSCLC cases was about 2.2 million. It is estimated that by 2030, this figure will reach about 2.6 million, with a CAGR of 2.7% from 2023 to 2030.

Global incidence of NSCLC, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.8%
2027E-2030E	2.6%



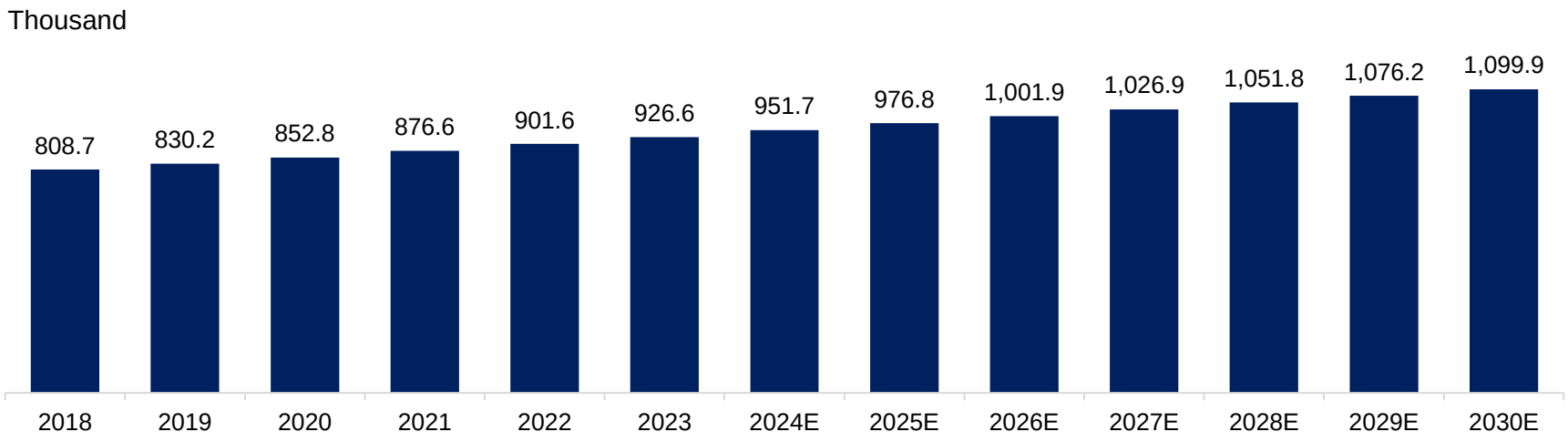
Source: NCCR, Frost & Sullivan Analysis

Incidence of NSCLC in China, 2018-2030E

- In 2023, the number of China NSCLC cases was about 926.6 thousand. It is estimated that by 2030, this figure will reach about 1,099.9 thousand, with a CAGR of 2.5% from 2023 to 2030.

Incidence of NSCLC in China, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.6%
2027E-2030E	2.3%

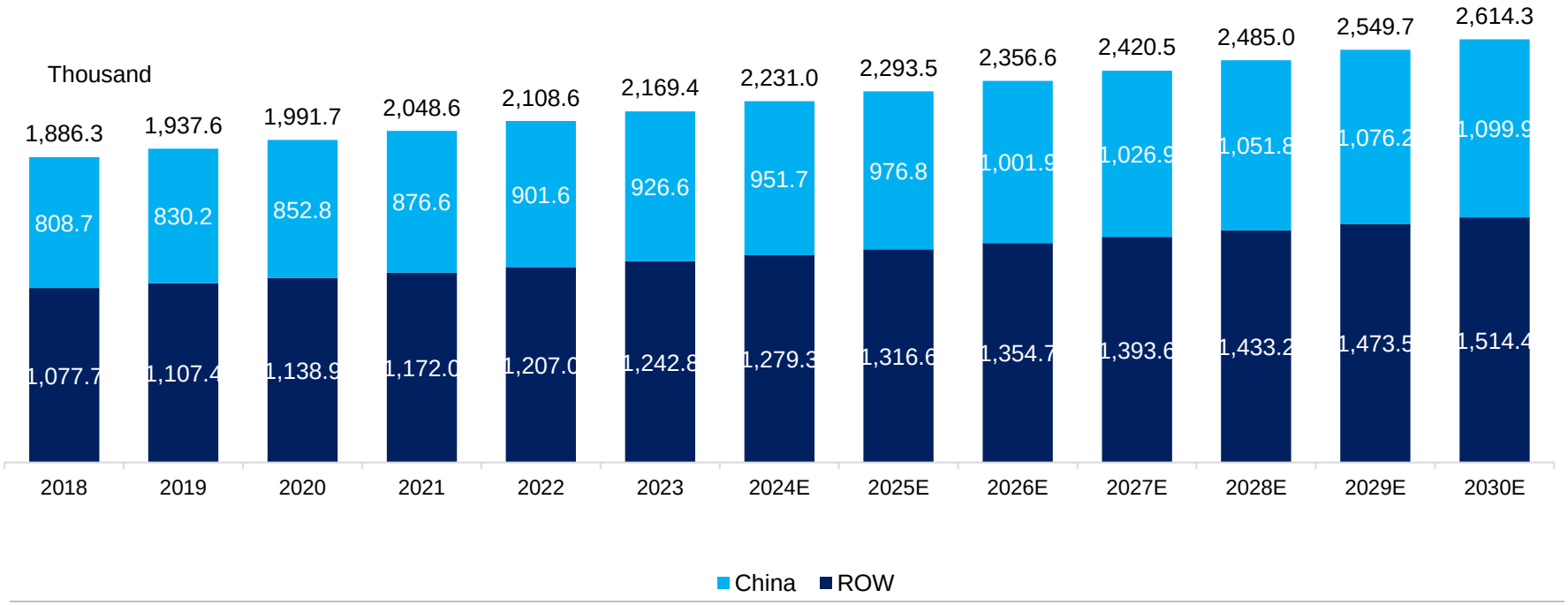


Source: NCCR, Frost & Sullivan Analysis

China and Global Incidence of NSCLC, 2018-2030E

China and Global Incidence of NSCLC, 2018-2030E

CAGR	China	ROW	Total
2018-2023	2.8%	2.9%	2.8%
2023-2027E	2.6%	2.9%	2.8%
2027E-2030E	2.3%	2.8%	2.6%

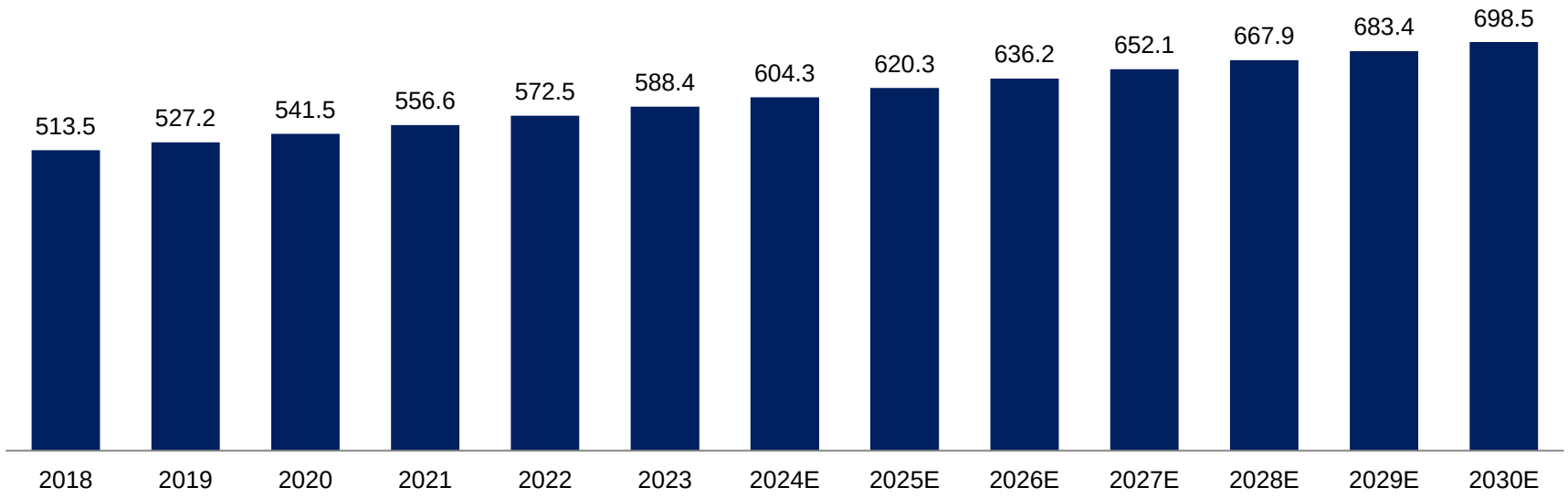


Source: Frost & Sullivan Analysis

Incidence of Advanced NSCLC in China, 2018-2030E

Incidence of Advanced NSCLC in China, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.6%
2027E-2030E	2.3%



Source: NCCR, Frost & Sullivan analysis

Global Incidence of Advanced NSCLC, 2018-2030E

Global Incidence of Advanced NSCLC, 2018-2030E

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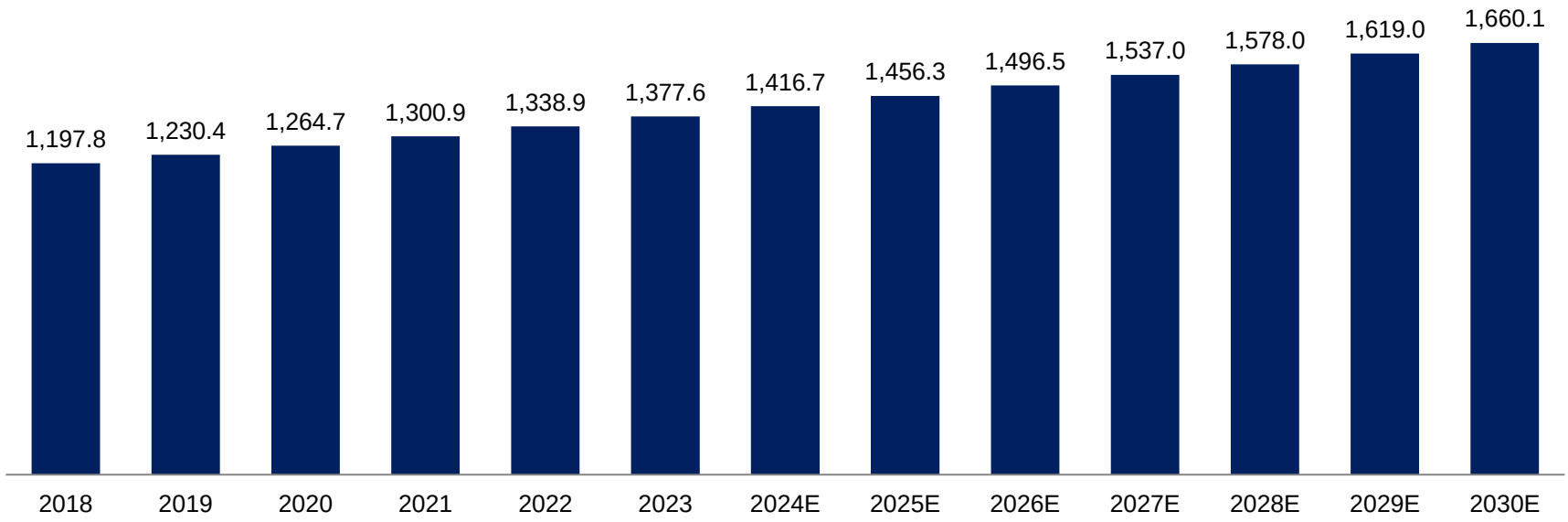
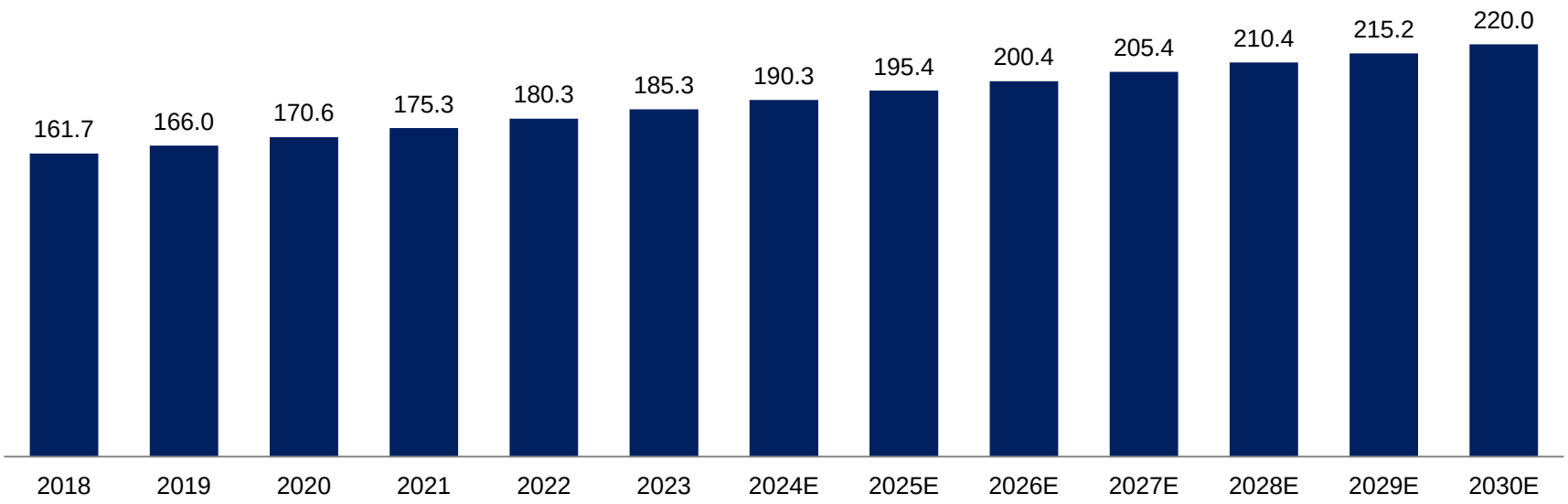


Source: NCCR, Frost & Sullivan analysis

Incidence of NSCLC Brain Metastasis in China, 2018-2030E

Incidence of NSCLC Brain Metastasis in China, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.6%
2027E-2030E	2.3%



Source: NCCR, Frost & Sullivan analysis

Global Incidence of NSCLC Brain Metastasis, 2018-2030E

Global Incidence of NSCLC Brain Metastasis, 2018-2030E

Period	CAGR
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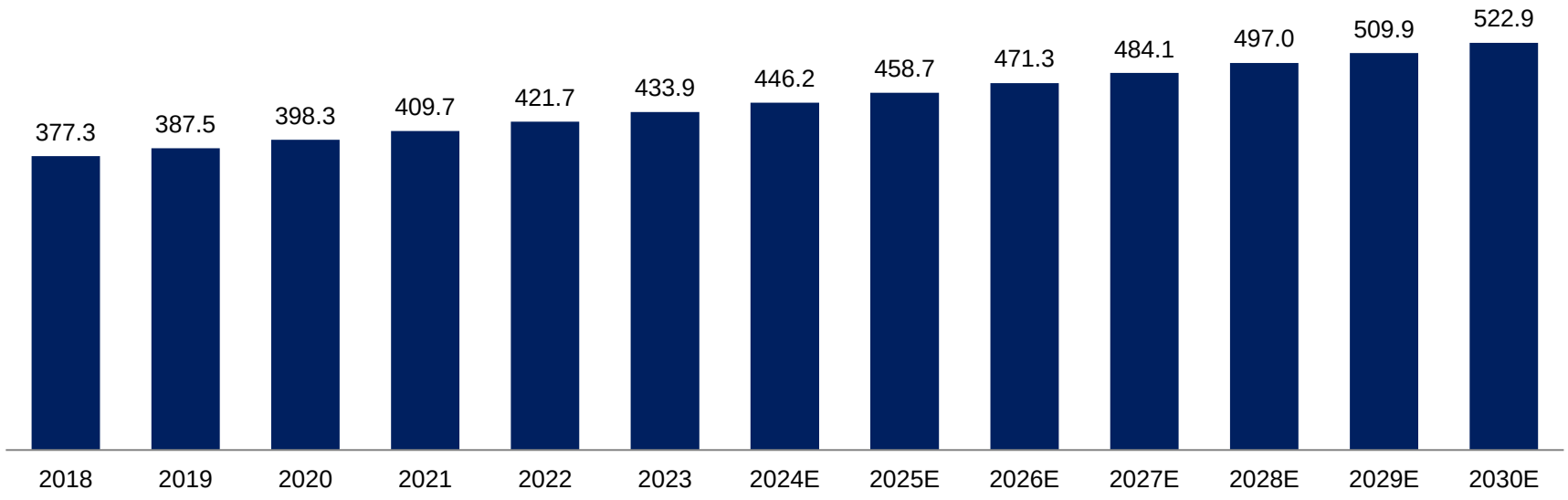
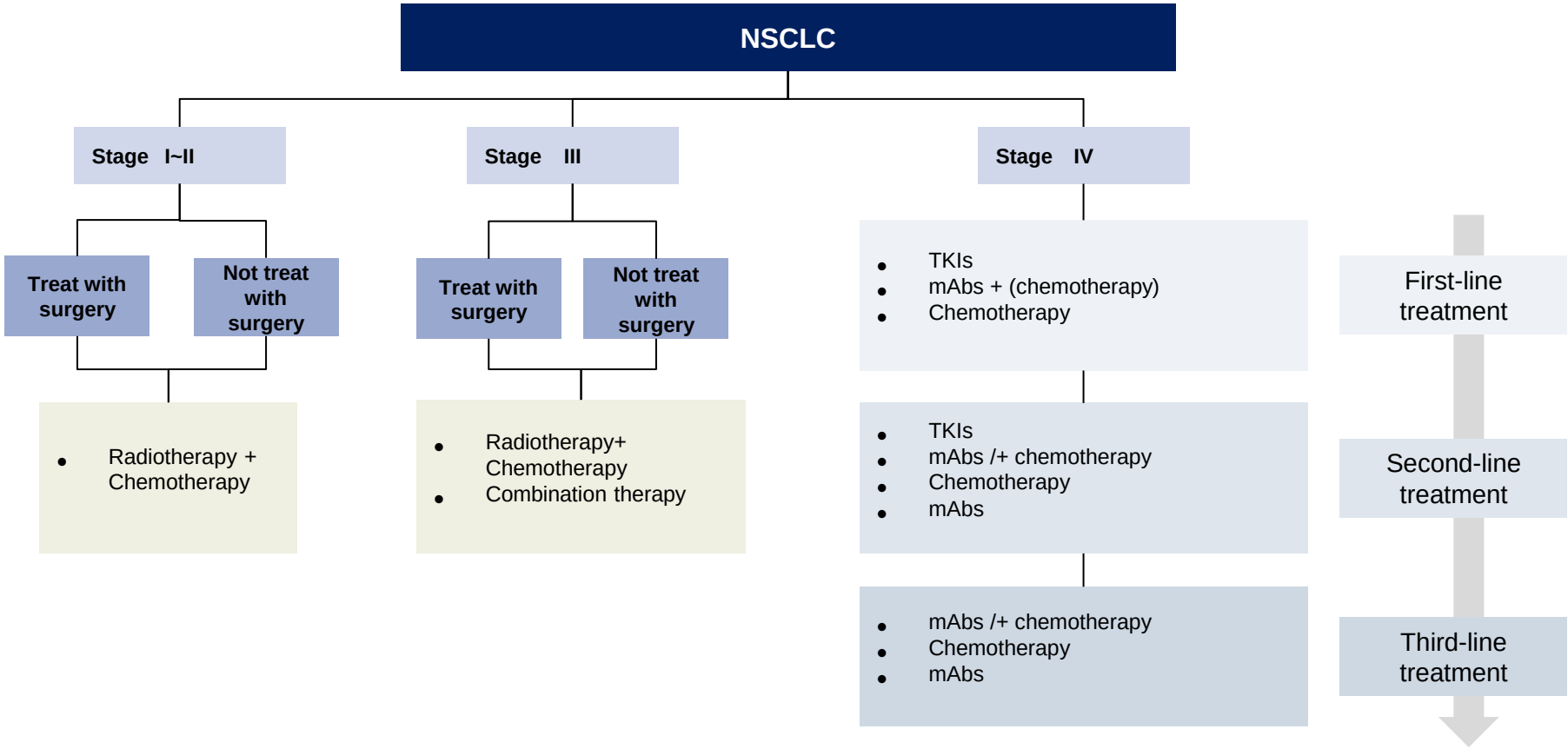


Source: NCCR, Frost & Sullivan analysis

CSCO Treatment Paradigm for Advanced NSCLC

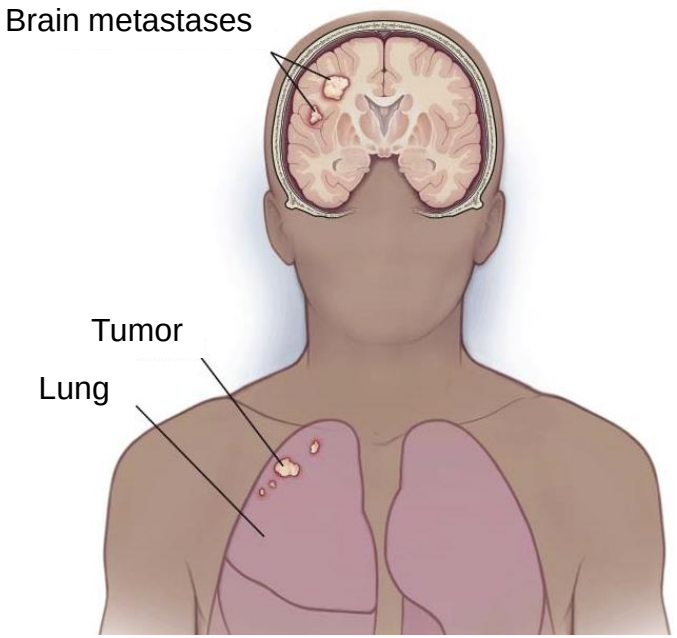


Notes: TKI=tyrosine kinase inhibitor;

Source: CSCO 2023, Frost & Sullivan Analysis

Overview of Lung Cancer Brain Metastasis

- Brain metastases are the most common intracranial tumors in adults and their incidence is increasing, primarily driven by lung cancer. As the most common cancer with brain metastases, approximately 16%-20% of lung cancer patients have brain metastases at the time of diagnosis. Cancer patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements have a higher incidence rate, with up to 50% to 60% of patients developing brain metastases during the course of their disease.
- The current treatment of lung cancer brain metastases combines local therapy (such as radiation, surgery) and systemic therapy. However, due to the existence of the blood-brain barrier, patients with lung cancer brain metastases have limited benefit from existing therapies. Targeted drugs and new chemotherapy drugs are trying to prolong the survival time and quality of life of patients with lung cancer and brain metastases.



Treatment Paradigm of NSCLC Brain Metastasis

NSCLC Brain Metastasis

- Radiotherapy
- Double-drug chemotherapy based on platinum drugs mainly cisplatin and carboplatin + bevacizumab
- Immune checkpoint inhibitors
- TKIs + topical treatment
- Alectinib / ceritinib / ensartinib (ALK fusion positive)

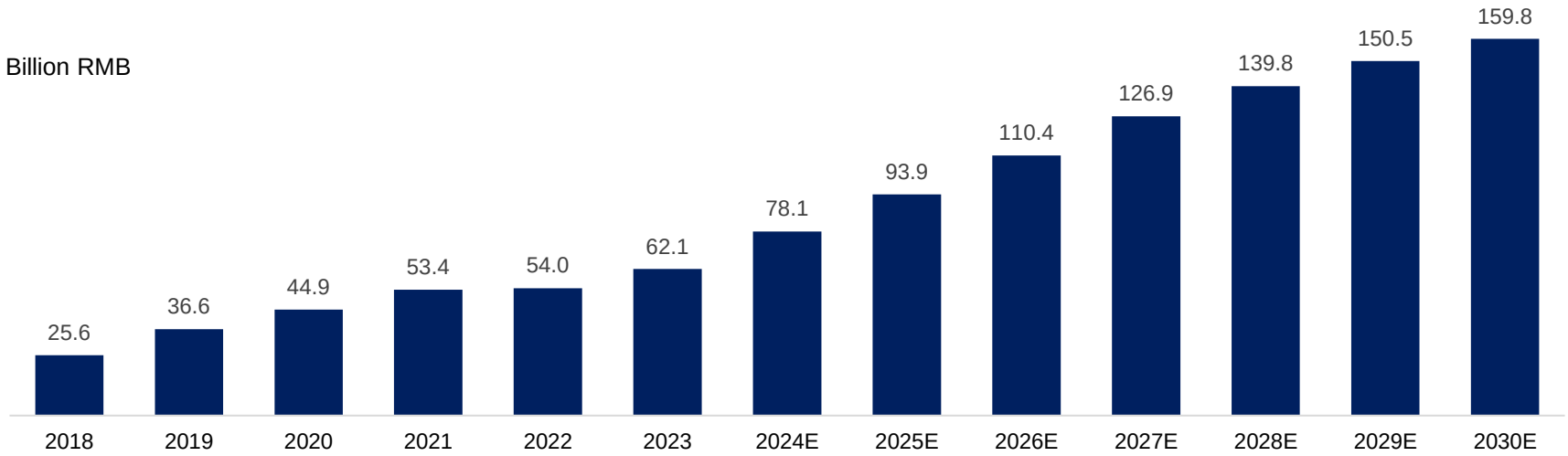
Source: Literature Review, CSCO, Frost & Sullivan analysis

NSCLC Drug Market in China, 2018-2030E

- China's NSCLC drug market size will reach RMB62.1 billion in 2023, with a CAGR of 19.4% from 2018 to 2023. Due to the large number of patients in China and the continuous expansion of medical insurance coverage, the market size will climb to RMB126.9 billion and RMB159.8 billion in 2027 and 2030 respectively.

NSCLC Drug Market in China, 2018-2030E

Period	CAGR
2018-2023	19.4%
2023-2027E	19.5%
2027E-2030E	8.0%



Source: Note: Market size calculations already take clinical trial success rates into account.

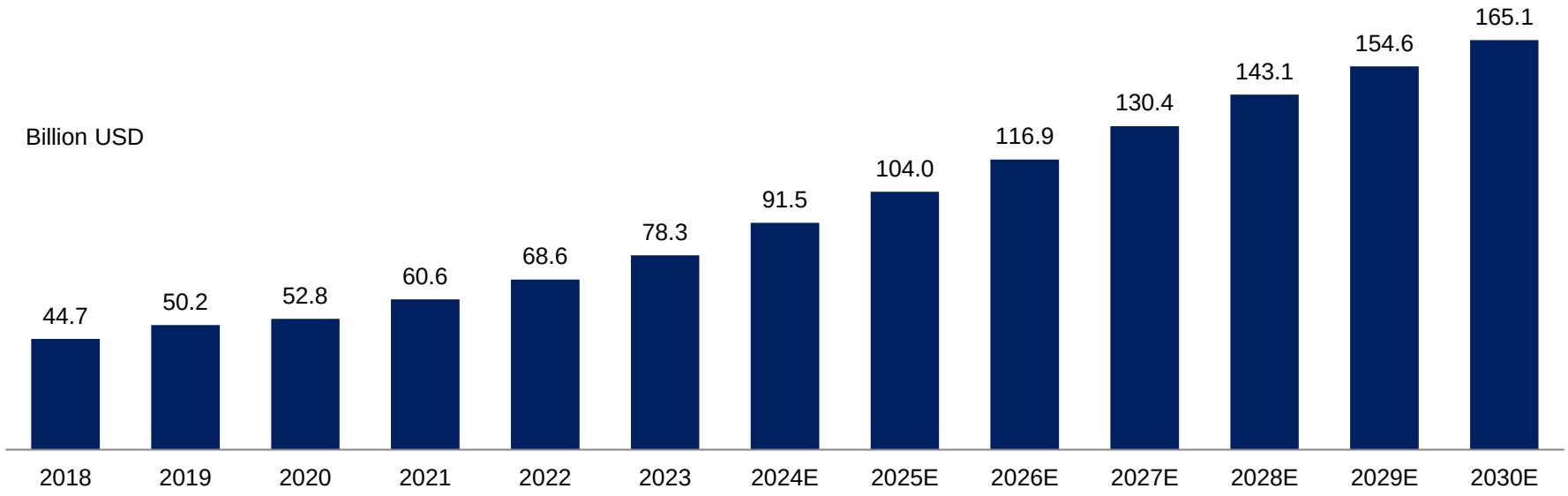
Source: Frost & Sullivan Analysis

Global NSCLC Drug Market, 2018-2030E

- The global NSCLC drug market size will reach USD78.3 billion in 2023, with a CAGR of 11.9% from 2018 to 2023. The market size is expected to reach USD130.4 billion in 2027, with a CAGR of 13.6% from 2023 to 2027. The market will further grow to USD165.1 billion in 2030, with a CAGR of 8.2% from 2027 to 2030.

Global NSCLC Drug Market, 2018-2030E

Period	CAGR
2018-2023	11.9%
2023-2027E	13.6%
2027E-2030E	8.2%



Source: Note: Market size calculations already take clinical trial success rates into account.

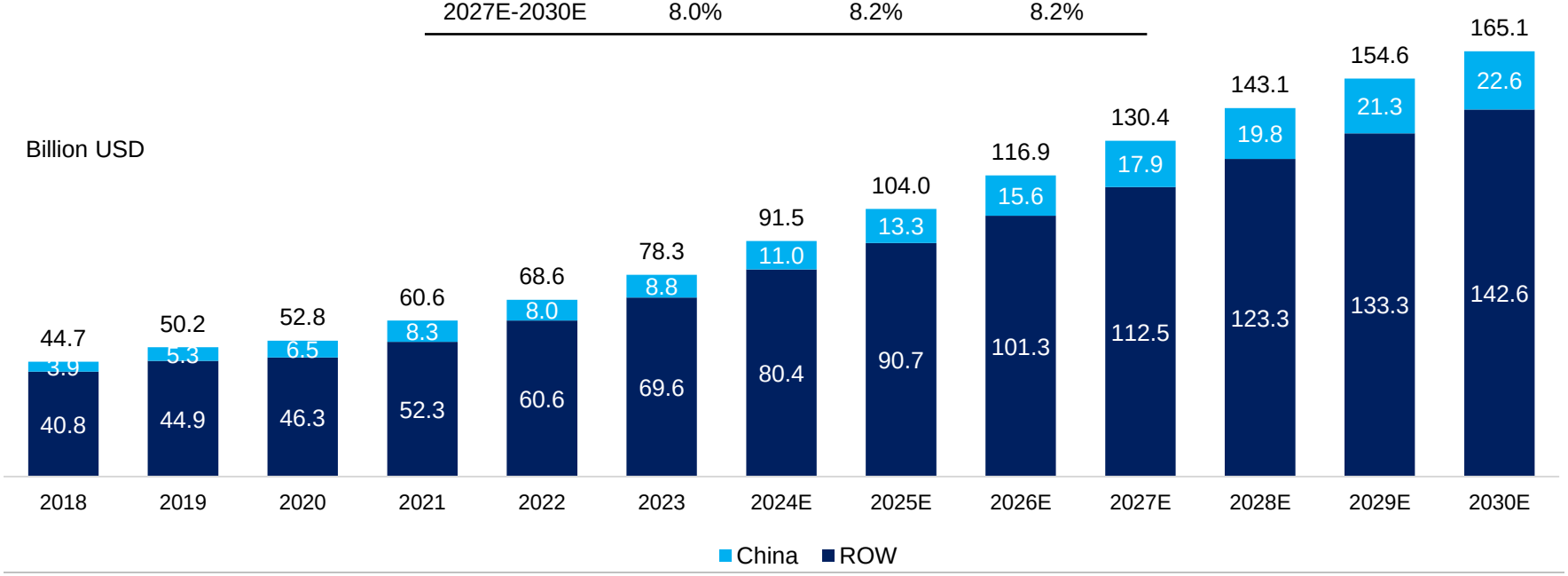
Source: Frost & Sullivan Analysis

Breakdown of Global NSCLC Drug Market, 2018-2030E

- The global NSCLC drug market size will reach USD78.3 billion in 2023, with a CAGR of 11.9% from 2018 to 2023. The market size is expected to reach USD130.4 billion in 2027, with a CAGR of 13.6% from 2023 to 2027. The market will further grow to USD165.1 billion in 2030, with a CAGR of 8.2% from 2027 to 2030.

Breakdown of global NSCLC drug market, 2018-2030E

CAGR	China	ROW	Total
2018-2023	17.8%	11.3%	11.9%
2023-2027E	19.5%	12.8%	13.6%
2027E-2030E	8.0%	8.2%	8.2%



Source: Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of NSCLC in China

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of NSCLC in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cos RMB
Docetaxel	TAXOTERE	Sanofi	1997	Class B	910 (0.5ml:20mg)	43,680
Vinorelbine	NAVELBINE	Pierre Fabre	1999	Class B	283 (1ml:10mg)	34,020
Paclitaxel	TAXOL	BMS	1999	Class A	489 (5ml:30mg)	39,138
Paclitaxel liposome	LIPUSU	Luye pharma	2003	Class B	228 (30mg)	16,416
Vinorelbine (soft capsules)	NAVELBINE	Pierre Fabre	2014	Class B	780 (20mg)	131,070
Paclitaxel polymer micelles	ZISHENG	Yizhong Pharmaceutical	2021	NA	1690(30mg)	216,320

Source: NMPA, Company Website, Frost & Sullivan Analysis

Note: 1. As of May 31, 2024, only the brand name, company and treatment cost of the original drug are included.

Analysis of other Main Approved Drugs for the Treatment of NSCLC in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Route of administration	
Gemcitabine	Gemzar	Eli Lilly	1999	Class B	272(0.2g)	43,592	Injection	
Cisplatin*	Platinol	BMS	2002	Class A	76(50ml:50mg)	2,432	Injection	
Bevacizumab	Avastin	Roche	2010	Class B	1,500(4ml:100mg)	243,000	Injection	Unr
Sintilimab	Tyvyt	Innovent	2018	Class B	1,080(10ml:100mg)	41,040	Injection	E adv E
Pembrolizumab	Keytruda	MSD	2018	NA	17,918(4ml:0.1g)	358,360	Injection	Loca EG neg
Erlotinib	Tarceva	Roche	2006	Class B	57(0.15g)	18,881	Oral	Loca
Osimertinib	Tagrisso	AstraZeneca	2017	Class B	166(80mg)	60,422	Oral	NSC und de prog
Afatinib	Giotrif	Boehringer Ingelheim	2017	Class B	140(40mg)	47,040	Oral	EG

Source: NMPA, Company Website, Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of NSCLC in the US

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of NSCLC in the US

Generic Name	Brand Name	Company	Approval Date
Vinorelbine	NAVELBINE	Pierre Fabre	1994
Docetaxel	TAXOTERE	Sanofi	1996
Paclitaxel	TAXOL	HQ SPCLT PHARMA	1992
Paclitaxel (albumin-bound)	ABRAXANE	BMS	2005

Note: As of May 31, 2024, only the brand name and company of the original drug are included.

Source: FDA, Company Website, Frost & Sullivan Analysis

Pipeline of microtubule Inhibitor Drugs under Clinical Development(above phase III) in China for the Treatment of NSCLC

- Among the microtubule inhibitor chemotherapy drugs currently under clinical development for the treatment of NSCLC, only utidelone is an innovative chemotherapy drug molecule.

Pipeline of microtubule Inhibitor Drugs under Clinical Development above phase II) in China for the Treatment of NSCLC

Drug Name	Company	Clinical Stage	First Post Date
Utidelone injection	Biostar pharmaceutical	Phase III	2022-12-08

Note: As of May 31, 2024.

Source: CDE, Frost & Sullivan Analysis

Comparison of Competing Chemotherapy Drugs for Advanced NSCLC - I

Clinical Efficacy Data Comparison					
Drug Name	**Utidelone**	**Ixabepilone**	**Eribulin**	**Docetaxel**	**Album Paclitaxel**
Trial Code	BG01-1801	J Clin Oncol 25	NCT01454934	TAX317	BMC Cancer (2017) 17:683
Number of Patients Enrolled	26	69	270	49	31
ORR/%	19%	11.6%	12.2%	6.0%	19.3%
PFS/Month	4.37	1.5[1]	3.0	3.1[2]	4.5
OS/Month	>16	7.3	9.5	7.2[3]	15.7
1 Year Survival Rate	69%	38%	40%	40%	54.8%

Note: 1. Time to progression (TTP) is 1.5 months.
2. Time to progression (TTP) is 12.3 weeks, which is approximately 3.1 months.
3. Overall OS including docetaxel 75mg/m2 and 100mg/m2 dose groups.

Source: FDA, NMPA, Literature Review, Frost & Sullivan Analysis

Comparison of Competing Chemotherapy Drugs for Advanced NSCLC - II

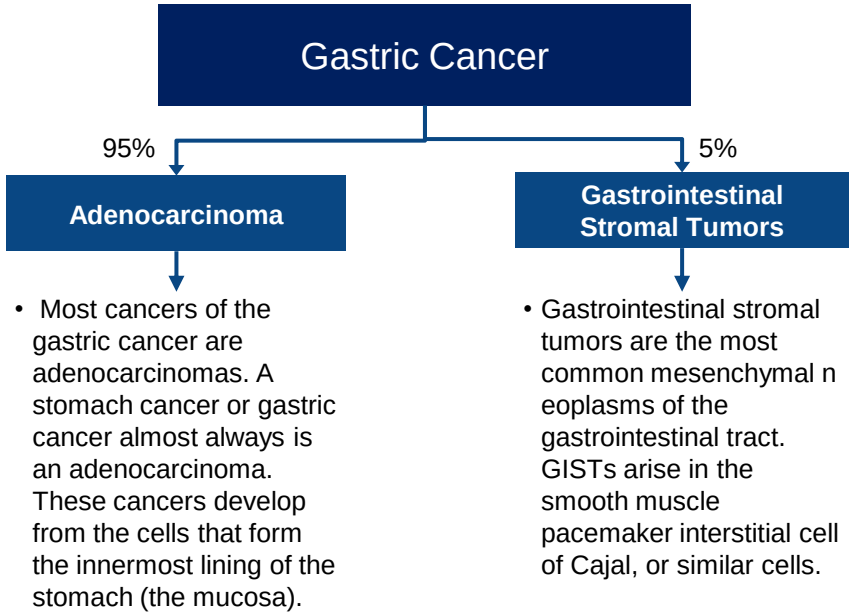
Safety Comparison (Incidence Of Major Adverse Events (Grade 3-4))					
Drug Name	**Utidelone**	**Ixabepilone**	**Eribulin**	**Docetaxel**	**Album Paclitaxel**
Number Of Patients Enrolled	26	69	270	55	31
Neutropenia	3.8%[1]	17.0%	48.7%	67.3%	38.6%
Febrile Neutropenia	0.0%	1.0%	N/A	1.8%	12.9%
Leukopenia	3.8%	9.0%	19.3%	N/A	22.5%
Thrombocytopenia	0.0%	2.0%	N/A	0.0%	0.0%
Peripheral Neurotoxicity	23%	6.0%	3.3%	3.6%	9.6%

Note: 1. Neutropenic events with Utidelone were all grade 3 adverse events.

Source: FDA, NMPA, Literature Review, Frost & Sullivan Analysis

Overview of Gastric Cancer

- Gastric cancer is cancer developing from the lining of the stomach. The cancer may spread from the stomach to other parts of the body, particularly the liver, lungs, bones, lining of the abdomen and lymph nodes. Most of the time, stomach cancer develops in stages over years.
- Early symptoms may include heartburn, upper abdominal pain, nausea and loss of appetite. Later signs and symptoms may include weight loss, yellowing of the skin, etc.



● The most relevant factor ○ The least relevant factor

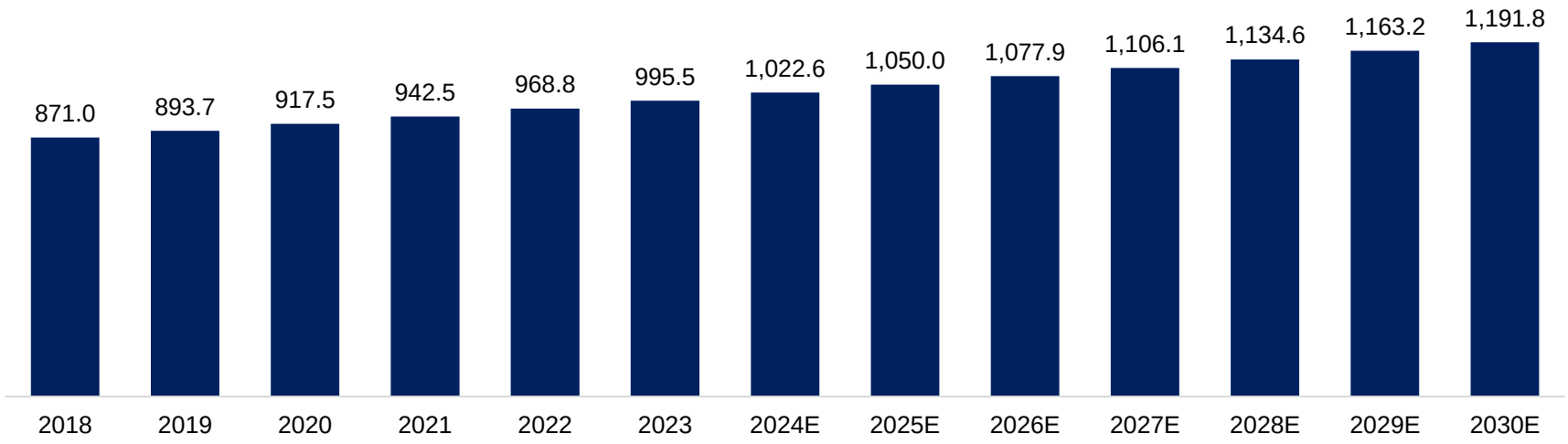
Source: NIH, Frost & Sullivan Analysis

Global Incidence of Gastric Cancer, 2018-2030E

- Global new cases of gastric cancer has reached 995.5 thousand in 2023 with a CAGR of 2.7% from 2018 to 2023. It is estimated to be 1,191.8 thousand in 2030, representing a CAGR of 2.6% from 2023 to 2030.

Global incidence of Gastric Cancer, 2018-2030E

Period	CAGR
2018-2023	2.7%
2023-2027E	2.7%
2027E-2030E	2.5%



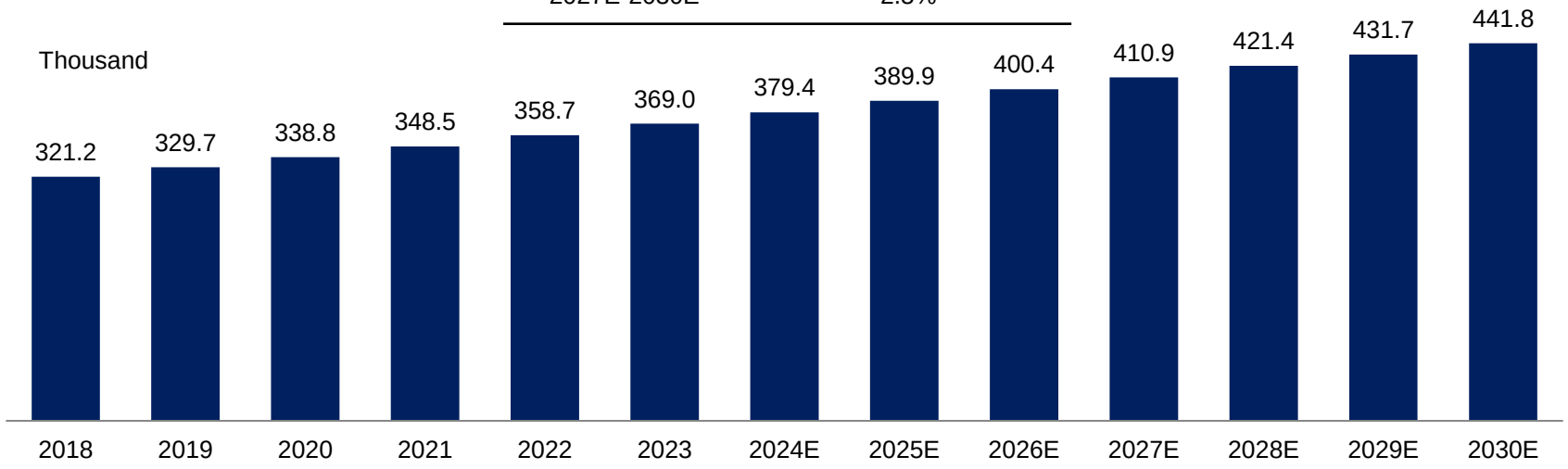
Source: ACS, Frost & Sullivan Analysis

Incidence of Gastric Cancer in China, 2018-2030E

- Gastric cancer is one of the most frequently occurring cancers in China and there is an obvious geographical distribution. China new cases of gastric cancer has reached 369.0 thousand in 2023. There are around 23.7% people with gastric cancer are HER2-positive in China.
- The increased pressure, unhealthy diet will continuously increase the risk of developing gastric cancer in China. It is expected to be 441.8 thousand in 2030, with a CAGR of 2.6% from 2023 to 2030.

Incidence of Gastric Cancer in China, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.7%
2027E-2030E	2.5%

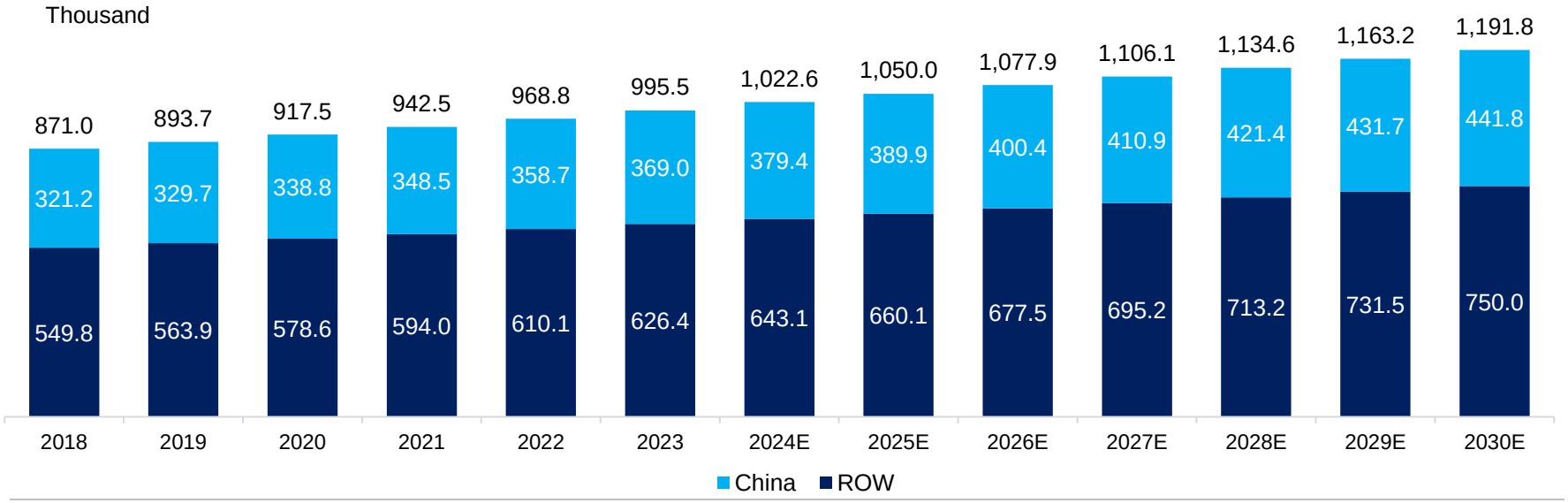


Source: NCCR, Frost & Sullivan Analysis

China and Global Incidence of Gastric Cancer, 2018-2030E

China and Global Incidence of GC, 2018-2030E

CAGR	China	ROW	Total
2018-2023	2.8%	2.6%	2.7%
2023-2027E	2.7%	2.6%	2.7%
2027E-2030E	2.5%	2.6%	2.5%

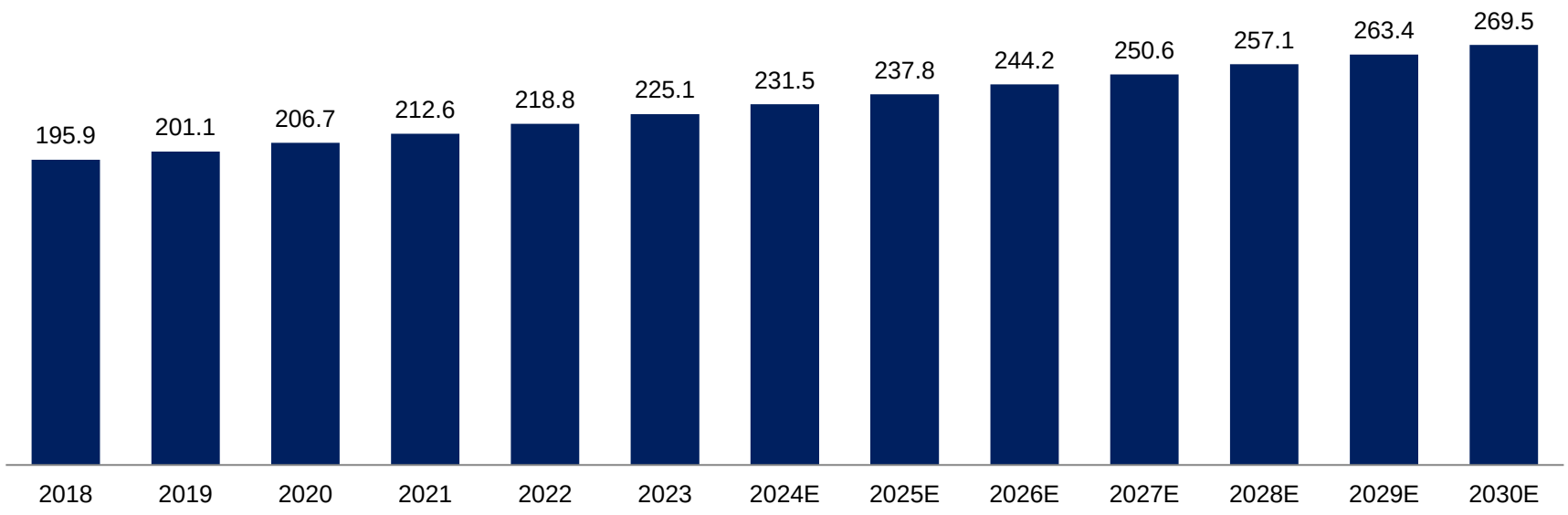


Source: Frost & Sullivan Analysis

Incidence of Advanced Gastric Cancer in China, 2018-2030E

Incidence of Advanced Gastric Cancer in China, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.7%
2027E-2030E	2.5%

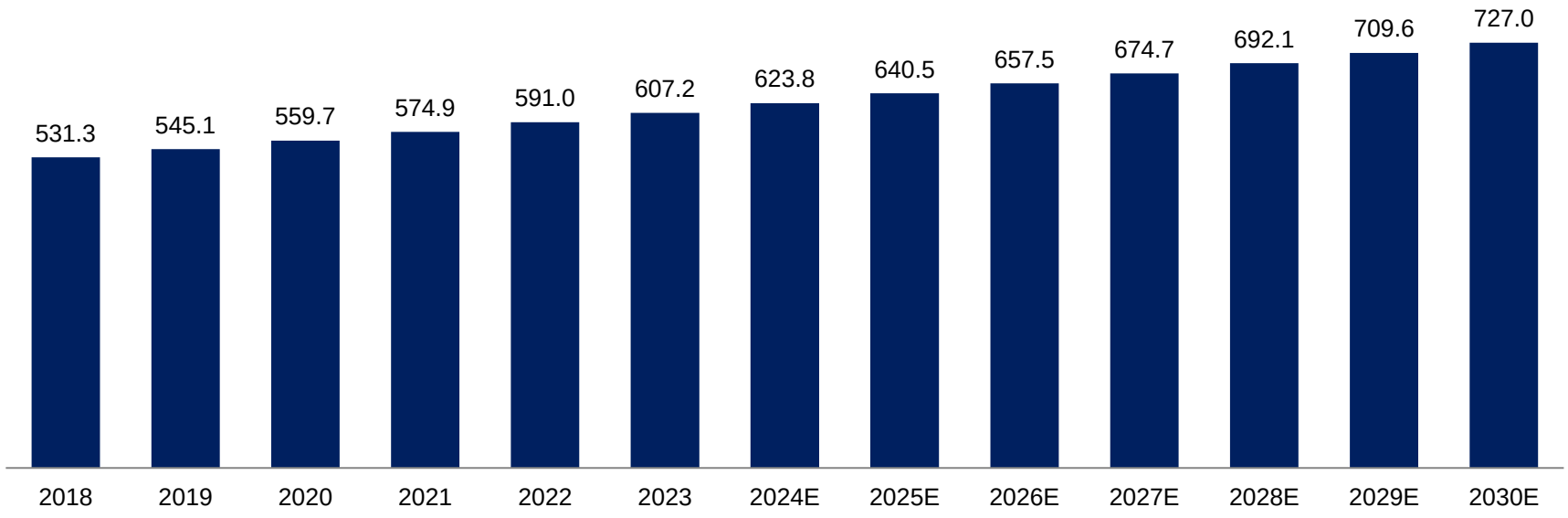


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Advanced Gastric Cancer, 2018-2030E

Global Incidence of Advanced Gastric Cancer, 2018-2030E

Period	CAGR
2018-2023	2.7%
2023-2027E	2.7%
2027E-2030E	2.5%



Source: NCCR, Frost & Sullivan analysis

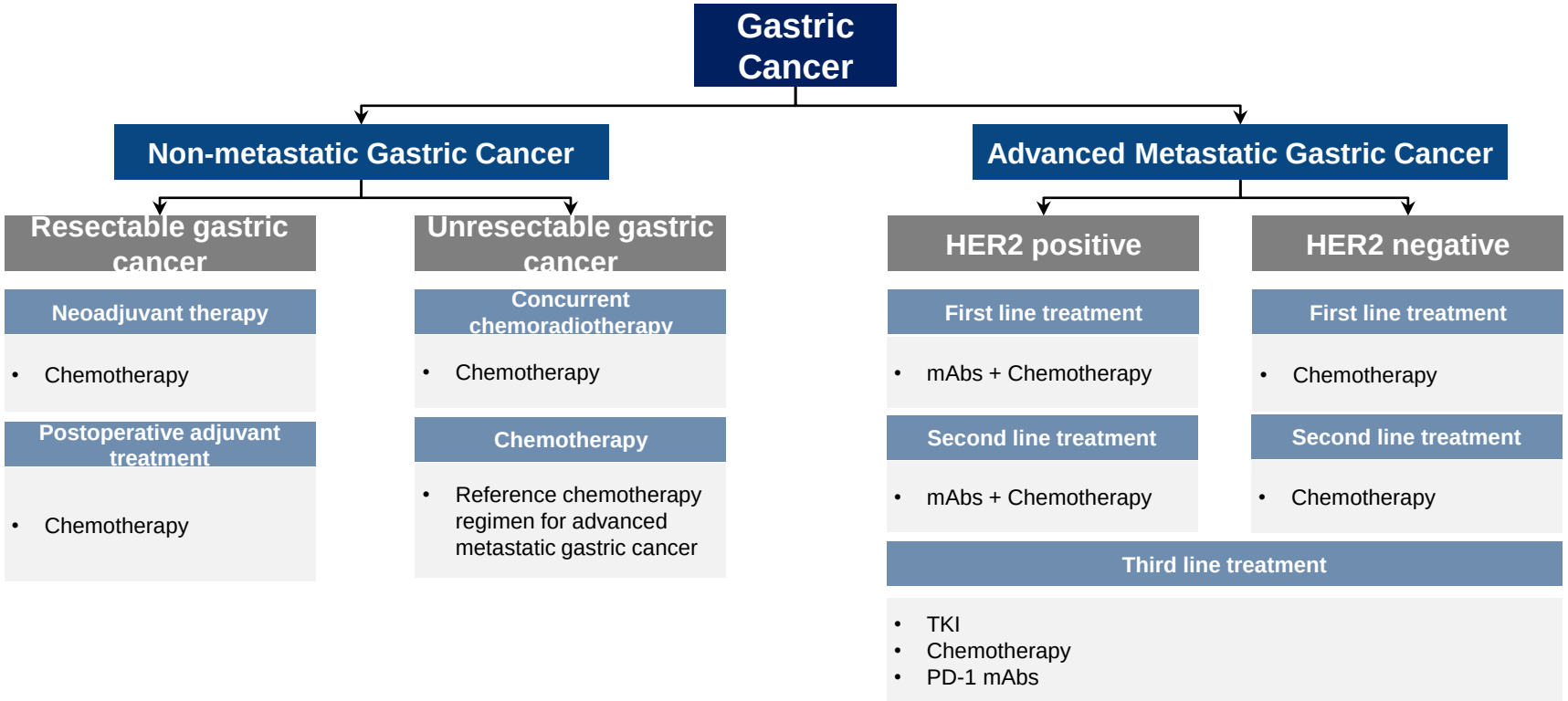
CSCO Treatment Paradigm for Gastric Cancer

CSCO gastric cancer treatment paradigm includes:

Neoadjuvant treatment (chemotherapy or chemoradiotherapy, chemotherapy drugs include platinum, taxanes, fluorouracil, etc.).

Adjuvant treatment (chemotherapy or chemoradiotherapy, chemotherapy drugs include oxaliplatin, capecitabine, S-1, docetaxel, etc.).

Advanced gastric cancer treatment (chemoradiotherapy, monoclonal antibody, monoclonal antibody combined with chemotherapy drugs, etc., the main chemotherapy drugs are 5-FU, platinum, taxanes, irinotecan, etc.).



Note: S-1: Tegafur + gimeracil + oteracil potassium. DCF: docetaxel+cisplatin+5-FU. mDCF: docetaxel + oxaliplatin + 5-FU, docetaxel + carboplatin + 5-FU. ECF: epirubicin + cisplatin + 5-FU. mECF: epirubicin + oxaliplatin + 5-FU, epirubicin + cisplatin + capecitabine, epirubicin + oxaliplatin + capecitabine.

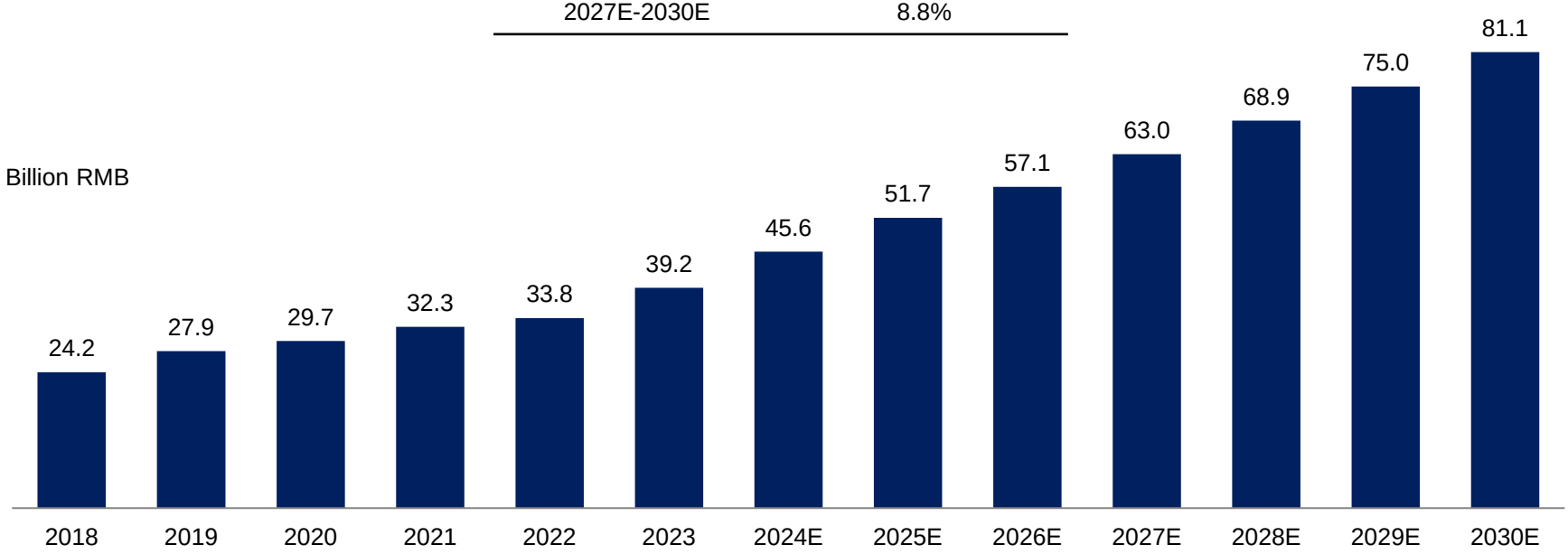
Source: CSCO, Frost & Sullivan Analysis

Gastric Cancer Drug Market in China, 2018-2030E

- China's gastric cancer drug market size will reach RMB39.2 billion in 2023, with a CAGR of 10.1% from 2018 to 2023. Due to the large number of patients in China and the continuous expansion of medical insurance coverage, the market size will climb to RMB63.0 billion and RMB81.1 billion in 2027 and 2030 respectively.

Gastric Cancer Drug Market in China, 2018-2030E

Period	CAGR
2018-2023	10.1%
2023-2027E	12.6%
2027E-2030E	8.8%



Source: Note: Market size calculations already take clinical trial success rates into account.

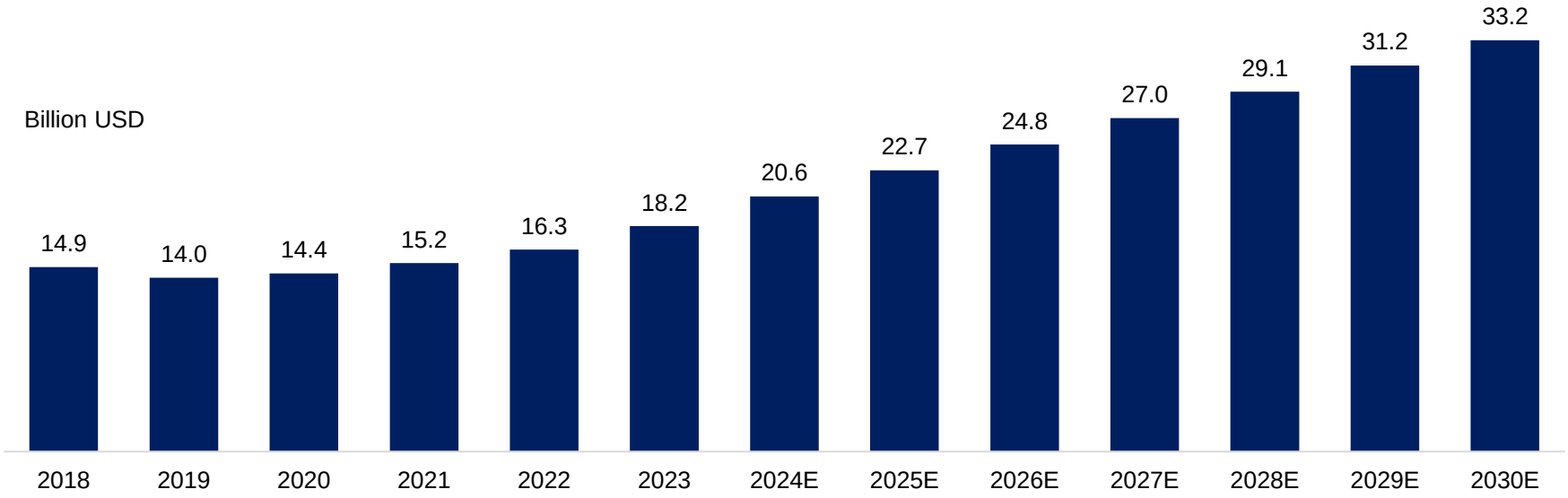
Source: Frost & Sullivan Analysis

Global Gastric Cancer Drug Market, 2018-2030E

- The global gastric cancer drug market size will reach USD18.2 billion in 2023, with a CAGR of 4.1% from 2018 to 2023. The market size is expected to reach USD27.0 billion in 2027, with a CAGR of 10.3% from 2023 to 2027. The market will further grow to USD33.2 billion in 2030, with a CAGR of 7.2% from 2027 to 2030.

Global Gastric Cancer Drug Market, 2018-2030E

Period	CAGR
2018-2023	4.1%
2023-2027E	10.3%
2027E-2030E	7.2%



Source: Note: Market size calculations already take clinical trial success rates into account.

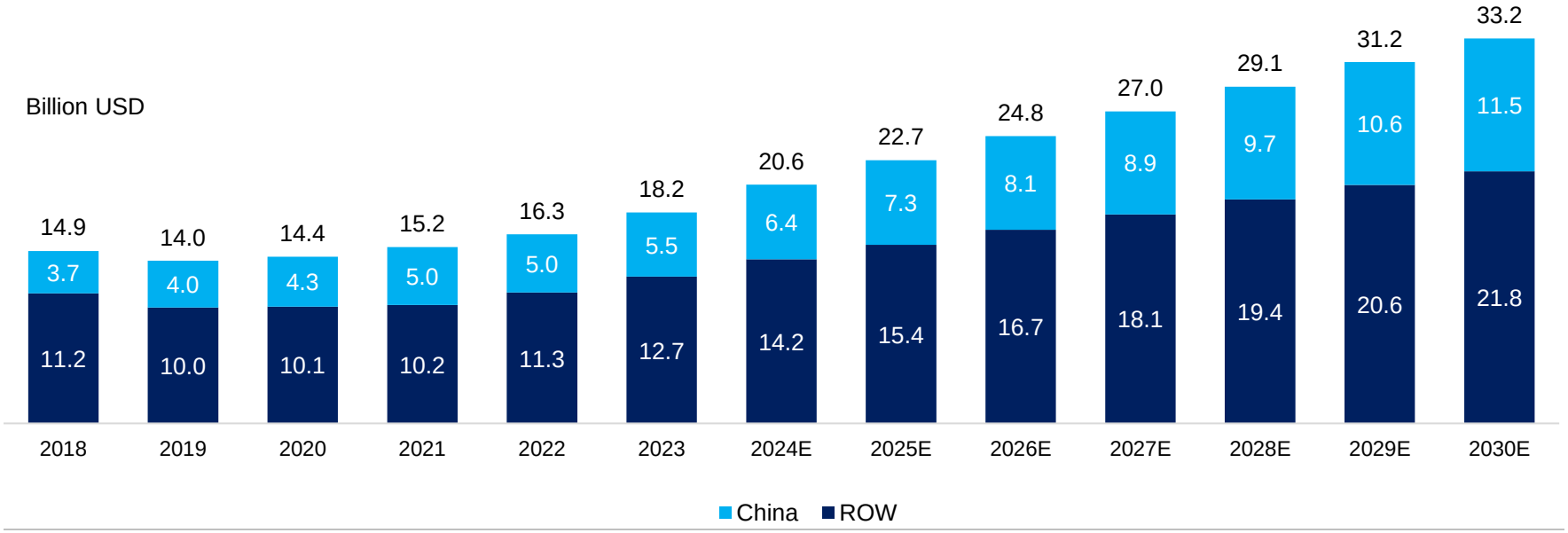
Source: Frost & Sullivan Analysis

Breakdown of Global Gastric Cancer Drug Market, 2018-2030E

- The global gastric cancer drug market size will reach USD18.2 billion in 2023, with a CAGR of 4.1% from 2018 to 2023. The market size is expected to reach USD27.0 billion in 2027, with a CAGR of 10.3% from 2023 to 2027. The market will further grow to USD33.2 billion in 2030, with a CAGR of 7.2% from 2027 to 2030.

Breakdown of global gastric cancer drug market, 2018-2030E

CAGR	China	ROW	Total
2018-2023	8.7%	2.4%	4.1%
2023-2027E	12.6%	9.2%	10.3%
2027E-2030E	8.8%	6.4%	7.2%



Source: Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Gastric Cancer in China

- Commonly used chemotherapy drugs for gastric cancer mainly include: platinum, taxanes, capecitabine, fluorouracil, etc. Among them, microtubule inhibitors are widely used in various lines of treatment for advanced gastric cancer. Although paclitaxel injection and albumin-paclitaxel have not been approved for gastric cancer, due to the widespread off-label use of chemotherapy drugs, they are widely used in the actual clinical treatment of first-line and above advanced gastric cancer.
- The current treatment for advanced gastric cancer is chemotherapy. First-line chemotherapy mainly uses drugs such as platinum, fluorouracil, and taxanes. After resistance to first-line chemotherapy, chemotherapy drugs that have not been used before are usually used clinically. However, the effect of second-line and above chemotherapy is poor, and the survival time of patients is usually less than 6 months. Therefore, there is an urgent clinical need for new chemotherapy drugs that can effectively overcome drug resistance and improve patient prognosis.

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Gastric Cancer in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Route of administration
Docetaxel	TAXOTERE	Sanofi	1997	Class B	910 (0.5ml:20mg)	50,961	Injection

Note: 1. As of May 12 2024, only the brand name and company of the original drug are included.

2. The annual treatment cost is estimated based on an average body surface area of 1.6m2 and 8 treatment cycles per year. The unit price is calculated based on the pre-me

Source: NMPA, Company Website, Frost & Sullivan Analysis

Analysis of other Main Approved Drugs for the Treatment of GC in China

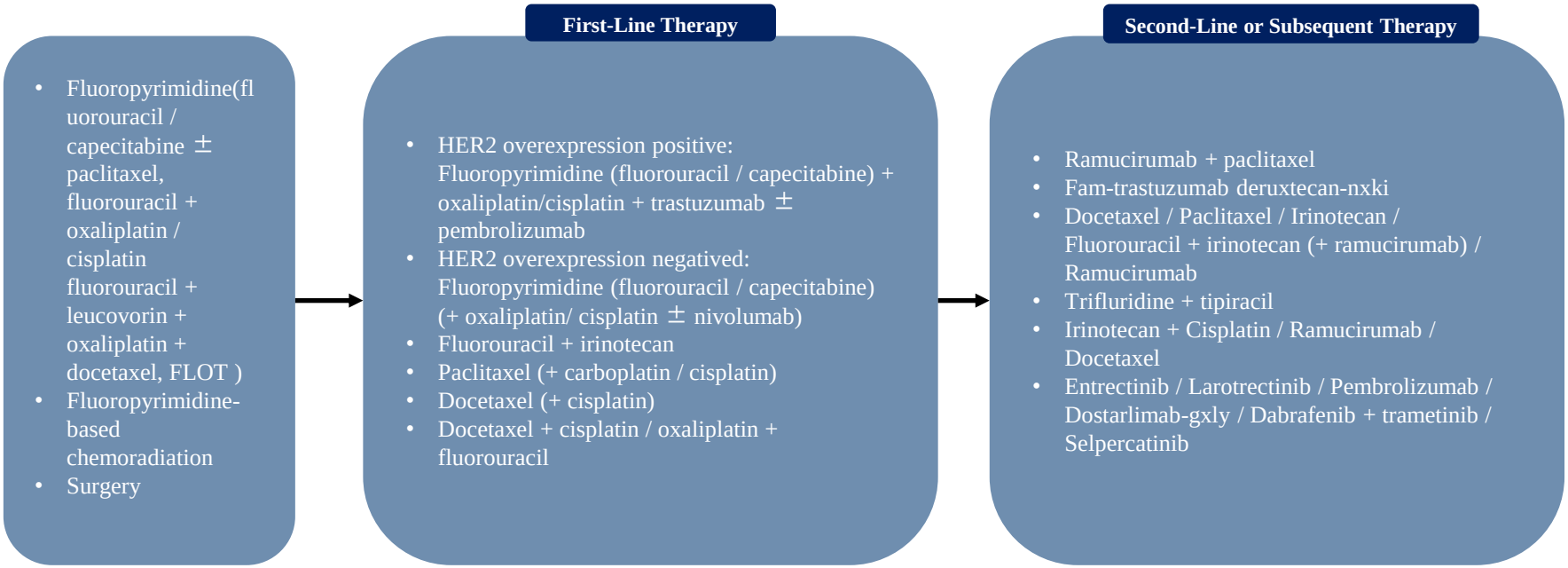
Analysis of other Representative Approved Drugs for the Treatment of GC in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Route of administration	Appr
Capecitabine	Xeloda	Roche	2000	Class B	22(0.5g)	19,730	Oral	Adjuvant chem first-line treatme g
Cisplatin*	Platinol	BMS	2002	Class A	76(50ml:50mg)	2,432	Injection	G
Sintilimab	Tyvyt	Innovent	2018	Class B	1,080(10ml:100 mg)	23,760	Injection	First-line treatm advanced, recu ad
Nivolumab	Opdivo	BMS	2018	NA	4,586(4ml:40mg)	467,847	Injection	First-line tre metastatic ga recurrent gastri previously rece trea
Apatinib	Aitan	Hengrui	2014	Class B	157.14(0425g)	34,885	Oral	Advanced gas progresses o previous system

Source: NMPA, Company Website, Frost & Sullivan Analysis

Treatment Paradigm of of Gastric Cancer from NCCN

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease

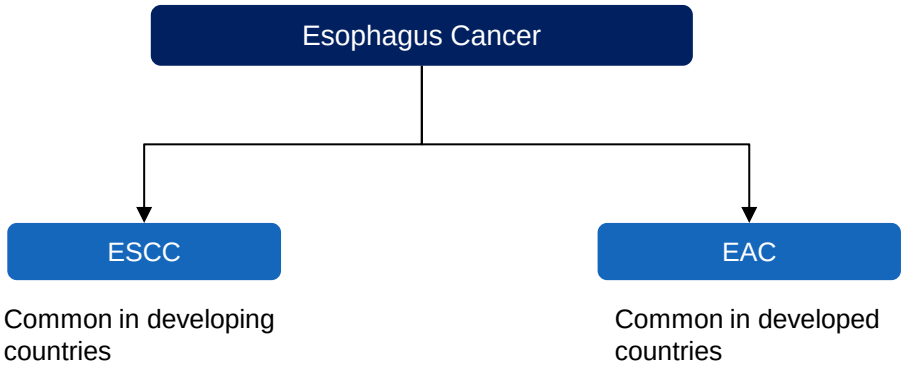


Notes:
Chemotherapy: T=docetaxel, paclitaxel and albumin-bound paclitaxel; X=capecitabine; N=navelbine; Cb=carboplatin; G=gemcitabine; LD=liposomal doxorubicin;
Therapeutic antibody: H=trastuzumab; P=pertuzumab;
Endocrine Therapy: AI=Aromatase inhibitor; F=fulvestrant; TAM=tamoxifen;
Small molecule targeted drug: L=lapatinib.

Source: NCCN 2023, Frost & Sullivan Analysis

Overview of Esophagus Cancer

- Esophagus cancer, one of the most common cancer around the world, arises from the lining cells of esophagus .
- Esophagus cancer cells that derived from different layers of esophagus wall behave differently. There are two main types of esophagus cancer, based on the type of cell it starts in. The esophageal squamous-cell carcinoma(ESCC) is more common in the developing world while the esophageal adenocarcinoma(EAC) is more common in developed countries.



Typical Symptoms

- Trouble swallowing(the most common symptom)
- Chest pain
- Hoarseness
- Weight loss
- Chronic cough
- Vomiting

Risk Factors

Tobacco and alcohol

The use of tobacco products, including cigarettes, cigars, pipes, and chewing tobacco, is a major risk factor for esophageal cancer.

Age

Gender

Men are more likely than women to get esophageal cancer.

Diet

Frequently drinking very hot may increase the risk for the squamous cell type of esophageal cancer.

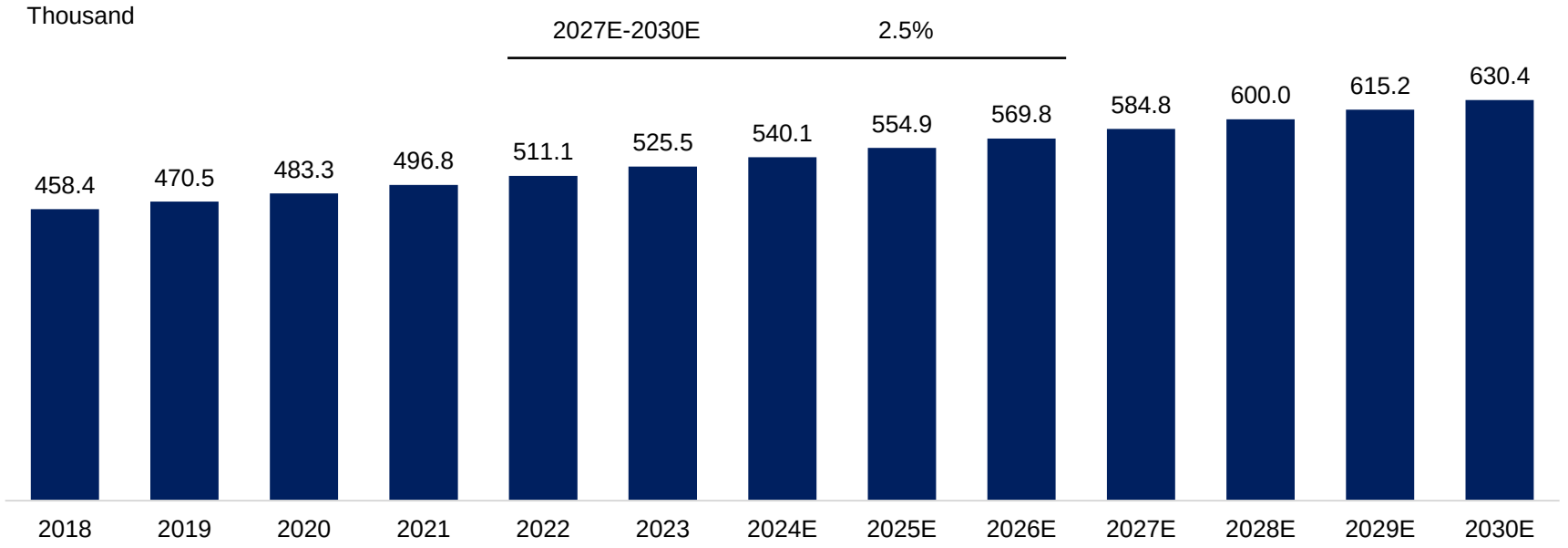
Source: ACS, NCCN Guideline, ESMO Clinical Practice Guidelines, Frost & Sullivan Analysis

Global Incidence of Esophagus Cancer, 2018-2030E

- Global new cases of esophagus cancer has reached 525.5 thousand in 2023 with a CAGR of 2.8% from 2018 to 2023. It is estimated to be 584.8 and 630.4 thousand in 2027 and 2030, representing a CAGR of 2.7% and 2.5% from 2023 to 2027 and 2027 to 2030, respectively.

Global incidence of Esophagus Cancer, 2018-2030E

Period	CAGR
2018-2023	2.8%
2023-2027E	2.7%
2027E-2030E	2.5%



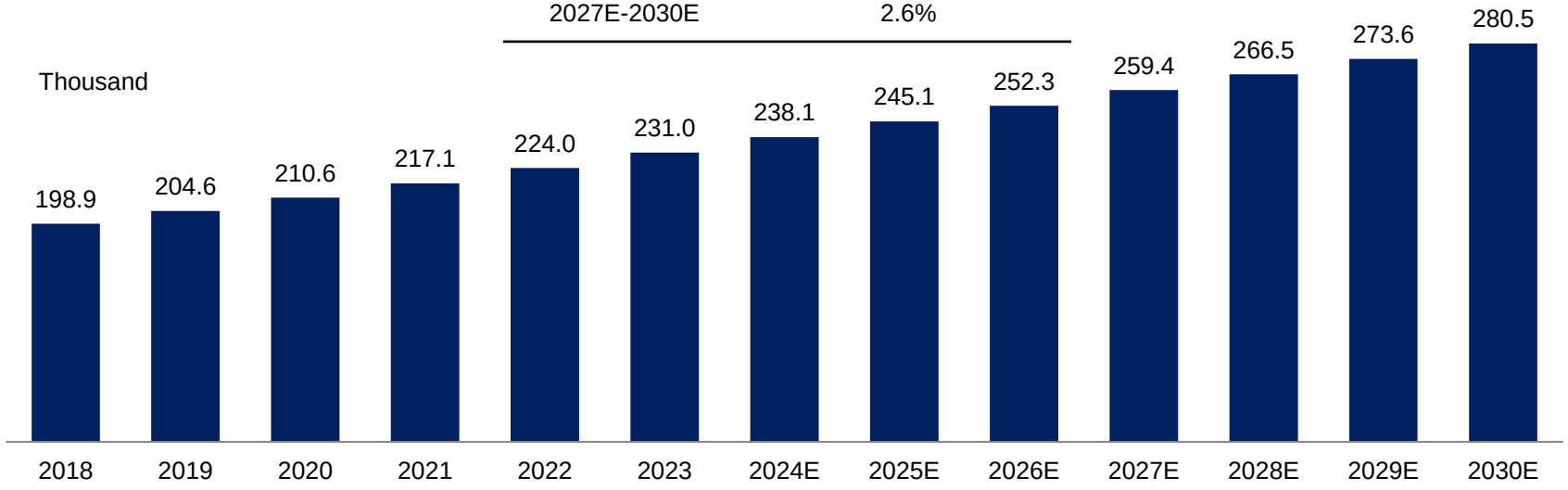
Source: ACS, Frost & Sullivan Analysis

Incidence of Esophagus Cancer in China, 2018-2030E

- Esophagus cancer is one of the most frequently occurring cancers in China and there is an obvious geographical distribution. The increased pressure, unhealthy diet will continuously increase the risk of developing esophagus cancer in China. It is expected to be 280.5 thousand in 2030, with a CAGR of 2.6% from 2027 to 2030.

Incidence of Esophagus Cancer in China, 2018-2030E

Period	CAGR
2018-2023	3.0%
2023-2027E	2.9%
2027E-2030E	2.6%

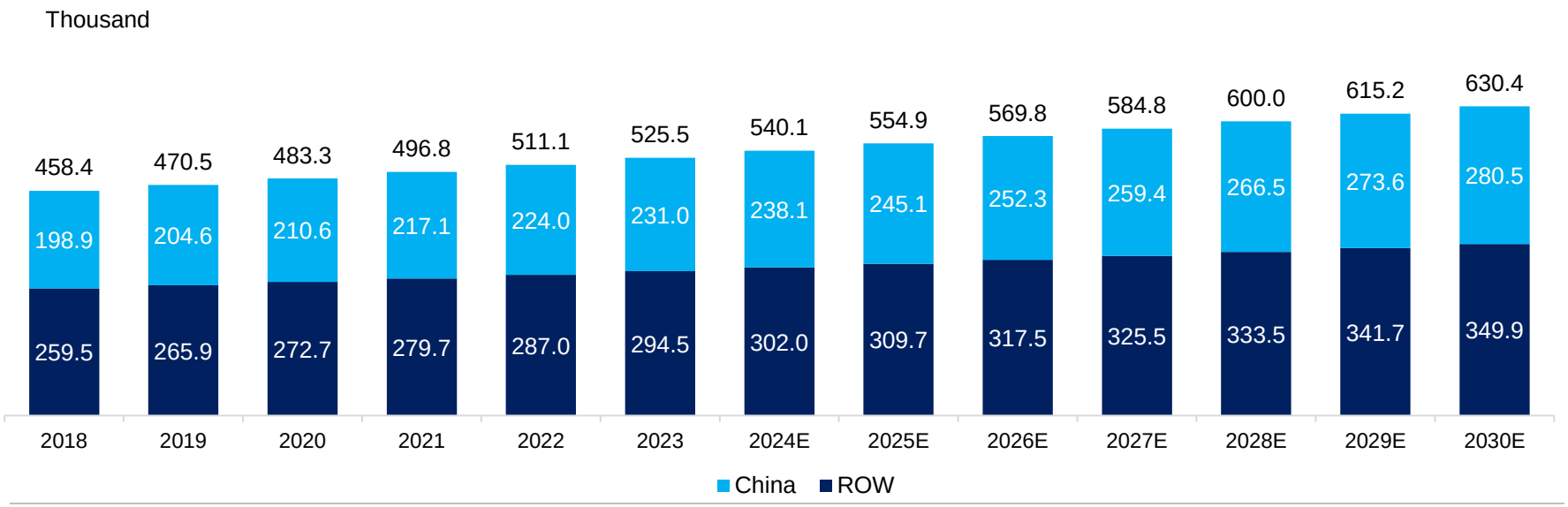


Source: NCCR, Frost & Sullivan Analysis

China and Global Incidence of Esophagus Cancer, 2018-2030E

China and Global Incidence of Esophagus Cancer, 2018-2030E

CAGR	China	ROW	Total
2018-2023	3.0%	2.6%	2.8%
2023-2027E	2.9%	2.5%	2.7%
2027E-2030E	2.6%	2.4%	2.5%

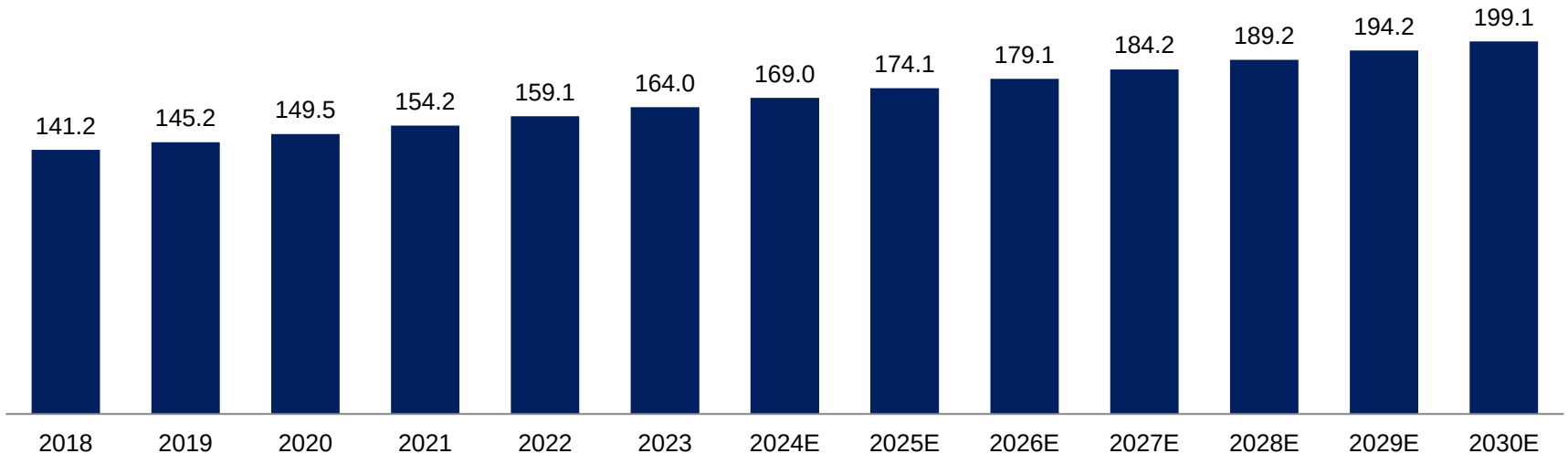


Source: Frost & Sullivan Analysis

Incidence of Advanced Esophagus Cancer in China, 2018-2030E

Incidence of Advanced Esophagus Cancer in China, 2018-2030E

CAGR	Global
2018-2023	3.0%
2023-2027E	2.9%
2027E-2030E	2.6%

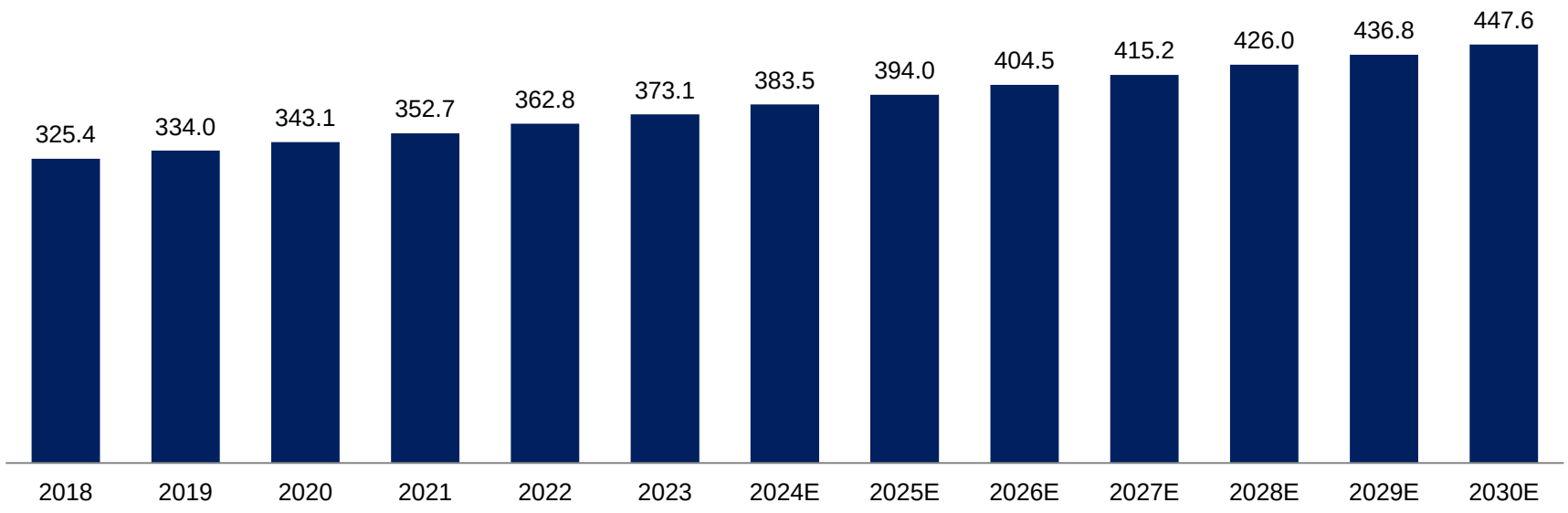


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Advanced Esophagus Cancer, 2018-2030E

Global Incidence of Advanced Esophagus Cancer, 2018-2030E

CAGR	Global
2018-2023	2.8%
2023-2027E	2.7%
2027E-2030E	2.5%



Source: NCCR, Frost & Sullivan analysis

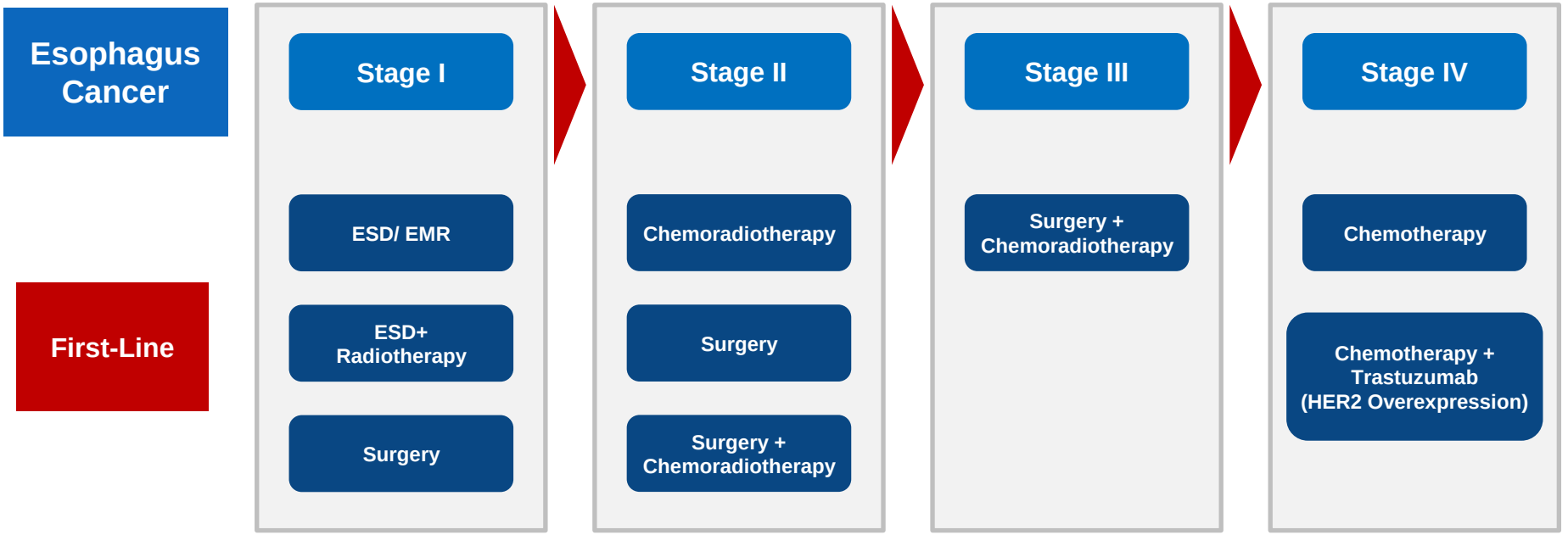
CSCO Treatment Diagram of Esophagus Cancer

CSCO esophageal cancer treatment diagram includes:

Neoadjuvant treatment (chemotherapy or chemoradiotherapy, chemotherapy drugs include platinum, taxanes, fluorouracil, etc.).

Adjuvant therapy (chemotherapy or chemoradiotherapy, nivolumab, platinum chemotherapy drugs, capecitabine, paclitaxel, docetaxel, etc.).

Treatment of advanced esophageal cancer (chemoradiotherapy, monoclonal antibodies, monoclonal antibodies combined with chemotherapy drugs, etc. The main chemotherapy drugs include 5-FU, platinum, taxanes, vinorelbine, irinotecan, etc.).



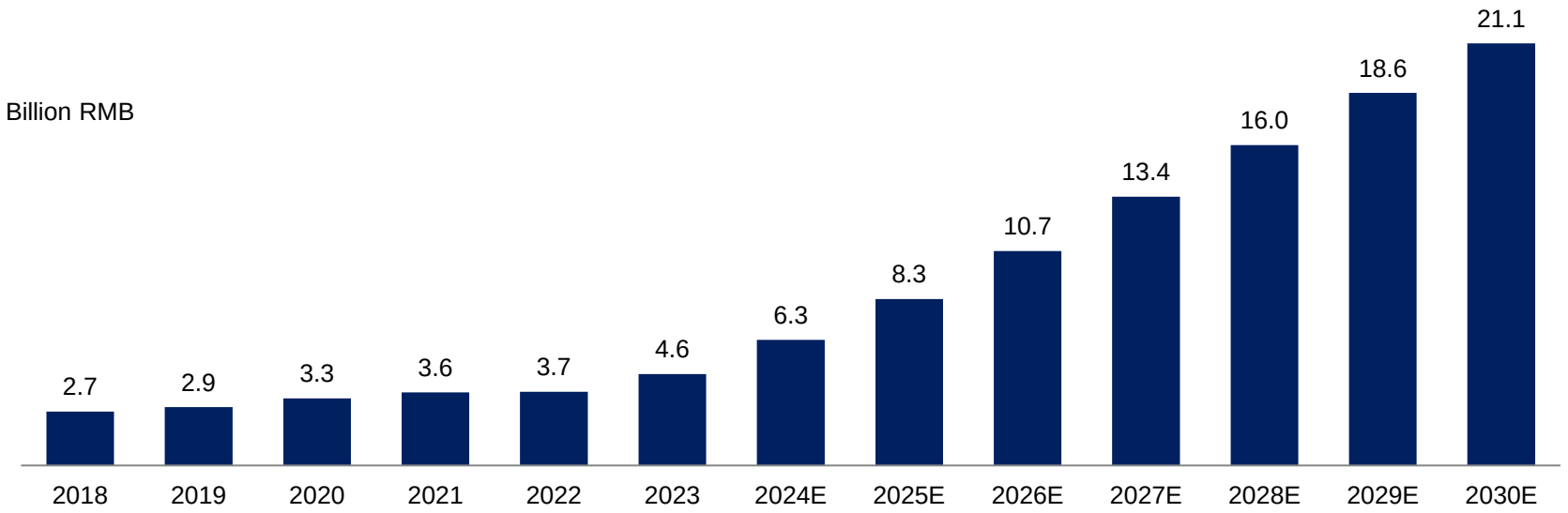
Abbreviation

Esophagus Cancer Drug Market in China, 2018-2030E

- China's esophagus cancer drug market size will reach RMB4.6 billion in 2023, with a CAGR of 10.3% from 2018 to 2023. Due to the large number of patients in China and the continuous expansion of medical insurance coverage, the market size will climb to RMB13.4 billion and RMB21.1 billion in 2027 and 2030 respectively.

Esophagus Cancer Drug Market in China, 2018-2030E

Period	CAGR
2018-2023	10.3%
2023-2027E	25.3%
2027E-2030E	14.7%



Source: Note: Market size calculations already take clinical trial success rates into account.

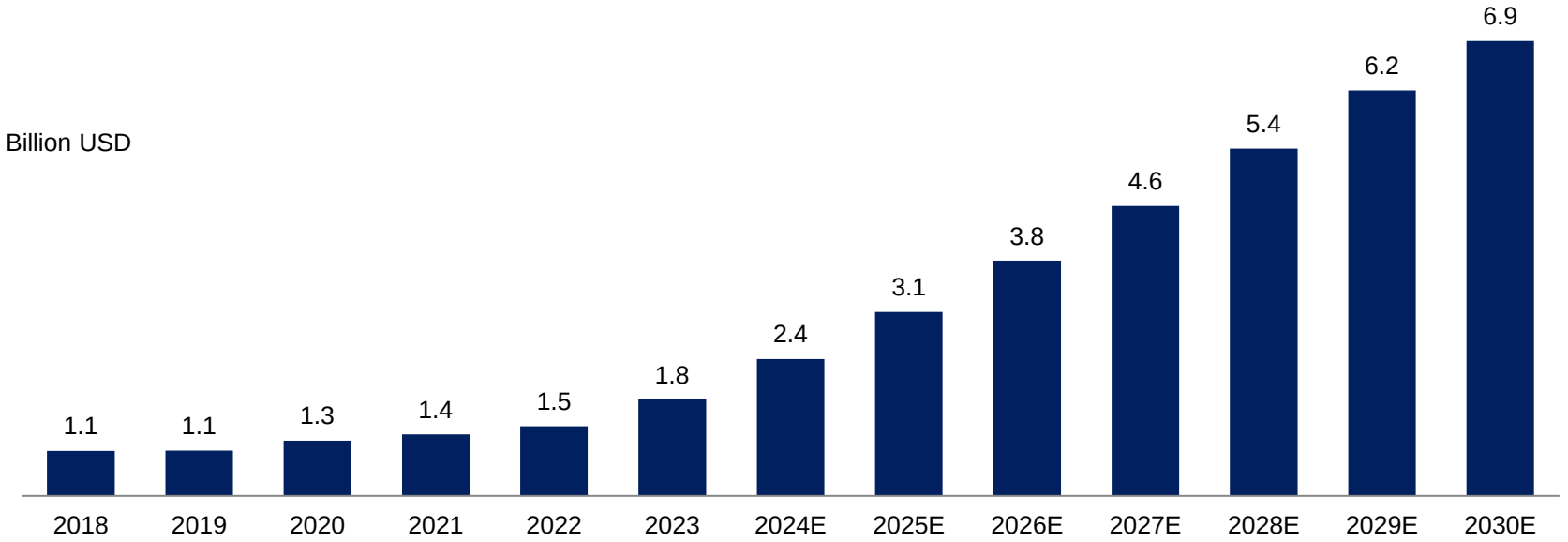
Source: Frost & Sullivan Analysis

Global Esophagus Cancer Drug Market, 2018-2030E

- The global esophagus cancer drug market size will reach USD1.8 billion in 2023, with a CAGR of 10.3% from 2018 to 2023. The market size is expected to reach USD4.6 billion in 2027, with a CAGR of 25.3% from 2023 to 2027. The market will further grow to USD6.9 billion in 2030, with a CAGR of 14.7% from 2027 to 2030.

Global Esophagus Cancer Drug Market, 2018-2030E

Period	CAGR
2018-2023	10.3%
2023-2027E	25.3%
2027E-2030E	14.7%



Source: Note: Market size calculations already take clinical trial success rates into account.

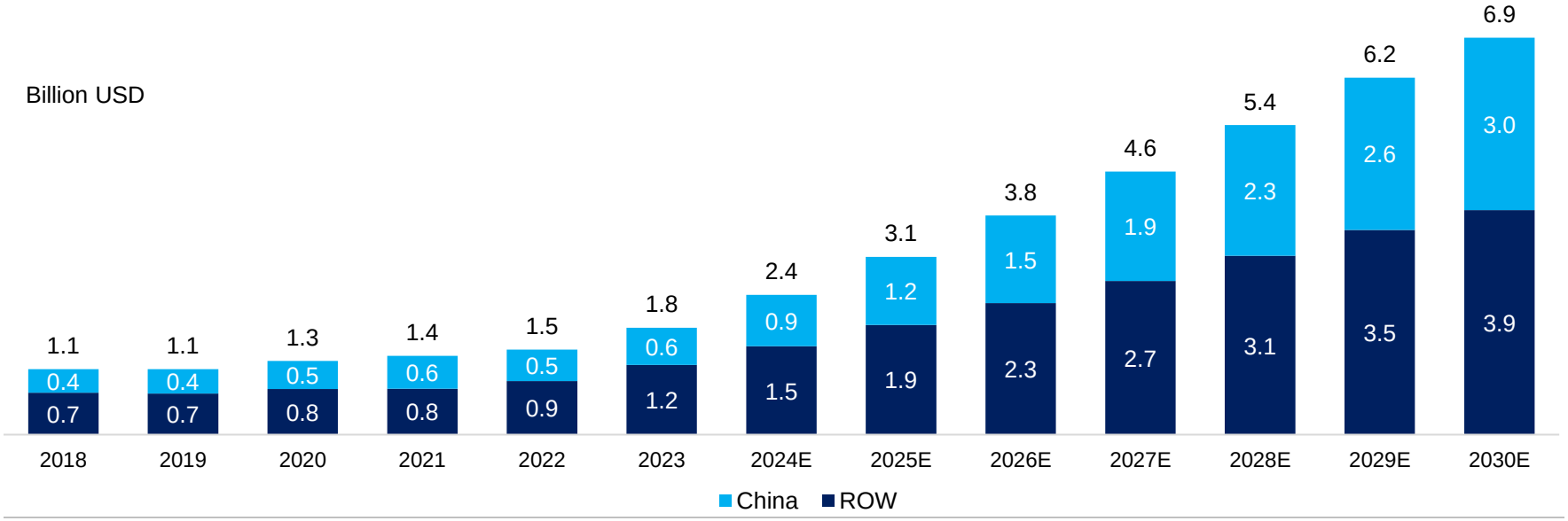
Source: Frost & Sullivan Analysis

Breakdown of Global Esophagus Cancer Drug Market, 2018-2030E

- The global esophagus cancer drug market size will reach USD1.8 billion in 2023, with a CAGR of 10.3% from 2018 to 2023. The market size is expected to reach USD4.6 billion in 2027, with a CAGR of 25.3% from 2023 to 2027. The market will further grow to USD6.9 billion in 2030, with a CAGR of 14.7% from 2027 to 2030.

Breakdown of global esophagus cancer drug market, 2018-2030E

CAGR	China	ROW	Total
2018-2023	9.6%	10.7%	10.3%
2023-2027E	31.0%	21.9%	25.3%
2027E-2030E	16.3%	13.5%	14.7%



Source: Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Esophagus Cancer in China

- The first-line treatment of esophageal cancer mainly uses drugs such as platinum, fluorouracil, and taxanes, while the second-line treatment mainly uses other chemotherapy drugs that have not been used before. However, the results of second-line and above treatments are not ideal, and the survival time of patients is usually less than one year. Therefore, there is an urgent clinical need for new chemotherapy drugs that can effectively overcome drug resistance and improve patient prognosis. Although paclitaxel injection and albumin-paclitaxel have not been approved for esophageal cancer, due to the widespread off-label use of chemotherapy drugs, they are widely used in the actual clinical treatment of advanced esophageal cancer.

Analysis of Approved microtubule Inhibitor Drugs for the Treatment of Esophagus Cancer in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Rou admini
Vindesine	-	-	1995	Class B	77(0.1g)	12,362	Inje

Note: 1. As of May 31, 2024, only the brand name and company of the original drug are included.

2. The annual treatment cost is estimated based on an average body surface area of 1.6m2 and 8 treatment cycles per year. The unit price is calculated based on the pre-me

Source: NMPA, Company Website, Frost & Sullivan Analysis

Analysis of other Main Approved Drugs for the Treatment of EC in China

Analysis of other Representative Approved Drugs for the Treatment of EC in China

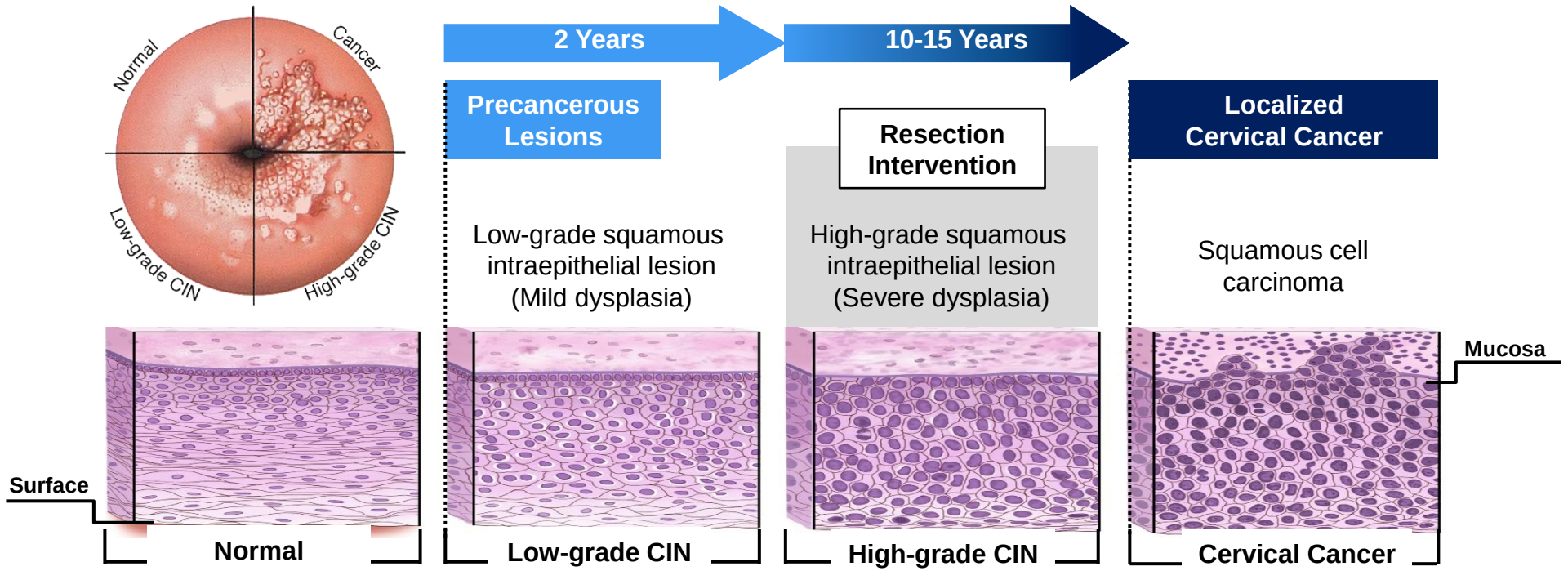
Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost/ RMB	Route of
Cisplatin*	Platinol	BMS	2002	Class A	76(50ml:50mg)	2,432	
Sintilimab	Tyvyt	Innovent	2018	Class B	1,080(10ml:100mg)	23,760	
Nivolumab	Opdivo	BMS	2018	NA	4,586(4ml:40mg)	357,766	
Pembrolizumab	Keytruda	MSD	2018	NA	17,918(4ml:0.1g)	179,180	

Source: NMPA, Company Website, Frost & Sullivan Analysis

Overview of Cervical Cancer

- Cervical cancer is another one of the few cancer types that is recommended for regular screening among average-risk populations who have no physical signs or symptoms of cancer, due to its high incidence, high mortality, long tumor development cycle, well defined precancerous stages and heavy treatment burden. Cervical cancer can be prevented or cured if detected at early stages. A precancerous cervical lesion in cervix uteri, which is also called an cervical intraepithelial neoplasia (CIN), may progress to cervical cancer if they remain in the cervix for a long period of time. In about 10% of cases, low-grade CIN progress to high-grade CIN within 2 years. High-grade CIN have the potential to develop into squamous cell carcinoma or adenocarcinoma over about 10 to 15 years if left untreated. Squamous cell carcinoma or adenocarcinoma are cancers that start in the cells lining or gland cells of the cervix. Around 90% of cervical cancers are squamous cell cancers.
- Treatment usually is not required for low-grade CIN. Only 1% of cases of low-grade CIN progress to cervical cancer. Ablation and resection procedures, like Loop electrosurgical excision procedure (LEEP), are recommended for high-grade CIN because it can reduce the risk of cervical cancer by 95% in the first 8 years after treatment.

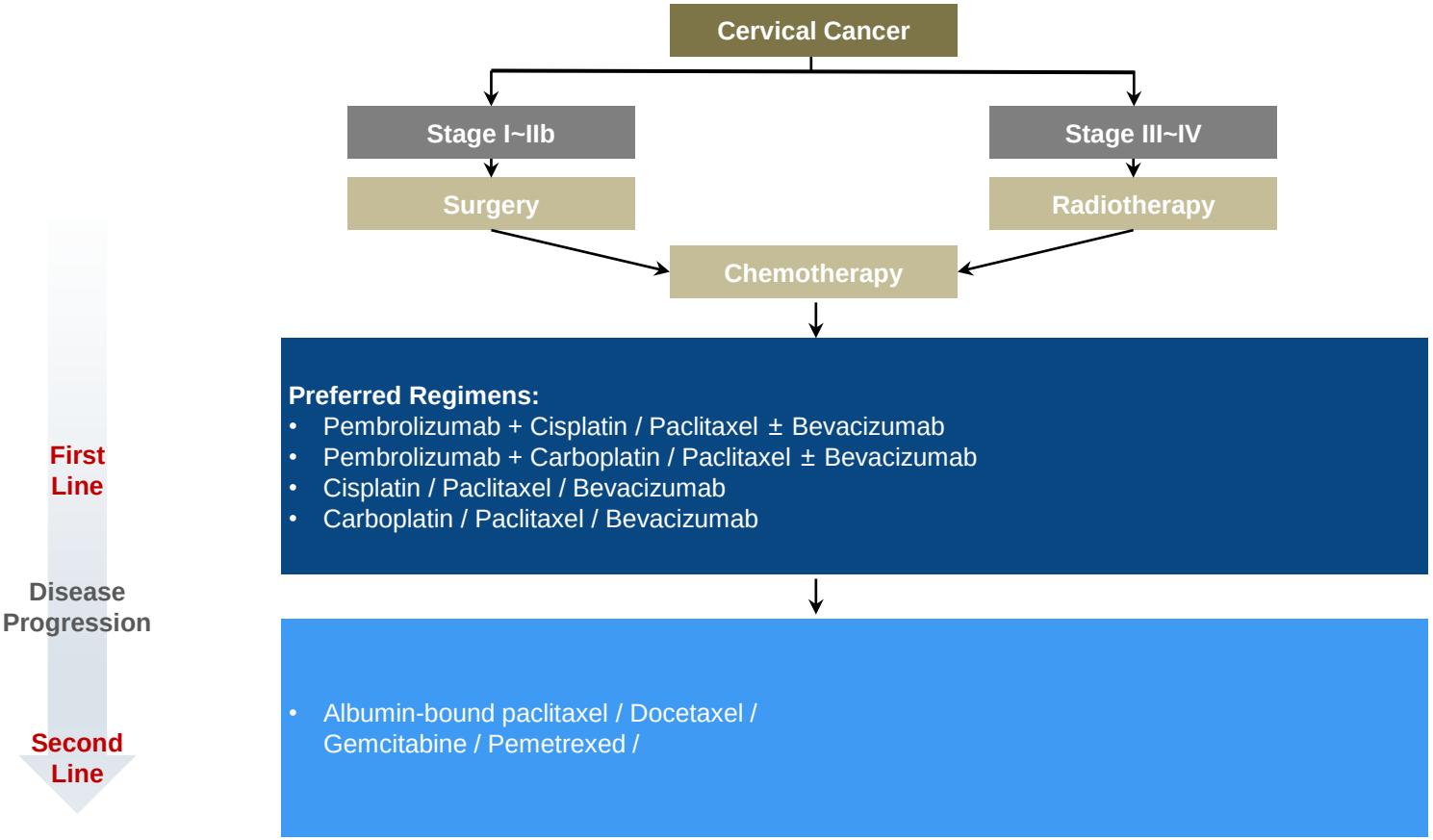
Progression of CIN to Cervical Cancer (From Precancerous Lesion to Localized Cervical Cancer)



Source: Literature Review, Frost & Sullivan Analysis

Treatment Paradigm of Cervical Cancer-NCCN

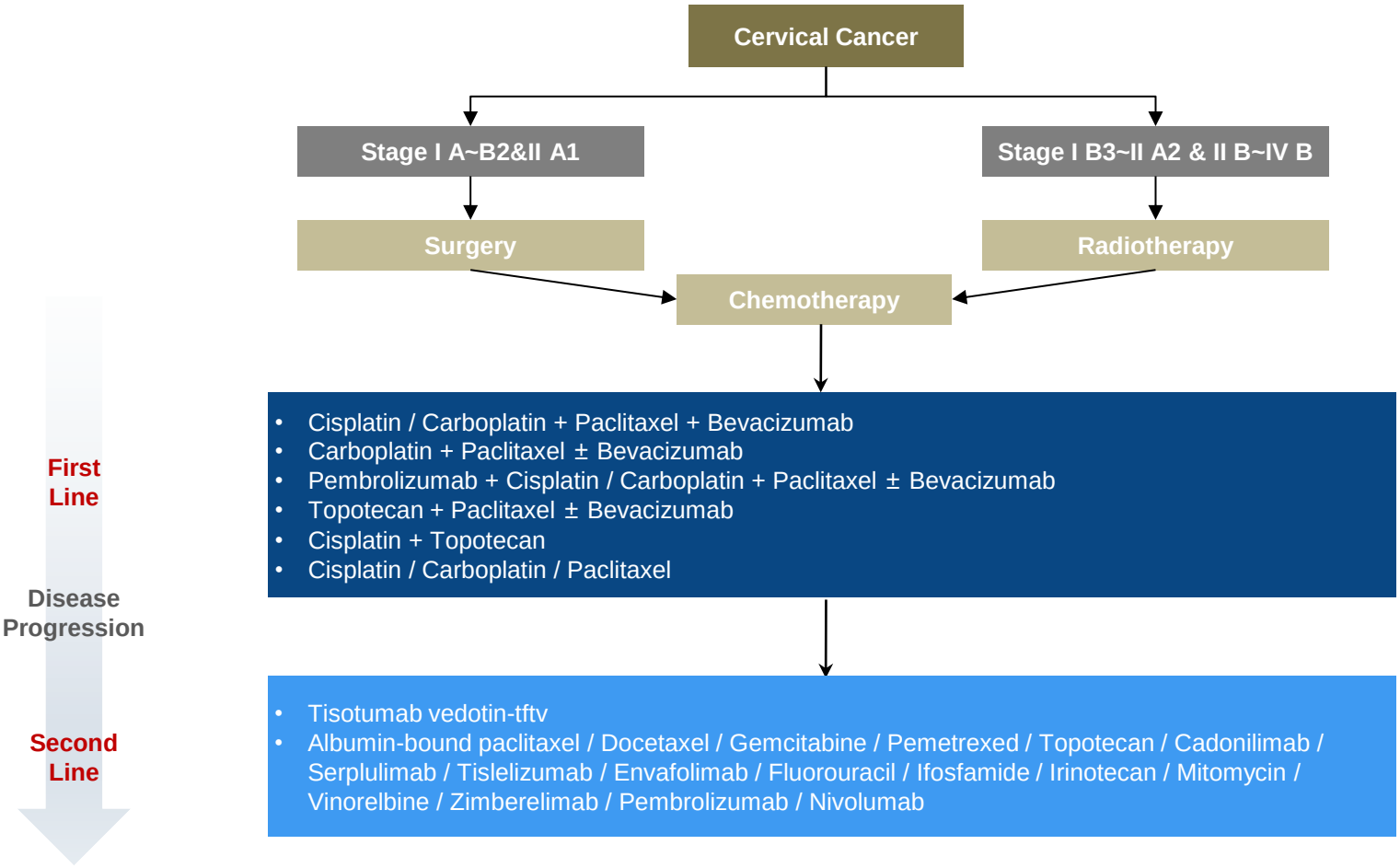
- The treatment of cervical cancer mainly includes surgery and radiotherapy. Chemotherapy is widely used in combination with surgery and radiotherapy and in the treatment of advanced recurrent cervical cancer, using platinum (mainly cisplatin) based monotherapy or combined chemotherapy.
- HPV therapeutic vaccine can be used in all lines of treatment.



Source: NCCN 2022, Frost & Sullivan Analysis

Treatment Paradigm of Cervical Cancer-CSCO

- The treatment of cervical cancer mainly includes surgery and radiotherapy. Chemotherapy is widely used in combination with surgery and radiotherapy and in the treatment of advanced recurrent cervical cancer, using platinum (mainly cisplatin) based monotherapy or combined chemotherapy.



Source: CSCO 2023

Clinical Efficacy Results of Cervical Cancer

	mPFS (month)	ORR	mOS (month)	Patients base-line situation	Medication
First line	10.4	68.0%	24.4 (ITT population)	Patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent	Pembrolizumab and chemotherapy ± bevacizumab
Second Line	7	39.5%	Not Reached	Recurrent or metastatic cervical cancer patients including had at least one measurable lesion after prior lines of treatment and had completed one or more post-baseline tumor assessments	PD-1 (camrelizumab or sintilimab) as a monotherapy or in combination with chemotherapy or chemotherapy and anti-angiogenic therapy
Subsequent Line	4	28.6%			

Source:
1. Pembrolizumab label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf
2. Efficacy and Prognostic Factors for Response to PD-1 Inhibitors in Advanced Cervical Carcinoma: A Retrospective Study. https://www.dovepress.com/efficacy-and-prognostic-factors-for-response-to-pd-1-inhibitors-in-adv-peer-reviewed-fulltext-article-DDDT#

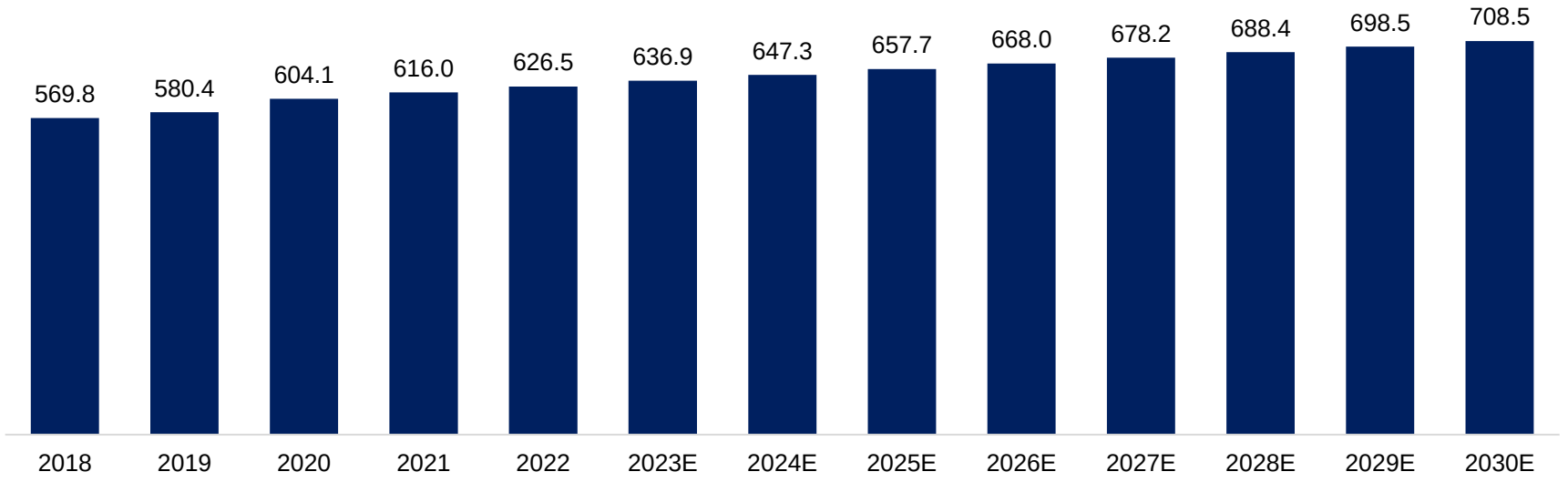
Source: Frost & Sullivan Analysis

Global Incidence of Cervical Cancer, 2018-2030E

- Global new cases of cervical cancer has reached 626.5 thousand in 2022 with a CAGR of 2.4% from 2018 to 2022. It is estimated to be 668.0 and 708.5 thousand in 2026 and 2030, representing a CAGR of 1.6% and 1.5% from 2022 to 2026 and 2026 to 2030, respectively.

Global incidence of Cervical Cancer, 2018-2030E

CAGR	Global
2018-2022	2.4%
2022-2026E	1.6%
2026E-2030E	1.5%



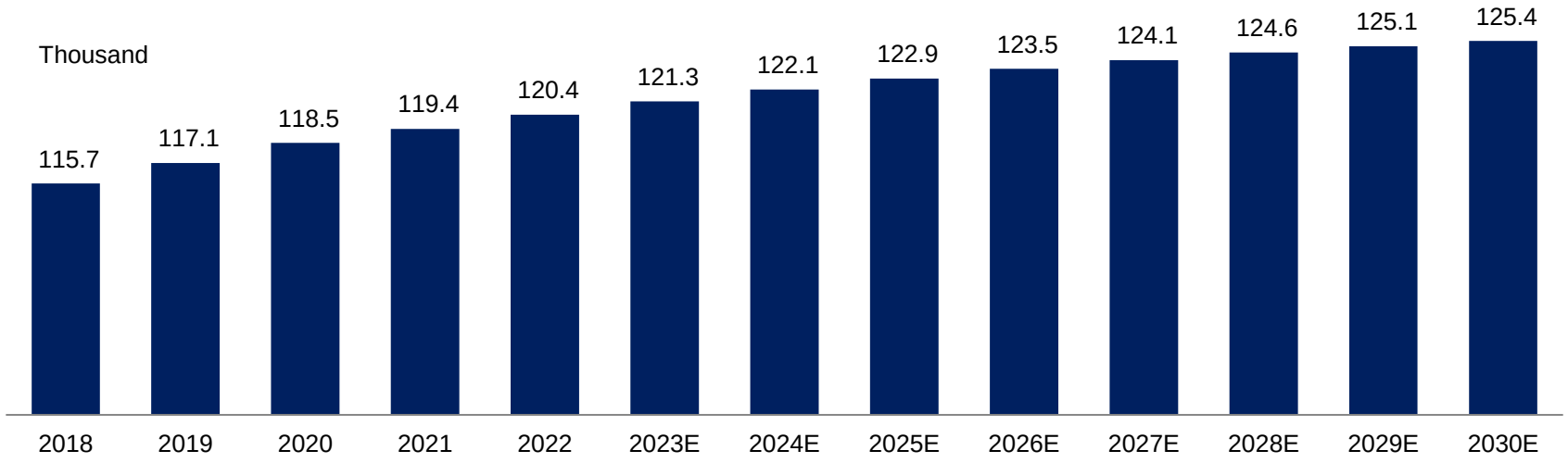
Source: ACS, Frost & Sullivan Analysis

Incidence of Cervical Cancer in China, 2018-2030E

- Cervical cancer is one of the most frequently occurring cancers in. The increased pressure, unhealthy diet will continuously increase the risk of developing cervical cancer in China. It is expected to be 125.4 thousand in 2030, with a CAGR of 0.4% from 2026 to 2030.

Incidence of Cervical Cancer in China, 2018-2030E

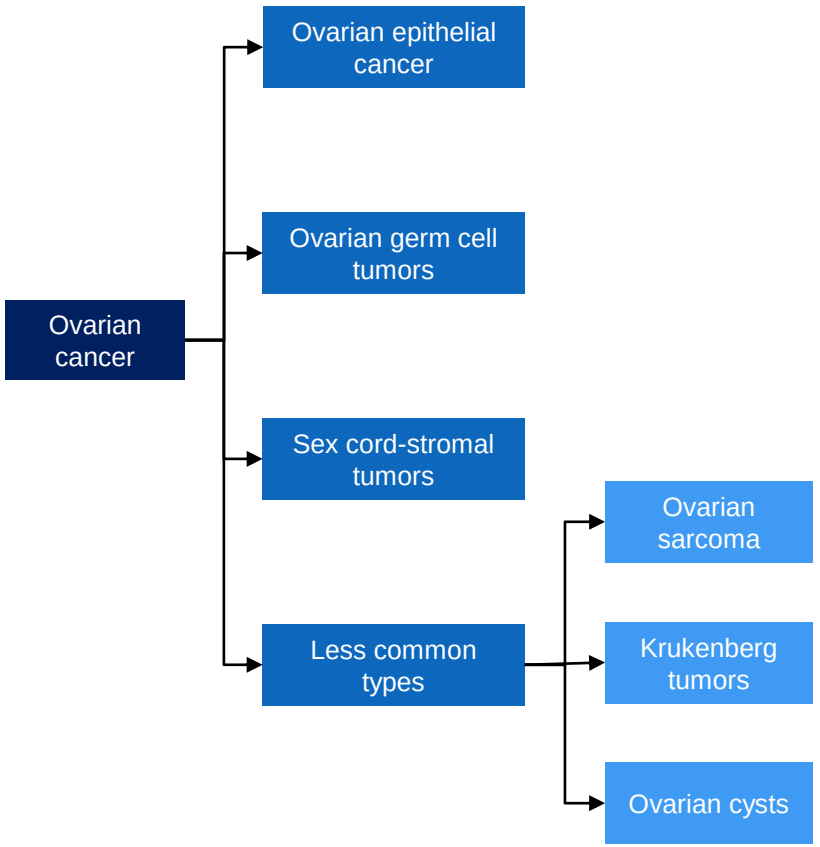
CAGR	Global
2018-2022	1.0%
2022-2026E	0.6%
2026E-2030E	0.4%



Source: NCCR, Frost & Sullivan Analysis

Overview of Ovarian Cancer

Pathological subtypes of ovarian cancer



Overview

1 Brief Introduction

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

2 Symptom

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

3 Diagnosis

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

4 Risk Factors

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

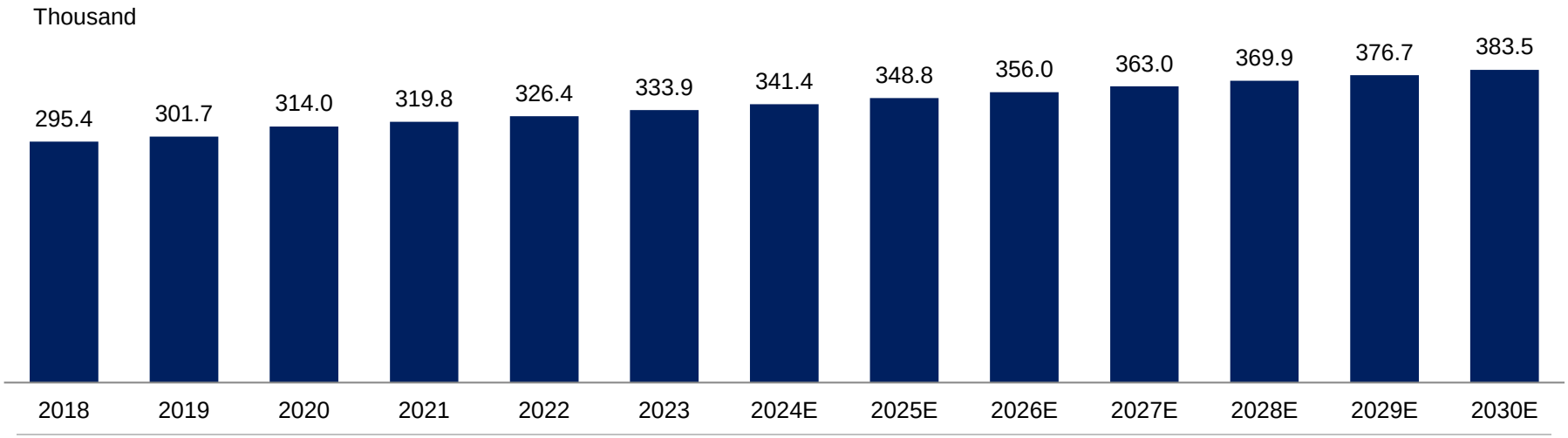
Source: Literature Review, Frost & Sullivan Analysis

Incidence of Ovarian Cancer Globally, 2018-2030E

- In 2018, global incidence of ovarian cancer had reached 295.4, thousand which further reached 333.9 thousand in 2023 with a CAGR of 2.5%. It is predicted that the number will continue to grow, and reach 363.0 thousand by the year of 2027, 383.5 thousand by the year of 2030, with CAGR of 2.1% and 1.8% respectively.

Global Incidence of Ovarian Cancer, 2018-2030E

Period	CAGR
2018-2023	2.5%
2023-2027E	2.1%
2027E-2030E	1.8%



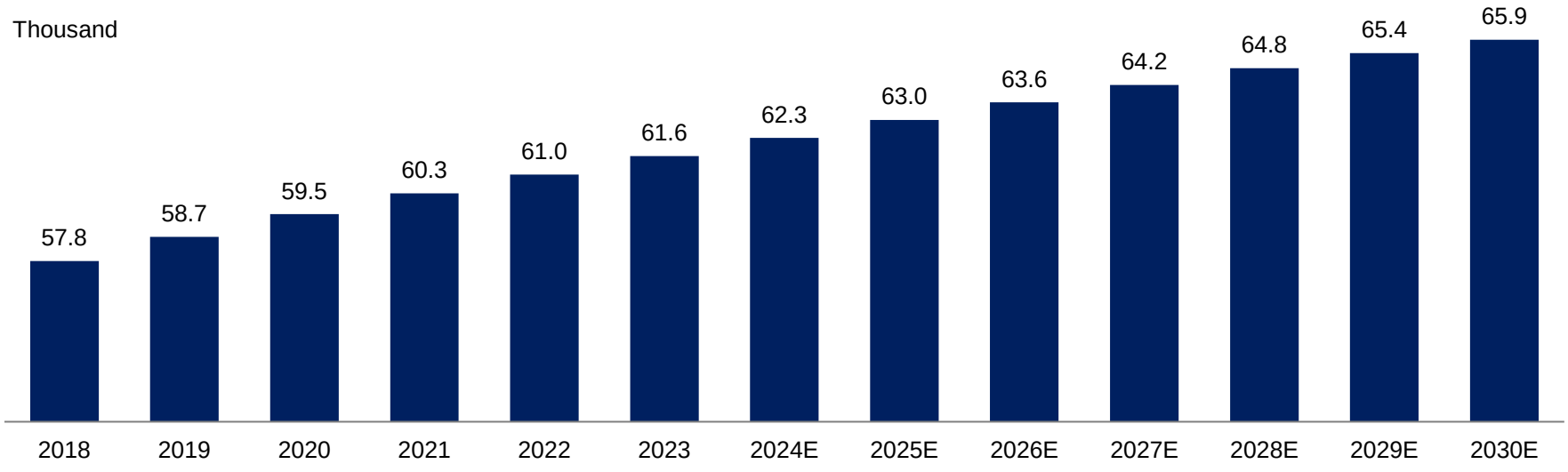
Source: Frost & Sullivan analysis

Incidence of Ovarian Cancer in China, 2018-2030E

- In 2018, the incidence of ovarian cancer in China reached 57.8 thousand, and reached 61.6 thousand in 2023 with a CAGR of 1.3%. It is predicted that the number will continue to grow, and reach 64.2 thousand by the year of 2027, 65.9 thousand by the year of 2030, with CAGR of 1.0% and 0.8% respectively.

China Incidence of Ovarian Cancer, 2018-2030E

Period	CAGR
2018-2023	1.3%
2023-2027E	1.0%
2027E-2030E	0.8%

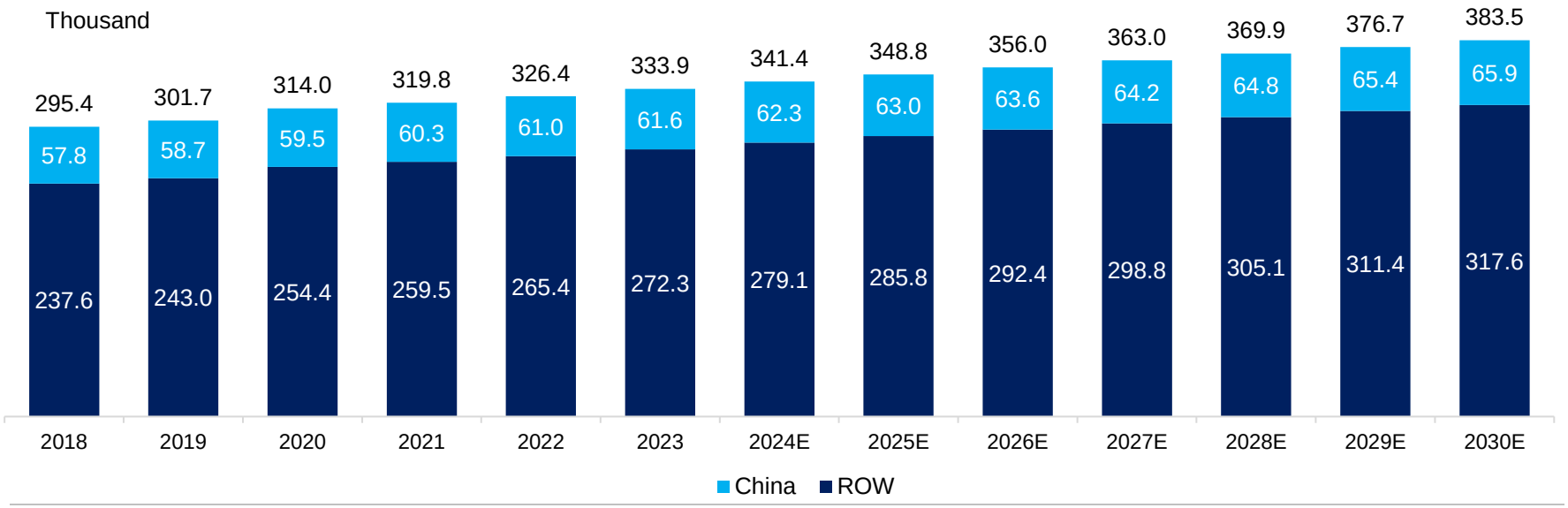


Source: Frost & Sullivan analysis

China and Global Incidence of Ovarian Cancer , 2018-2030E

China and Global Incidence of Ovarian Cancer , 2018-2030E

CAGR	China	ROW	Total
2018-2023	1.3%	2.8%	2.5%
2023-2027E	1.0%	2.3%	2.1%
2027E-2030E	0.8%	2.1%	1.8%

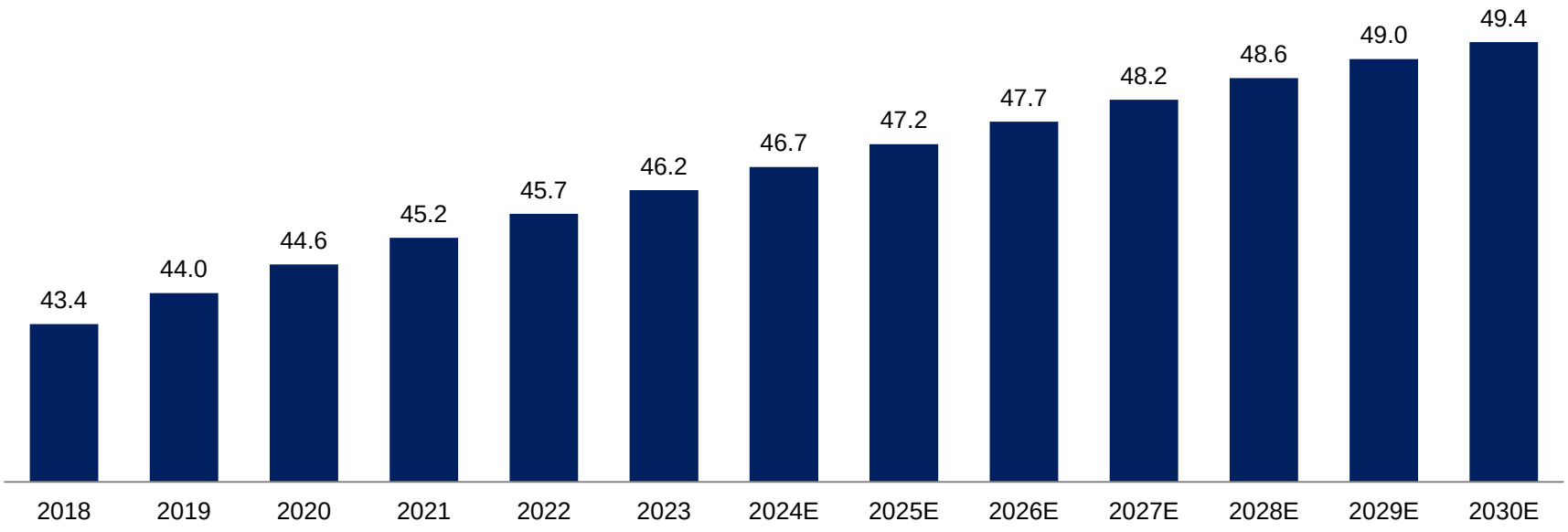


Source: Frost & Sullivan Analysis

Incidence of Advanced Ovarian Cancer in China, 2018-2030E

Incidence of Advanced Ovarian Cancer in China, 2018-2030E

Period	CAGR
2018-2023	1.3%
2023-2027E	1.0%
2027E-2030E	0.8%

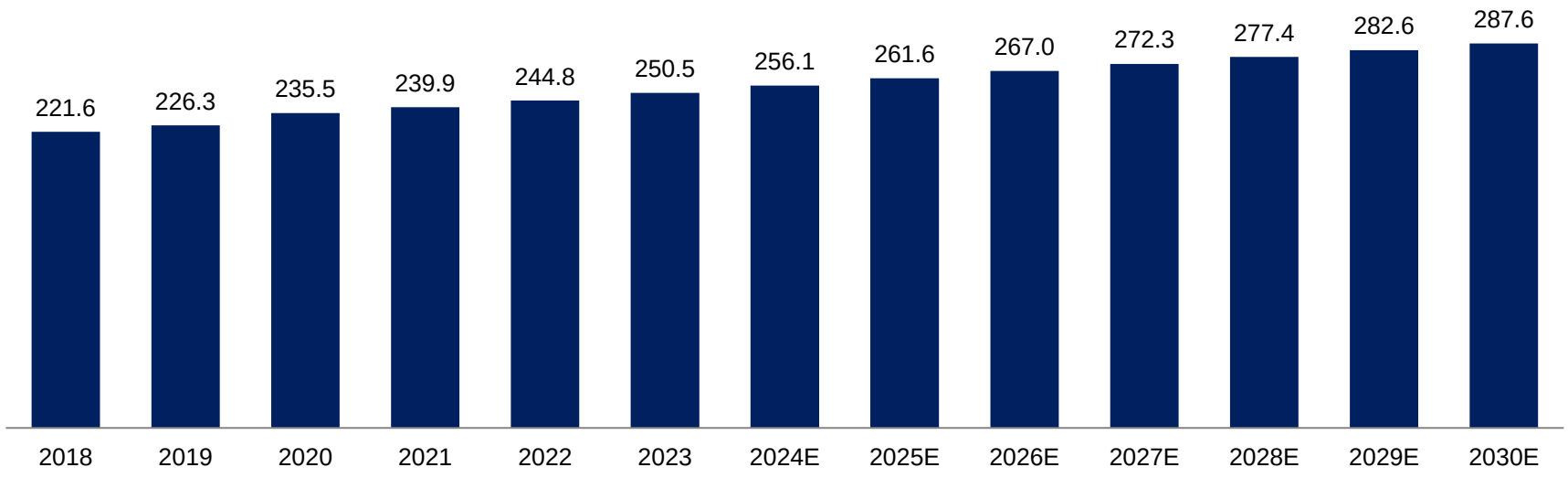


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Advanced Ovarian Cancer, 2018-2030E

Global Incidence of Advanced Ovarian Cancer, 2018-2030E

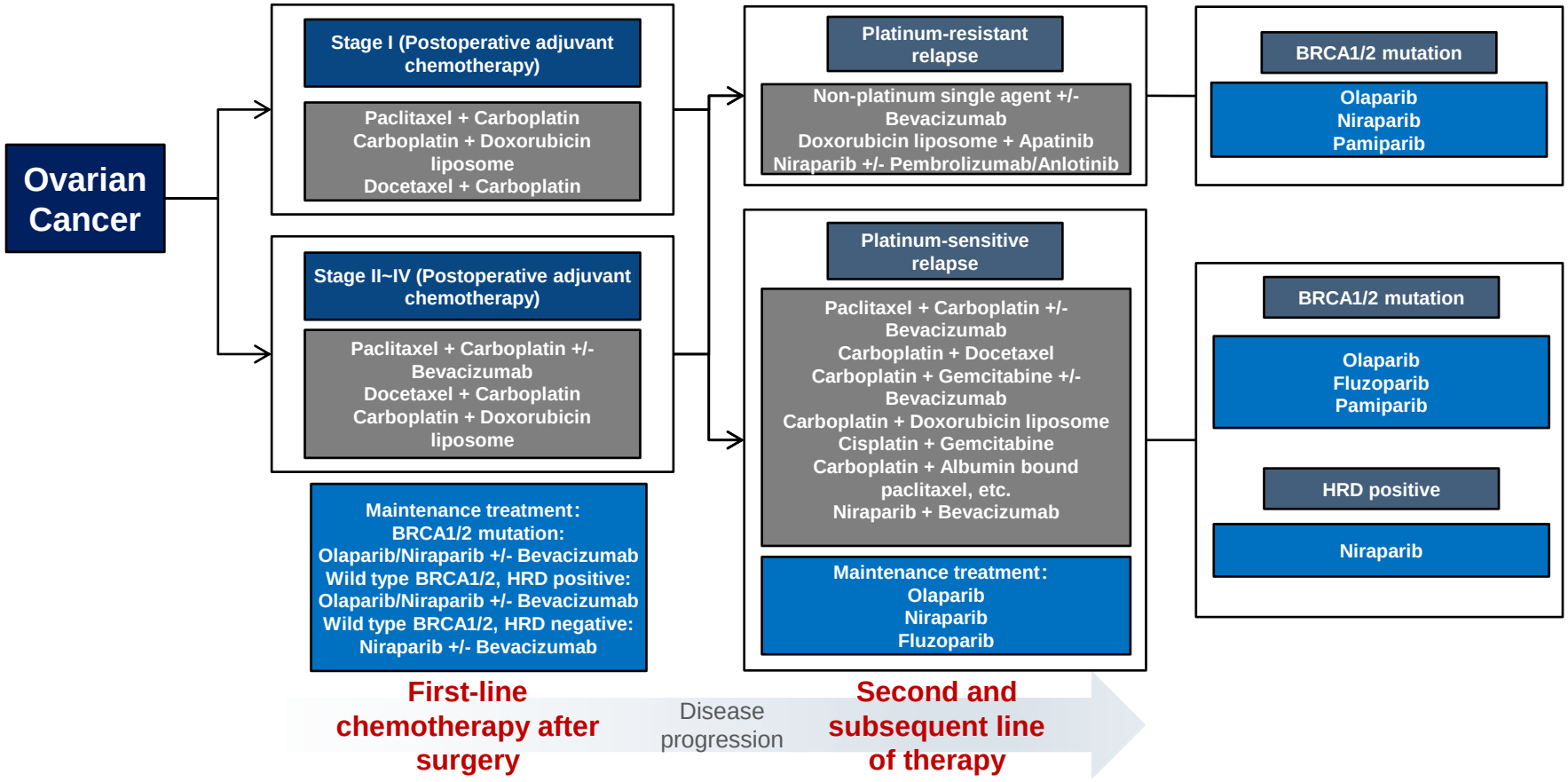
Period	CAGR
2018-2023	2.5%
2023-2027E	2.1%
2027E-2030E	1.8%



Source: NCCR, Frost & Sullivan analysis

Treatment Paradigm of Ovarian Cancer in China

- The treatment paradigm for ovarian cancer contains surgery, postoperative adjuvant chemotherapy（first-line）and second-line therapy: Adjuvant chemotherapy mainly uses paclitaxel, carboplatin, doxorubici, docetaxel, etc. Second-line therapy can be categorized by platinum-based chemotherapy, non-platinum chemotherapy, and other drugs. Chemo drugs includes cisplatin, carboplatin, gemcitabine, doxorubicin, paclitaxel, docetaxel, etc.



Source: Guideline for Diagnosis and Treatment of Ovarian Cancer (2022), Guidelines for Clinical Application of PARP Inhibitors in Ovarian Cancer (2022), Frost & Sullivan Analysis

Growth Drivers and Future Trends of Ovarian Cancer Drug Market

Increasing Patient Pool	• Ovarian cancer is the second most common gynecologic cancer in the United States. Ovarian cancer is also one of the female malignancies that cause a huge medical burden in China, with a high risk of death. The number of new ovarian cancer patients in Global and China in 2022 has reached 326.4 thousand and 57.0 thousand, and is expected to reach 353.0 thousand and 60.0 thousand in 2026, with a CAGR of 2.0% and 1.3%, respectively.
Increasing Treatment Options	• The deepening of basic biological research on ovarian cancer disease has brought about the most profound changes in treatment in this field, leading to the development of new drugs and drug combinations. Drugs for the treatment of ovarian cancer, especially for patients with platinum-resistant and recurrent ovarian cancer, are undergoing accelerated research and clinical trials. Emerging targets for the treatment of recurrent or drug-resistant ovarian cancer, such as AKT, PI3K, TOPI, WEE1, and related drugs are also under clinical development, which will provide ovarian cancer patients with more treatment options and further prolong survival. • With the increasing number of ovarian cancer patients, the demand for ovarian cancer drugs will further expand. In addition, with the launch of more drugs for ovarian cancer, especially for recurrent and platinum-resistant ovarian cancer, and the development of combination therapy, the market size will gradually expand.
Personalized Treatment	• Ovarian cancer is not a single disease, but a group of related diseases with unique genetic and molecular features, some of which respond better to chemotherapy than others. Treatment of ovarian cancer will be gradually refined to the specific characteristics of each type, and then an individualized medical plan will be developed for the patient.

Source: Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor and other Representative Drugs for the Treatment of Ovarian Cancer in China

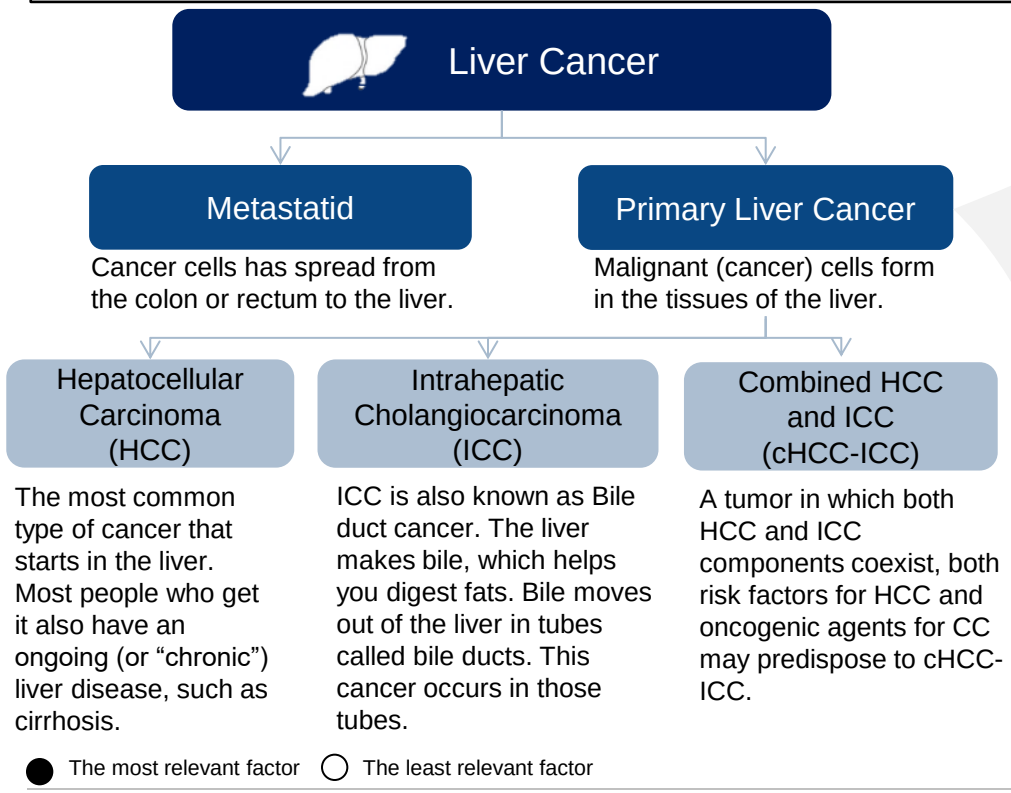
Analysis of Approved microtubule Inhibitor and other Representative Drugs for the Treatment of Ovarian Cancer in China

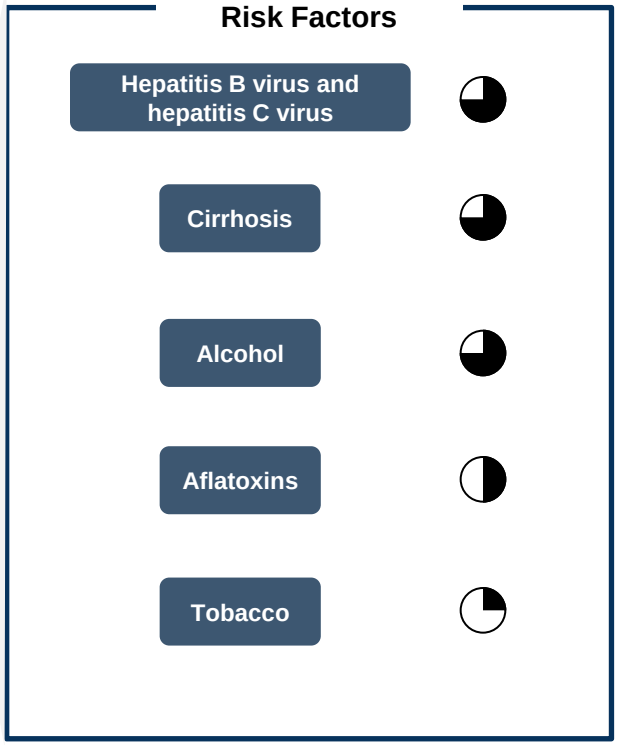
Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Median Treatment Cost RMB
Paclitaxel	TAXOL	BMS	1999	Class A	489 (5ml:30mg)	39,138
Paclitaxel liposome	LIPUSU	Luye pharma	2003	Class B	228 (30mg)	16,416
Cisplatin*	Platinol	BMS	2002	Class A	76(50ml:50mg)	2,432
Bevacizumab	Avastin	Roche	2010	Class B	1,500(4ml:100mg)	243,000
Olaparib	Lynparza	AstraZeneca	2018	Class B	90(150mg)	131,050
Niraparib	Zejula	Tesaro	2019	Class B	146(100mg)	159,432

Source: NMPA, Company Website, Frost & Sullivan Analysis

Overview of Liver Cancer

- The main responsibility of liver is to filter harmful substances from the blood, produces bile that helps in the digestion of fats, and stores sugar that the body uses for energy.
- Liver cancer could be classified into primary liver cancer and metastatic by the origins of tumor cells. Primary liver cancer, which starts from the tissues of the liver, is more common in East Asia area. Liver cancer is the fourth most frequent cancer and the second leading cause of death from cancer in China in 2018, while the most common type is hepatocellular carcinoma(HCC). HCC occurs in the setting of chronic liver inflammation, and is most closely linked to chronic viral hepatitis infection (hepatitis B or C) or exposure to toxins such as alcohol or aflatoxin. Overall speaking, in 2017, 80% of liver cancer and cirrhosis patients are caused by virus hepatitis.





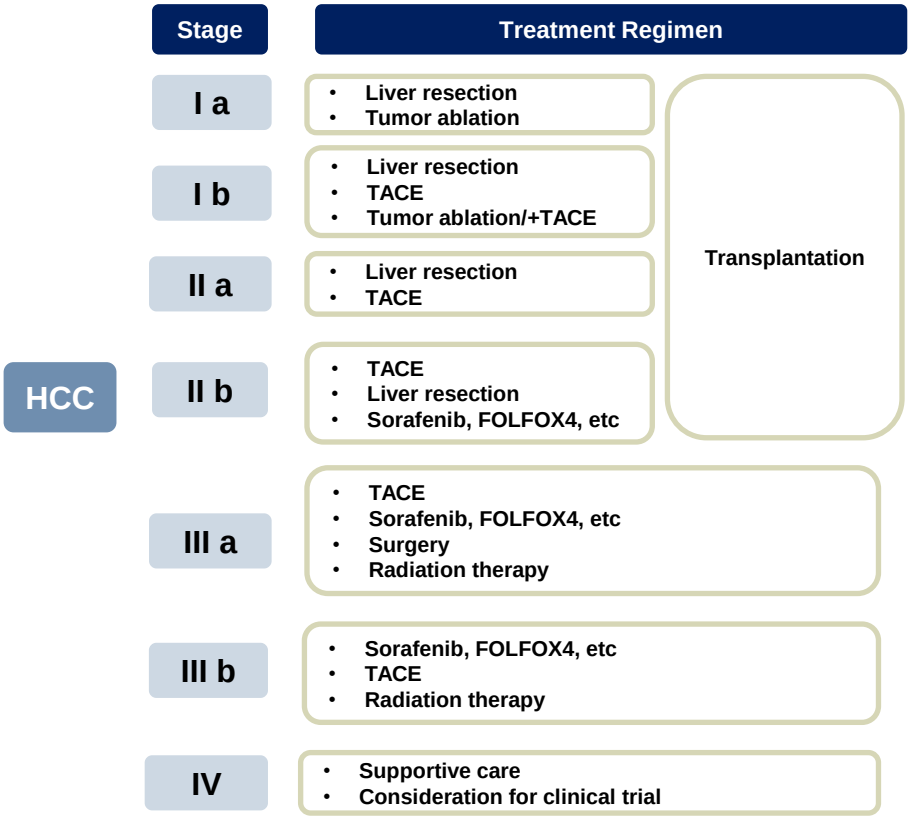
Source: NHFPC, Frost & Sullivan Analysis

NHFPC, Chinese 2017 guideline on the management of hepatocellular carcinoma

Treatment Overview of Liver Cancer

- The stages of liver cancer are defined by diameter and number of tumor, vascular invasion, extra-hepatic metastasis., which lead to the choice of cancer therapy.

Classification of Liver Cancer Therapy	
Surgery	Liver resection
	Transplantation
Localized treatments	Heating cancer cells
	Freezing cancer cells
	Percutaneous Radio frequency ablation
	Injecting alcohol into the tumor
Hepatic artery chemoembolization	Transcatheter arterial chemoembolization（TACE）
Radiation therapy	X-rays and protons
Drug therapy	Systematic chemotherapy
	Molecular targeted drug
	Immunotherapy
	Traditional Chinese Medicine



Notes:FOLFOX4: A chemotherapy treatment with leucovorin, 5-FU and Eloxatin, recommended for every two weeks.

NHFPC, Chinese 2017 guideline on the management of hepatocellular carcinoma

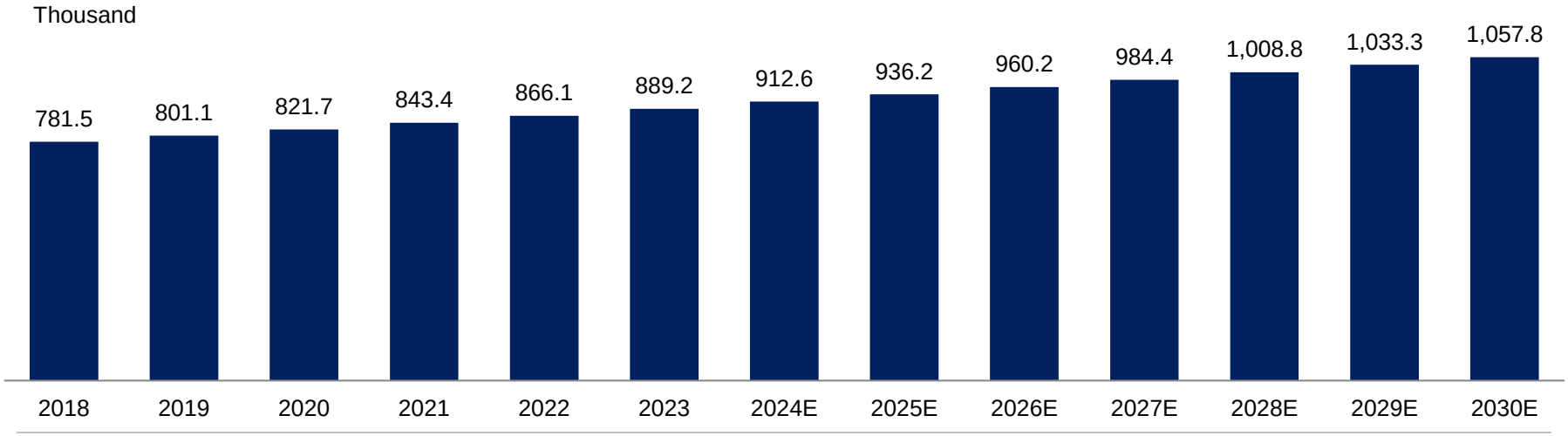
Source: NHFPC, Frost & Sullivan Analysis

Incidence of Liver Cancer Globally, 2018-2030E

- In 2018, global incidence of liver cancer had reached 781.5 thousand which further reached 889.2 thousand in 2023 with a CAGR of 2.6%. It is predicted that the number will continue to grow, and reach 984.4 thousand by the year of 2027, and 1,057.8 thousand by the year of 2030, with CAGR of 2.6% and 2.4% respectively.

Global Incidence of Liver Cancer, 2018-2030E

Period	CAGR
2018-2023	2.6%
2023-2027E	2.6%
2027E-2030E	2.4%



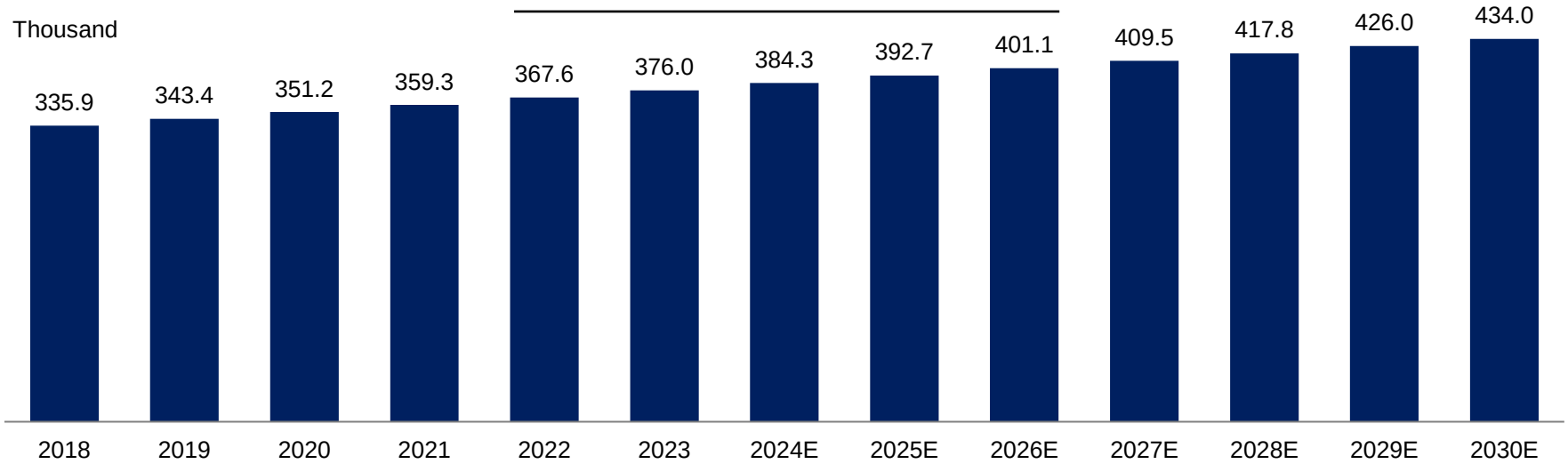
Source: Frost & Sullivan analysis

Incidence of Liver Cancer in China, 2018-2030E

- In 2018, the incidence of liver cancer in China reached 335.9 thousand, and reached 376.0 thousand in 2023 with a CAGR of 2.3%. It is predicted that the number will continue to grow, and reach 409.5 thousand by the year of 2027, 434.0 thousand by the year of 2030, with CAGR of 2.2% and 2.0% respectively.

China Incidence of Liver Cancer, 2018-2030E

Period	CAGR
2018-2023	2.3%
2023-2027E	2.2%
2027E-2030E	2.0%

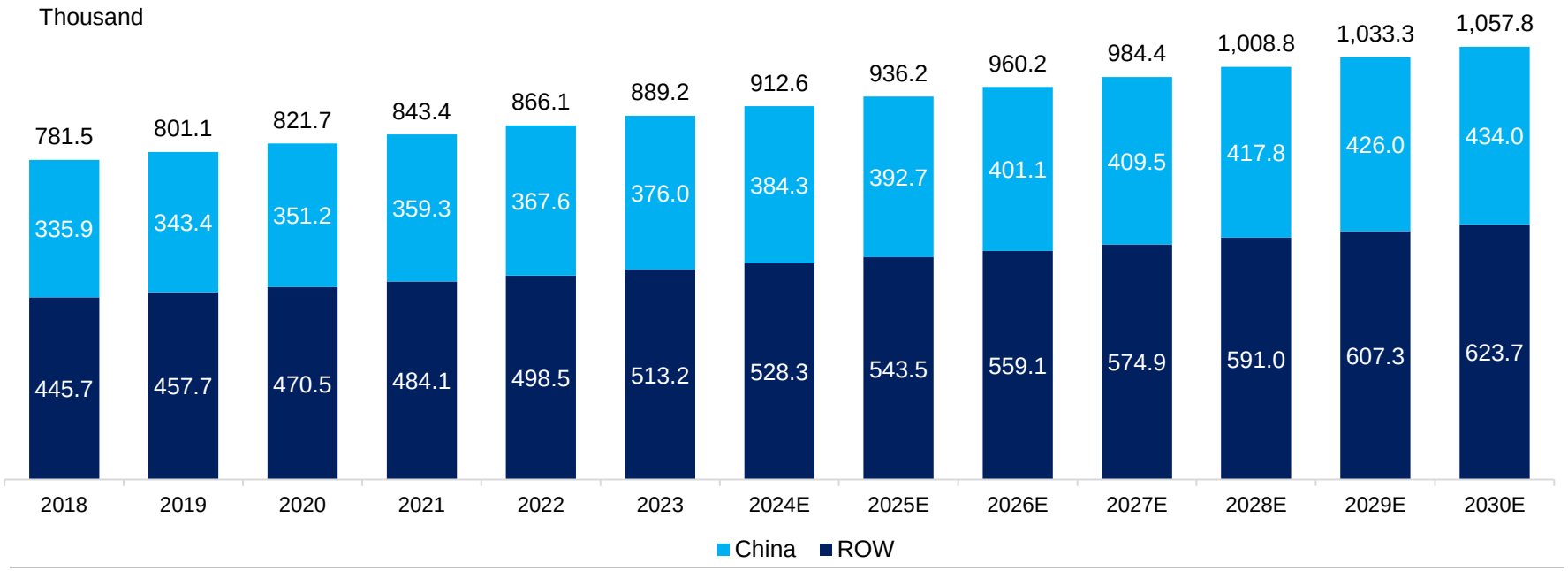


Source: Frost & Sullivan analysis

China and Global Incidence of Liver Cancer , 2018-2030E

China and Global Incidence of Liver Cancer , 2018-2030E

CAGR	China	ROW	Total
2018-2023	2.3%	2.9%	2.6%
2023-2027E	2.2%	2.9%	2.6%
2027E-2030E	2.0%	2.8%	2.4%

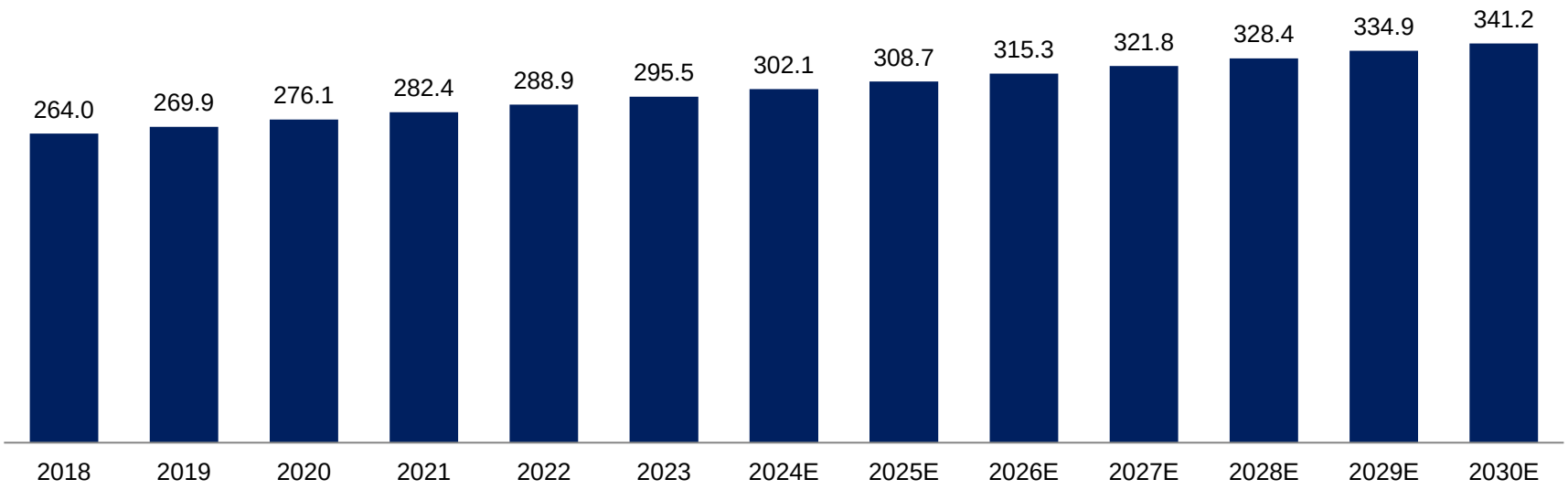


Source: Frost & Sullivan Analysis

Incidence of Advanced Liver Cancer in China, 2018-2030E

Incidence of Advanced Liver Cancer in China, 2018-2030E

Period	CAGR
2018-2023	2.3%
2023-2027E	2.2%
2027E-2030E	2.0%

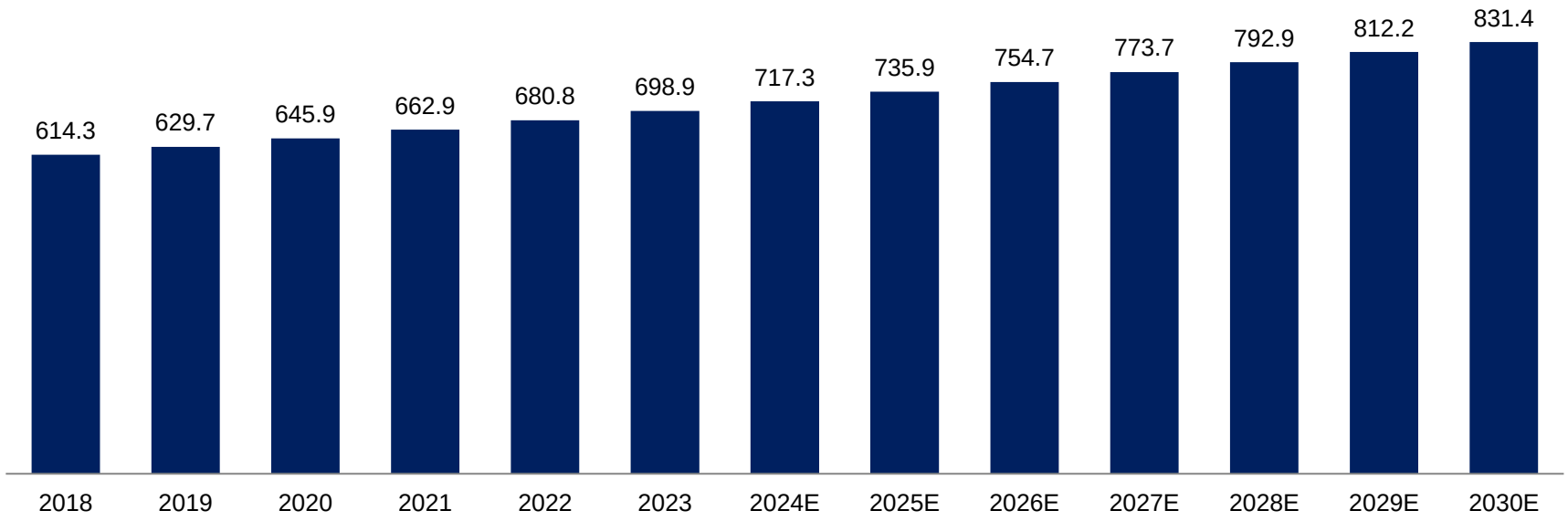


Source: NCCR, Frost & Sullivan analysis

Global Incidence of Advanced Liver Cancer, 2018-2030E

Global Incidence of Advanced Liver Cancer, 2018-2030E

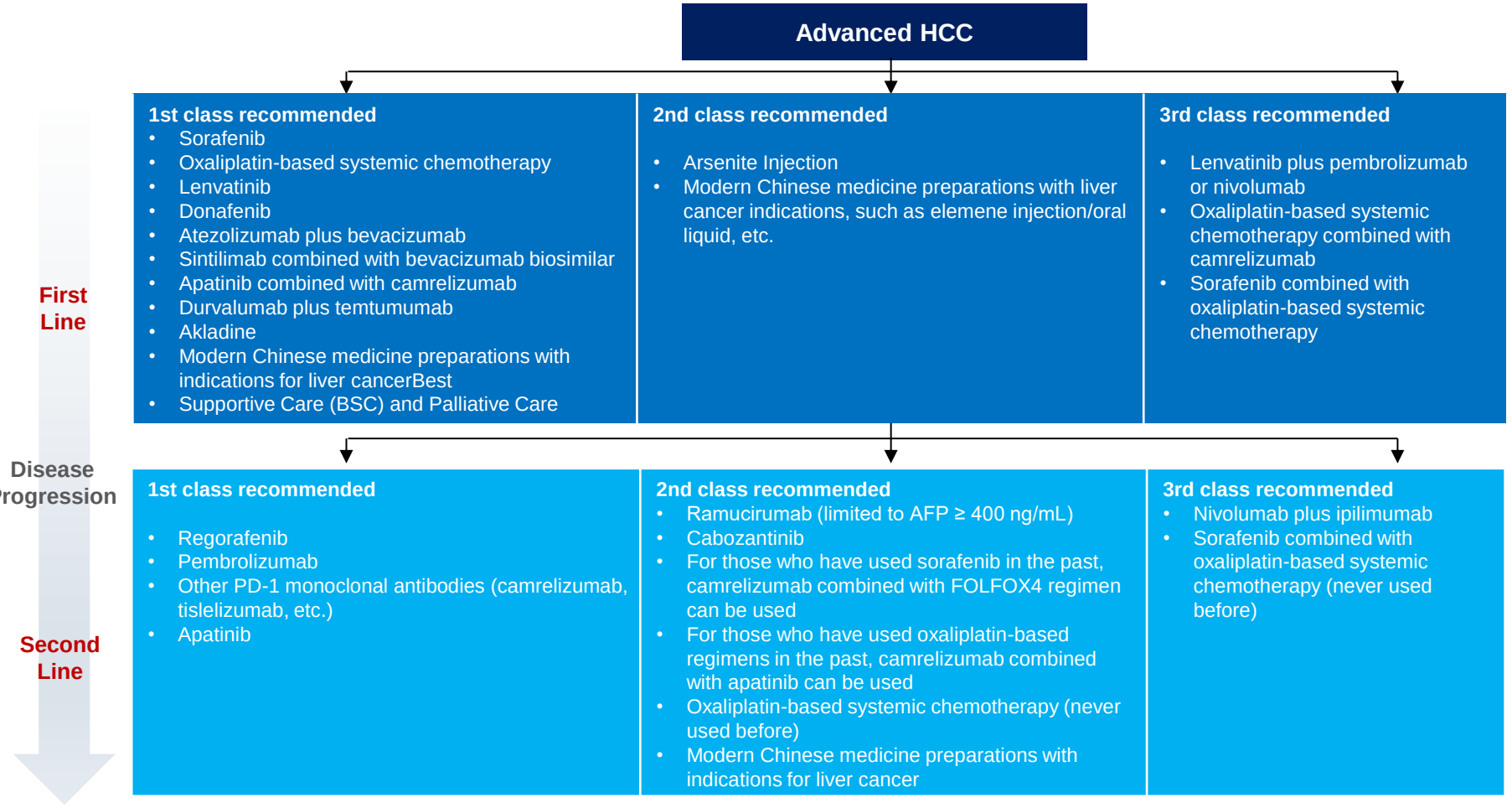
Period	CAGR
2018-2023	2.6%
2023-2027E	2.6%
2027E-2030E	2.4%



Source: NCCR, Frost & Sullivan analysis

Treatment Paradigm of HCC in China

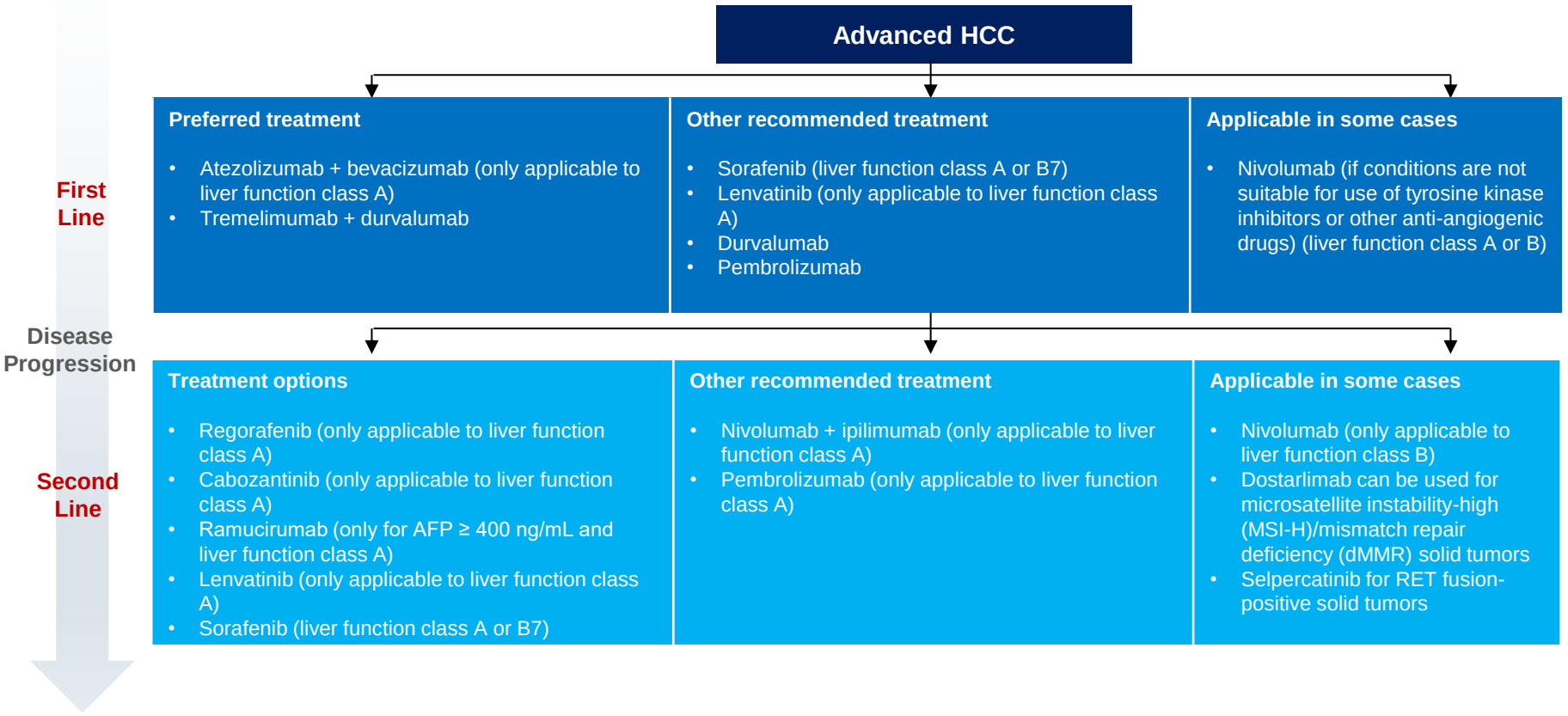
- Similar to the NCCN diagnosis and treatment guidelines, the drugs used to treat advanced hepatocellular carcinoma mainly include sorafenib, bevacizumab, atezolizumab, etc.



Source: CSCO, Frost & Sullivan analysis

Treatment Paradigm of HCC in the US

- The treatment of hepatocellular carcinoma is characterized by the participation of multiple disciplines and the coexistence of multiple treatment methods. Common treatment methods include liver resection, liver transplantation, ablation therapy, TACE, radiation therapy, systemic anti-tumor therapy and other methods. Choosing reasonable treatment methods for patients with liver cancer at different stages can maximize the efficacy. Antibody drugs suitable for the treatment of hepatocellular carcinoma mainly include atezolizumab, bevacizumab, tremelimumab, durvalumab, etc.



Source: NCCN, Frost & Sullivan analysis

Analysis of Approved microtubule Inhibitor and other Representative Drugs for the Treatment of Liver Cancer in China

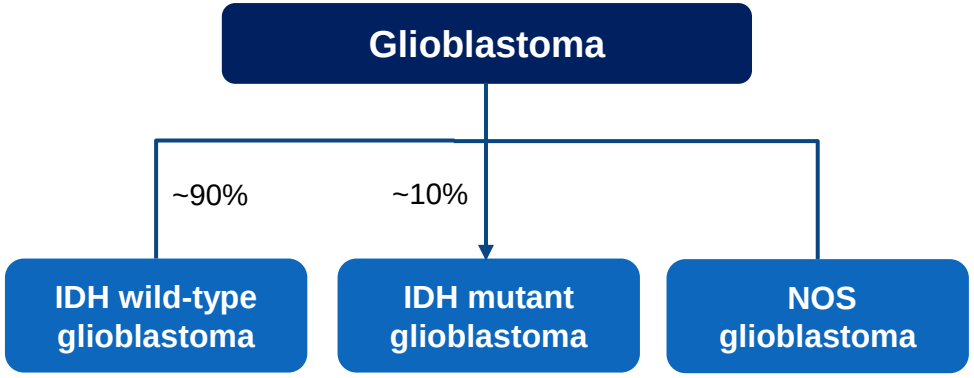
Analysis of Approved microtubule Inhibitor and other Representative Drugs for the Treatment of Liver Cancer in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Med Treatment RMB
Doxorubicin	Adriamycin	Pfizer	2000	Class A	21(10mg)	2,051
Oxaliplatin	Eloxatin	Sanofi	1998	Class B	1,760(50mg)	42,240
Bevacizumab	Avastin	Roche	2010	Class B	1,500(4ml:100mg)	135,000
Sintilimab	Tyvyt	Innovent	2018	Class B	1,080(10ml:100mg)	15,120
Pembrolizumab	Keytruda	MSD	2018	NA	17,918(4ml:0.1g)	143,344
Sorafenib	Nexavar	Bayer	2006	Class B	89(0.2g)	59,652
Donafenib	Zepsun	Zelgen	2021	Class B	65(0.1g)	28,771

Source: NMPA, Company Website, Frost & Sullivan Analysis

Overview of Glioblastoma

- Glioblastoma is one of the common brain tumors, also known as glioblastoma multiforme (GBM), a tumor located in the central nervous system. Glioblastoma is the most malignant astrocytic tumor, accounting for 52% of primary brain tumors. Most glioblastomas are primary tumors, and their pathogenesis is different from secondary tumors. The molecular changes of primary glioblastoma are mainly amplification and overexpression of epidermal growth factor receptor (EGFR), while the mutation of p53 is the main cause of secondary glioblastoma.



- Clinically equivalent to primary or new glioblastoma
- Commonly seen in patients over 55 years of age

- Approximate clinical glioblastoma secondary to a prior history of lower grade diffuse glioma
- More common in younger patients

- Glioblastoma lacking information on IDH mutations and failure to fully assess IDH

Risk factors

- Age (45 to 55 years old is the most common)
- Gender (more common in men)
- Genetic factors (genetic disease or family history)
- Long-term exposure to ionizing radiation such as radiation and X-rays
- Long-term exposure to chemicals or abuse of certain drugs
- Bad living habits, such as staying up late, smoking, drinking alcohol, and unhealthy eating
- Immune system dysfunction

Note: IDH=isocitrate dehydrogenase, NOS= nonspecific

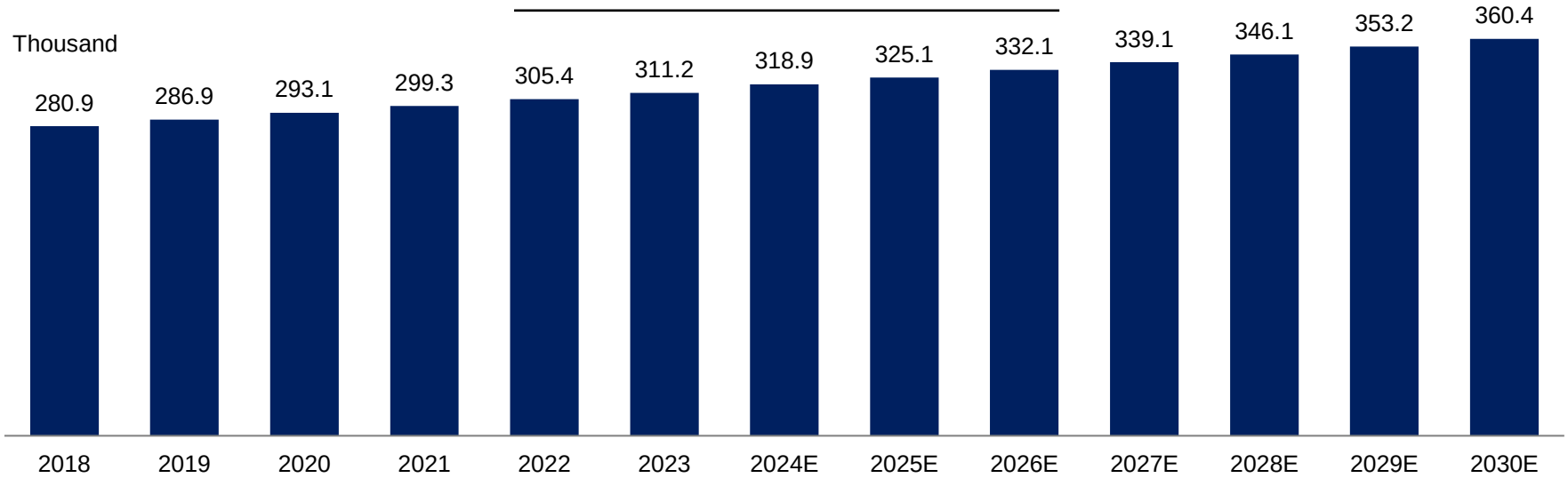
Source: Literature review, Frost & Sullivan Analysis

Incidence of Glioblastoma Globally, 2018-2030E

- In 2018, the incidence of glioblastoma globally reached 280.9 thousand, and reached 311.2 thousand in 2023 with a CAGR of 2.1%. It is predicted that the number will continue to grow, and reach 339.1 thousand by the year of 2027, 360.4 thousand by the year of 2030, with CAGR of 2.2% and 2.0% respectively.

Global Incidence of Glioblastoma, 2018-2030E

Period	CAGR
2018-2023	2.1%
2023-2027E	2.2%
2027E-2030E	2.0%



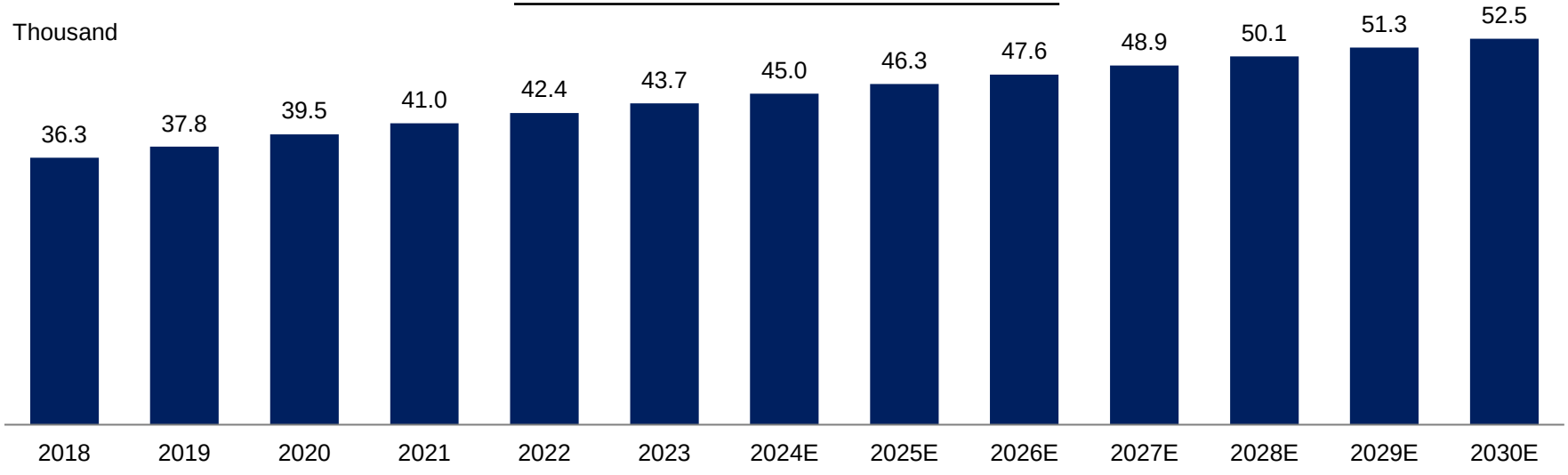
Source: Frost & Sullivan analysis

Incidence of Glioblastoma in China, 2018-2030E

- In 2018, the incidence of glioblastoma in China reached 36.3 thousand, and reached 43.7 thousand in 2023 with a CAGR of 3.8%. It is predicted that the number will continue to grow, and reach 48.9 thousand by the year of 2027, 52.5 thousand by the year of 2030, with CAGR of 2.8% and 2.4% respectively.

China Incidence of Glioblastoma, 2018-2030E

Period	CAGR
2018-2023	3.8%
2023-2027E	2.8%
2027E-2030E	2.4%

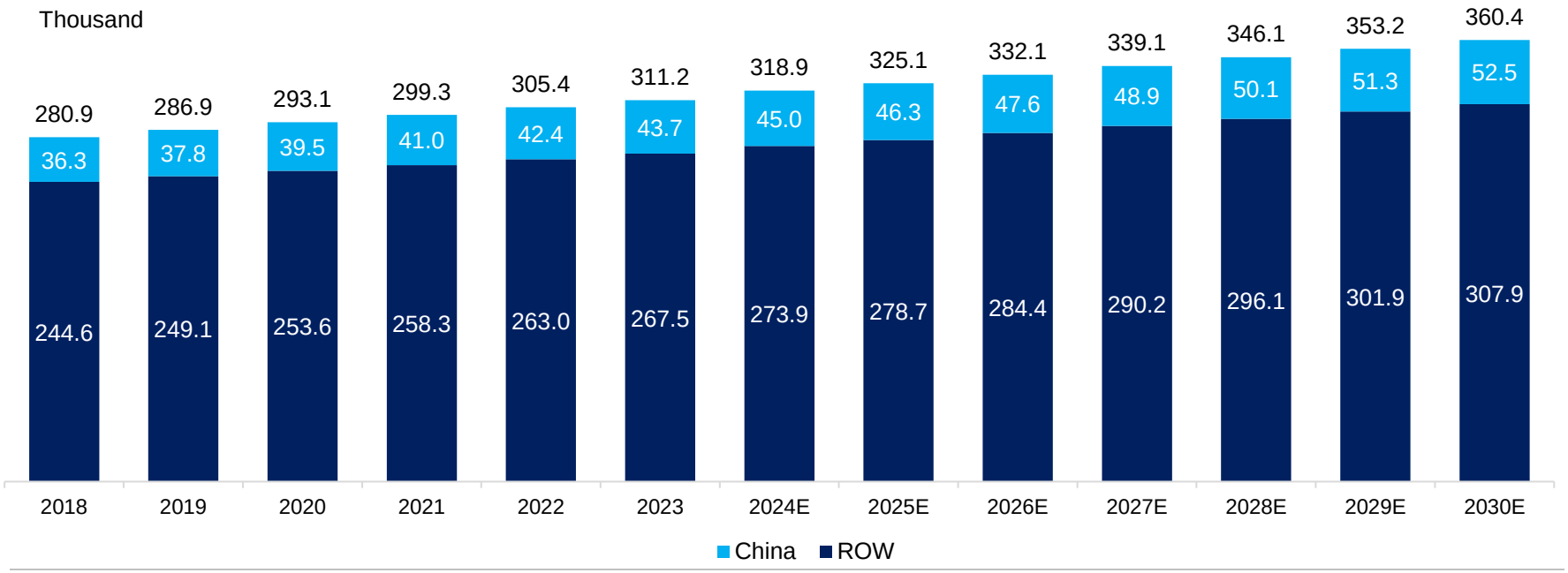


Source: Frost & Sullivan analysis

China and Global Incidence of Glioblastoma, 2018-2030E

China and Global Incidence of Glioblastoma, 2018-2030E

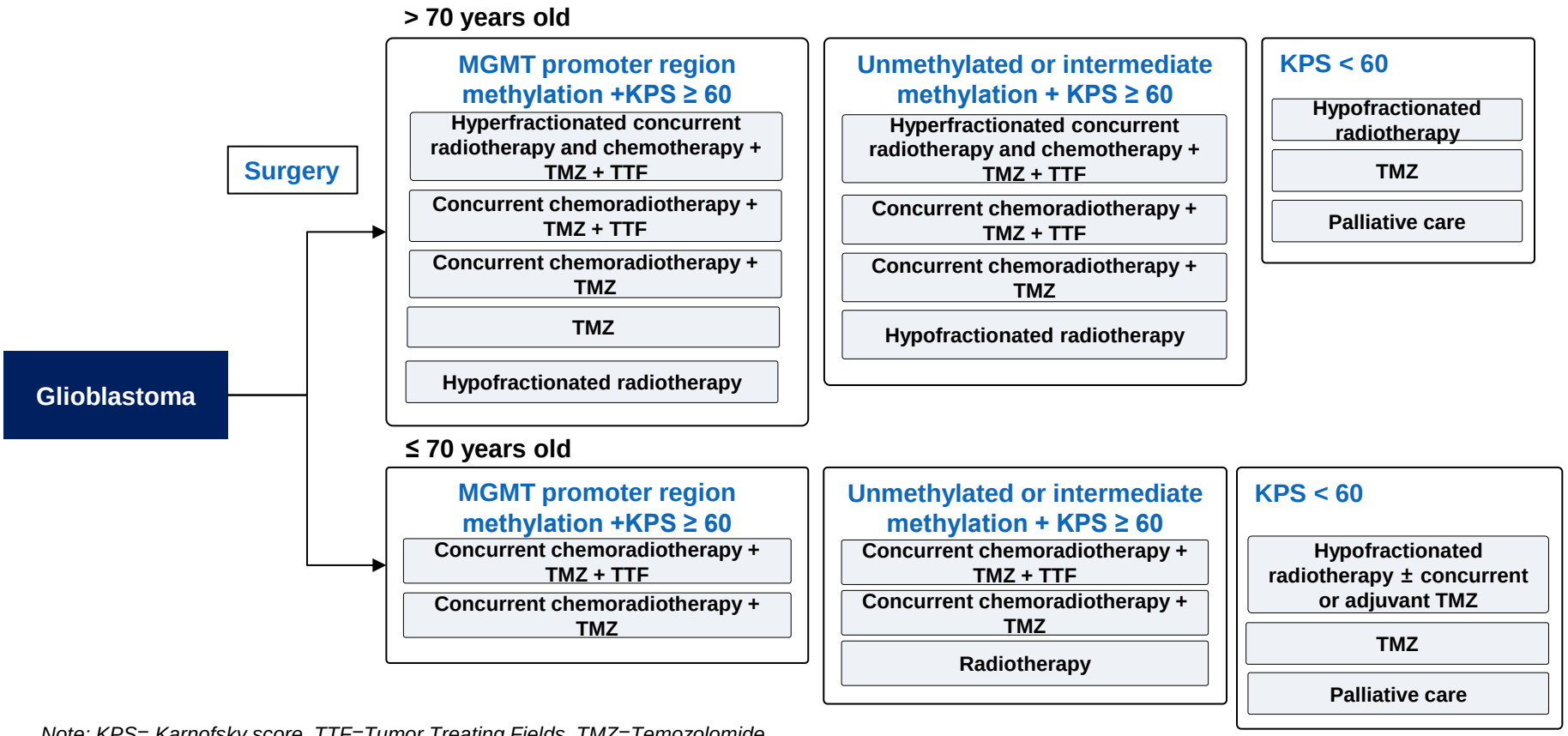
CAGR	China	ROW	Total
2018-2023	3.8%	1.8%	2.1%
2023-2027E	2.8%	2.1%	2.2%
2027E-2030E	2.4%	2.0%	2.0%



Source: Frost & Sullivan Analysis

Treatment Paradigm of Glioblastoma

- Glioblastoma is the most common primary brain cancer, and the recurrence of glioblastoma has become an important clinical issue because most patients relapse at the primary site. In China, current treatment options for recurrent glioblastoma include surgery, chemoradiotherapy combined with temozolomide (TMZ)and the use of bevacizumab.



Note: KPS= Karnofsky score, TTF=Tumor Treating Fields, TMZ=Temozolomide

Source: CSCO, Frost & Sullivan Analysis

Analysis of Approved microtubule Inhibitor and other Representative Drugs for the Treatment of GBM in China

Analysis of Approved microtubule Inhibitor and other Representative Drugs for the Treatment of GBM in China

Generic Name	Brand Name	Company	Approval Date	NRDL	2023 Median Price/ RMB	2023 Med Treatment RMB
Temozolomide	Temodal	MSD	2007	Class B	154(20mg)	74,136
Teniposide*	Vumon	BMS	2001	Class B	3,600(5ml:50mg)	129,600
Everolimus	Afinitor	Novartis	2013	Class B	117(5mg)	82,836
Bevacizumab	Avastin	Roche	2010	Class B	1,500(4ml:100mg)	90,000

Note: 1. As of Dec 31, 2023, only the brand name, company and treatment cost of the original drug are included.

2. The annual treatment cost is estimated based on an average body surface area of 1.6m2 and 8 treatment cycles per year, or the recommended medication cycle in the ins
The unit price is calculated based on the pre-medical insurance price of the original drug, and free drugs are not considered.

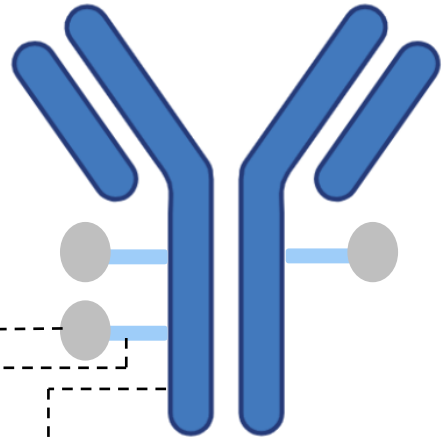
3. The original manufacturer of teniposide has been withdrawn from the China's market, and the reference price is the China resources double-crane pharmaceutical's produ

Source: NMPA, Company Website, Frost & Sullivan Analysis

Overview of Antibody-Drug Conjugate (ADC) Therapy

- ADCs are complex molecules composed of an antibody linked to a biologically active (anticancer) agent. ADC targets a specific antigen only found on target cells. Once it binds to the cell, it triggers internalization of the antibody, together with the drug, thus killing the cancer cell. This maximizes efficacy and minimizes systemic exposure. The main structure and mechanism of action of ADC are elaborated below.

Main Structure of ADC

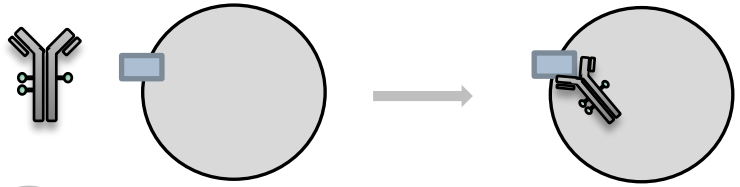


Antibody — Specific for a tumor-associated antigen that has restricted expression on normal cells

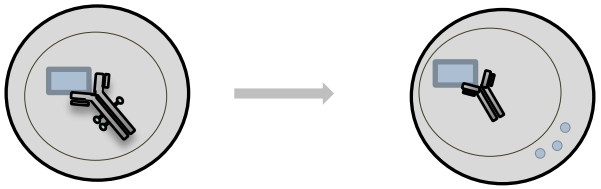
Linker — Attaches the cytotoxic agent to the antibody

Drug — Designed to kill target cells when internalized and released

Mechanism of Action of ADC



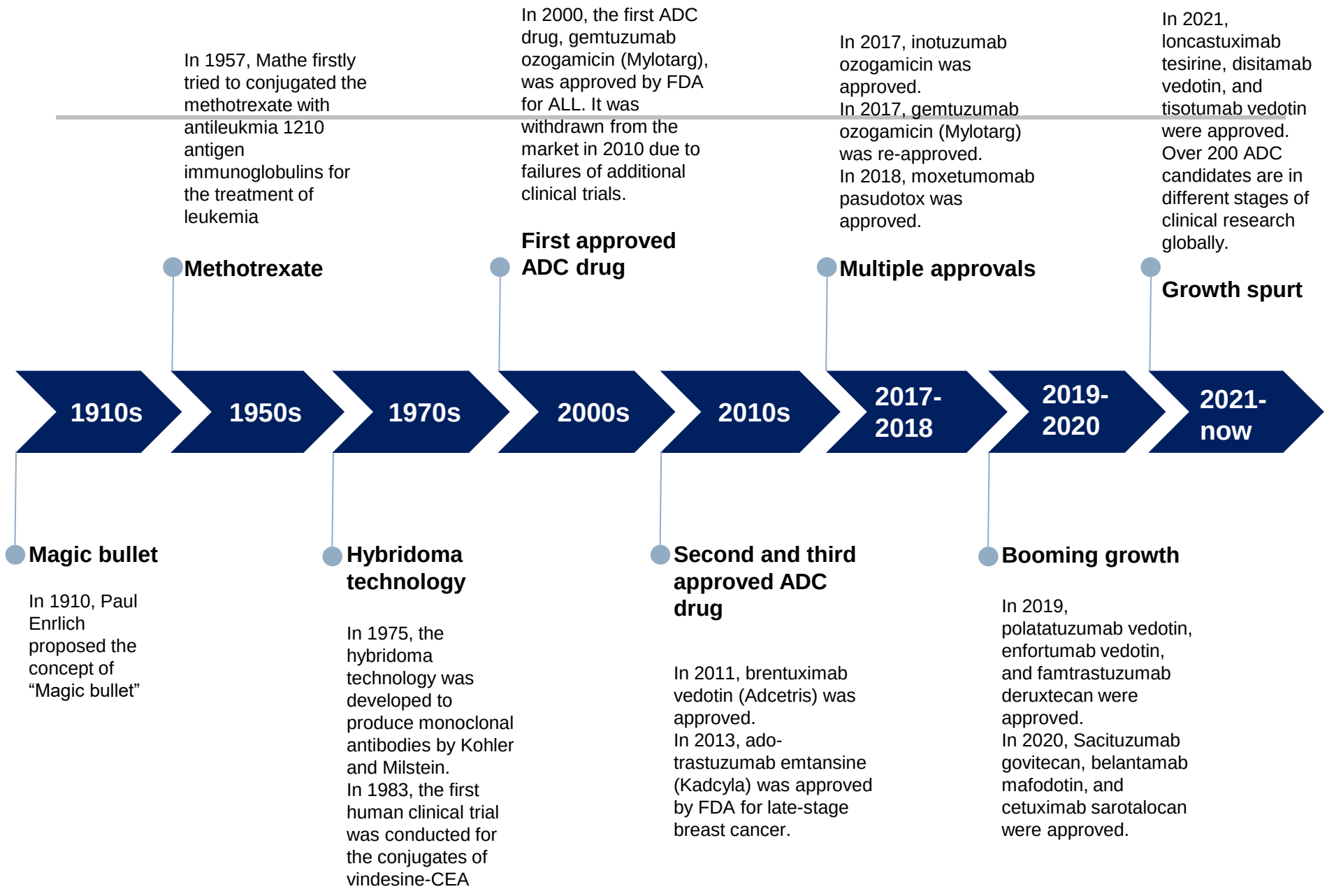
1. ADC binds to an receptor on the surface of cancer cells and the ADC-receptor complex is internalized.



2. The active cytotoxic agent is detached from the antibody and released within the cancer cell.

3. The cancer cell is killed by the cytotoxic agent and undergoes apoptosis

Source: Frost & Sullivan Analysis


1910s
1950s
1970s
2000s
2010s
2017-2018
2019-2020
2021-now
Magic bullet
In 1910, Paul Enrlich proposed the concept of “Magic bullet”
Methotrexate
In 1957, Mathe firstly tried to conjugated the methotrexate with antileukmia 1210 antigen immunoglobulins for the treatment of leukemia
Hybridoma technology
In 1975, the hybridoma technology was developed to produce monoclonal antibodies by Kohler and Milstein.
In 1983, the first human clinical trial was conducted for the conjugates of vindesine-CEA
First approved ADC drug
In 2000, the first ADC drug, gemtuzumab ozogamicin (Mylotarg), was approved by FDA for ALL. It was withdrawn from the market in 2010 due to failures of additional clinical trials.
Second and third approved ADC drug
In 2011, brentuximab vedotin (Adcetris) was approved.
In 2013, ado-trastuzumab emtansine (Kadcyla) was approved by FDA for late-stage breast cancer.
Multiple approvals
In 2017, inotuzumab ozogamicin was approved.
In 2017, gemtuzumab ozogamicin (Mylotarg) was re-approved.
In 2018, moxetumomab pasudotox was approved.
Booming growth
In 2019, polatatuzumab vedotin, enfortumab vedotin, and famtrastuzumab deruxtecan were approved.
In 2020, Sacituzumab govitecan, belantamab mafodotin, and cetuximab sarotalocan were approved.
Growth spurt
In 2021, loncastuximab tesirine, disitamab vedotin, and tisotumab vedotin were approved.
Over 200 ADC candidates are in different stages of clinical research globally.

Development of ADCs Therapy

Discovery of ADCs Therapy

- **1913** – Concept of targeted delivery of toxic agents against tumor cells proposed by Paul Ehrlich.
- **1983** – First successful ADCs clinical trial on using an anti-carcinoembryonic antigen antibody-vindesine conjugate.
- **1990s** – First-generation ADCs derived from the backbones of murines.
- **2000** – First ADC approved by FDA for treatment of acute myelogenous leukemia (Mylotarg®). It was withdrawn from the market in 2010 due to failures of additional clinical trials.
- **2011** – Second ADC approved by FDA for treatment of relapsed hodgkin lymphoma and systemic anaplastic large cell lymphoma (Adcetris®).
- **2013** – Third ADC approved by FDA for treatment of HER2-positive metastatic breast cancer (Kadcyla®).
- **2013** – Mylotarg® was re-introduced into US market.
- **2017** – Fourth ADC approved by FDA for treatment of refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (Besponsa®).
- **2019** – First ADC approved by NMPA for treatment of HER2-positive metastatic breast cancer (Kadcyla®).

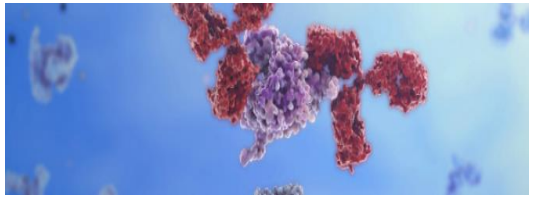
Therapeutic Advantages

1 Less off-target toxicity:

- In current ADCs therapies, antibody plays the role of delivering conjugated cytotoxic agent into tumor cells while the cytotoxic agent takes effect on killing tumor cells.
- Due to the high specificity of antibody and controllable drug activation and release mechanisms integrated in ADCs, the ADCs agent has much less off-target toxicity than a therapeutically comparable cytotoxic small molecule, which often has side effects as the drugs attack both normal and cancerous cells indiscriminately.

2 Higher potency:

- Because the cytotoxic agent is released and working inside tumor cells, lower concentrations of agents are required to elicit an equivalent therapeutic response compared to antibody, small molecule co-therapies, which mainly destroy the tumor cells on their surface or lack of specificity.



Source: Frost & Sullivan Analysis

Three Generations of ADCs

Generations	Conjugations	Linker	Payload	Limitations
1st generation (e.g. *Mylotarg 2010, Besponsa*)	Random lysines	Unstable	Low potency; e.g., conventional chemotherapy	Heterogeneity; lack of efficacy; systemic toxicity due to premature drug loss; highly immunogenic
2nd generation (e.g. *Adcetris* 2011; *Kadcyla* 2013)	Random lysines; Reduced interchain cysteines	Improved stability; cleavable vs. non-cleavable	~1000x more potent than chemo; anti-microtubule MOA; only active against proliferating cells	Heterogeneity; fast clearance for high DARs; premature drug loss; narrow TI; drug resistance
3rd generation (e.g. Polivy 2019; Padcev 2019; Enhertu 2019 and later approved ADCs)	Site specific adopted; engineered cysteins (e.g., THIOMAB); novel constructs	Stable in circulation; finetuned to match drug; release drugs in tumors	Highly potent; also DNA damaging MOA; target proliferating & non-proliferating cells; against modest target expression	Possible toxicity due to highly potent payloads; catabolism may be different across species

- The 1st generation of ADC drugs have a number of problems. 1) Acidic conditions can be appeared in other parts of the body, resulting in the uncontrollable release of toxic payload and unexpected off-target toxicity. Secondly, calicheamicin is hydrophobic that easy to cause antibody aggregation, accounting for the emergence of some defects, like short half-life, faster clearance, and immunogenicity. Moreover, the inconsistent DAR exerts an influence on pharmacokinetic and pharmacodynamic (PK/PD) parameters and therapeutic index of ADC drugs. Consequently, the first-generation ADCs demonstrate suboptimal therapeutic windows, indicating demands for 2nd and 3rd generation of ADC.
- 2nd generation of ADCs were subsequently launched after optimization of mAbs isotypes, cytotoxic payloads, as well as linkers. Nevertheless, there remain a number of unmet needs, such as insufficient therapeutic windows due to off-target toxicity, and aggregation or rapid clearance in those ADCs with high DAR.
- 3rd generation of ADC benefited form introduction of site-specific conjugation technology, the homogenous ADCs with well characterized DARs (2 or 4) and desired cytotoxicity were produced. ADCs with consistent DARs show less off-target toxicity and better pharmacokinetic efficiency. Moreover, fully humanized antibodies instead of chimeric antibodies are utilized in the third generation to reduce immunogenicity.

Source: Frost & Sullivan; Literature Review

Advantages of ADCs

Antibody

Pros

- **Targeting Specificity:** Antibodies can find specific antigens on cancer cells (extracellular) or other specific antigens on other cells which may interrupt cancer growth signaling pathway.

Cons

- **Insufficient Cytotoxicity:** Antibodies don't kill cancer cells directly, it may not be very effective in destroying cancer cells.
- **Limitation in Certain Cancer:** some antibodies may play import roles in other healthy cells, which may cause side effects.
- **Drug Resistance**

Chemotherapy

Pros

- **Toxicity:** Chemotherapies damage nucleus of cells when they divide, that say, chemotherapies destroy cancer cells directly.

Cons

- **Whole body cytotoxicity**: Chemotherapy circulates throughout patients' body in the blood stream, it also destroy healthy cells and tissue, which cause off-target cytotoxicity that may worsen patients' quality of life.
- **Limitation in Drug Selection:** Some potent cytotoxic agents may not be prescribed to patients due to the concerns for the damage it may bring to healthy cells.
- **Drug Resistance**

Small Molecules Inhibitors

Pros

- **Targeting Specificity:** Small molecule inhibitors usually targeting enzyme in the cancer cells (intracellular) to block certain pathway, and eventually interrupt with cancer growing.

Cons

- **Off-target cytotoxicity**: The target specificity is not as specific as antibodies, enzyme inhibitors may affect multiple biochemical reactions in healthy cells.
- **Drug Resistance**

Combining the Major Advantages in ADC Development

ADC

- **Targeting Specificity**: Antibody section provides cancer specific targeting, which direct the ADC drug to the cancer cells accurately.
- **Cytotoxicity:** Chemical drug payload provides sufficient cytotoxicity to destroy cancer cells. And due to its cancer cell targeting feature, ADC drug can treat patients with a higher dosage.
- **Drug Resistance Overcome:** Optimized ADC combination of mAbs and payloads may help to reduce, or even overcome drug resistance.
- **Penetrating Greater Patients Pool:** By exploring more cancer specific antibodies and novel chemical drugs with greater cytotoxicity, novel ADCs can be developed, which makes it possible for patients who can't be treated by the current approaches to get treated with novel ADCs, more cancer indications will be included in the ADC portfolio.
- **Example:** Kadcyla (ado-trastuzumab emtansine) is a ADC drug that combines HER2 specific antibody trastuzumab with a cytotoxin DM1, its antibody segments can deliver the DM1 payload to HER2 expressing breast cancer cells accurately, and it has showed potent efficacy in clinical practice.

Source: Frost & Sullivan Analysis

Advantages of ADCs – Clinical Performance

ADC drugs have shown promising efficacy data in clinical settings, both in refactory/relapsed disease and in patient subgroup who are lack of targeted therapies. Besides, the treatment line of ADC therapeutics are moving towards earlier lines, and the indications covered are also expanding.

Superior data on the effectiveness of ADC drugs in relapsed and refractory patients	Potential of moving to more advanced treatment line in multiple cancer types	ADC drug could offer new option for cancer patients currently lacking targeted therapies
Due to its high specificity characteristics, ADC drugs has shown advantages in patients who have previously received chemotherapy or targeted therapy. For example, for patients with advanced urothelial carcinoma who failed previous chemotherapy, the RC-48-C009 study (phase II) showed that the ORR of HER-2 positive patients treated with RC-48 monotherapy as second-line therapy reached 50.0%, and the mPFS was 5.3 months.	In addition late-line treatment, due to the high efficacy of ADC drugs and the low incidence of side effects, its treatment lines is also advancing to the front-line. For example, Brentuximab vedotin (developed by Seagen) combined with chemotherapy was approved by the FDA in 2018 for the use Systemically treated CD30+ PTCL. In addition, Rongchang Bio's RC-48 has shown significant effectiveness in clinical trials for the first-line treatment of urothelial carcinoma.	In a phase III trial, trastuzumab deruxtecan (DS-8201) reduced the risk of disease progression or death by 49% in the HR+, HER2 low expression patient population compared with chemotherapy, and the median PFS in the DS-8201 group was 10.1 months vs. 5.4 months in the chemotherapy group. This important breakthrough means that DS8201 may provide a treatment option for HR+/HER2- breast cancer patients who lack targeted therapy. In addition, ADC drugs also show good anti-tumor activity in the treatment of triple-negative breast cancer.

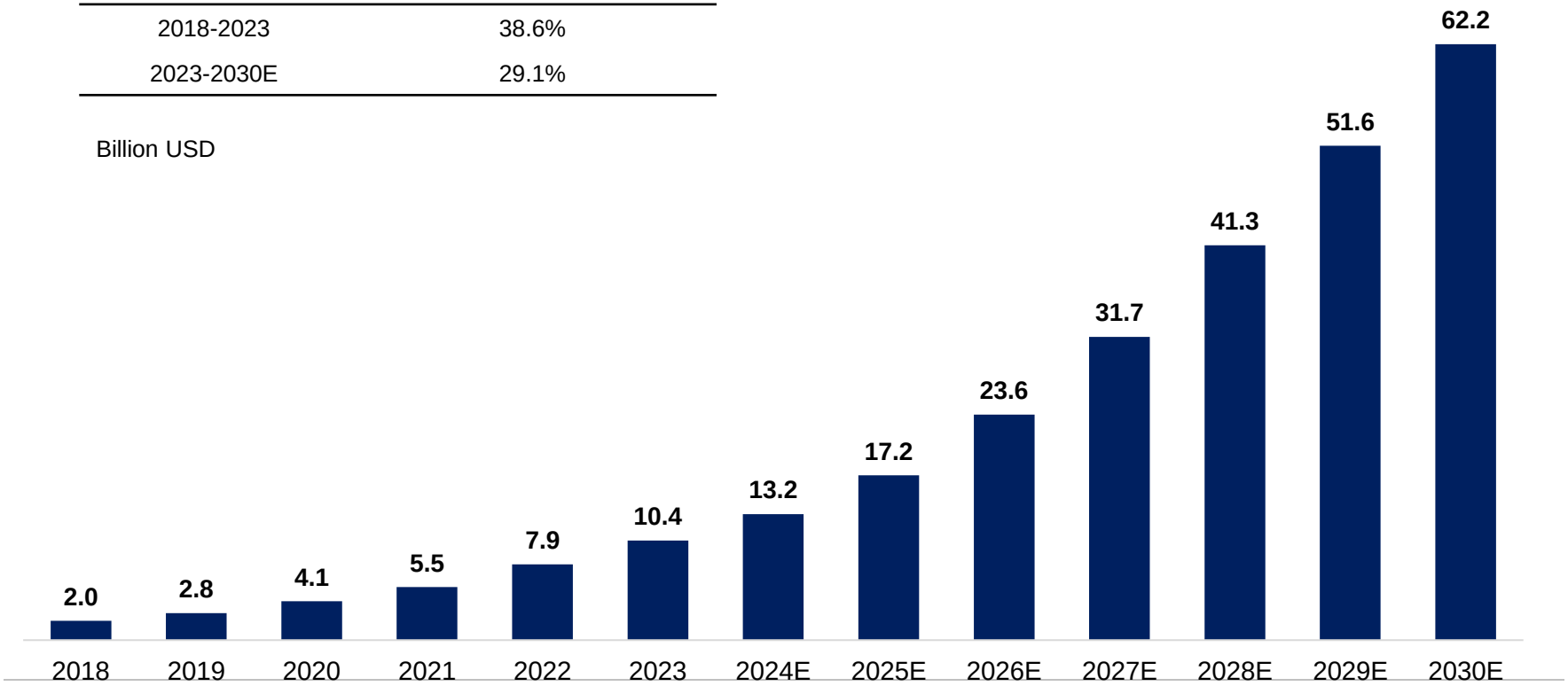
Source: Literature Review, Frost & Sullivan Analysis

Historical and Forecasting Global ADC Market Size, 2018-2030E

- The global ADC market has grown rapidly in the past four years, from USD 2.0 billion in 2018 to USD 10.4 billion in 2023, with a CAGR of 38.6%. It is expected to reach USD 31.7 billion in 2027 and USD 62.2 billion in 2030, with a CAGR of 29.1% from 2023 to 2030.

Historical and Forecasting Global ADC Market Size, 2018-2030E

CAGR	ADC
2018-2023	38.6%
2023-2030E	29.1%



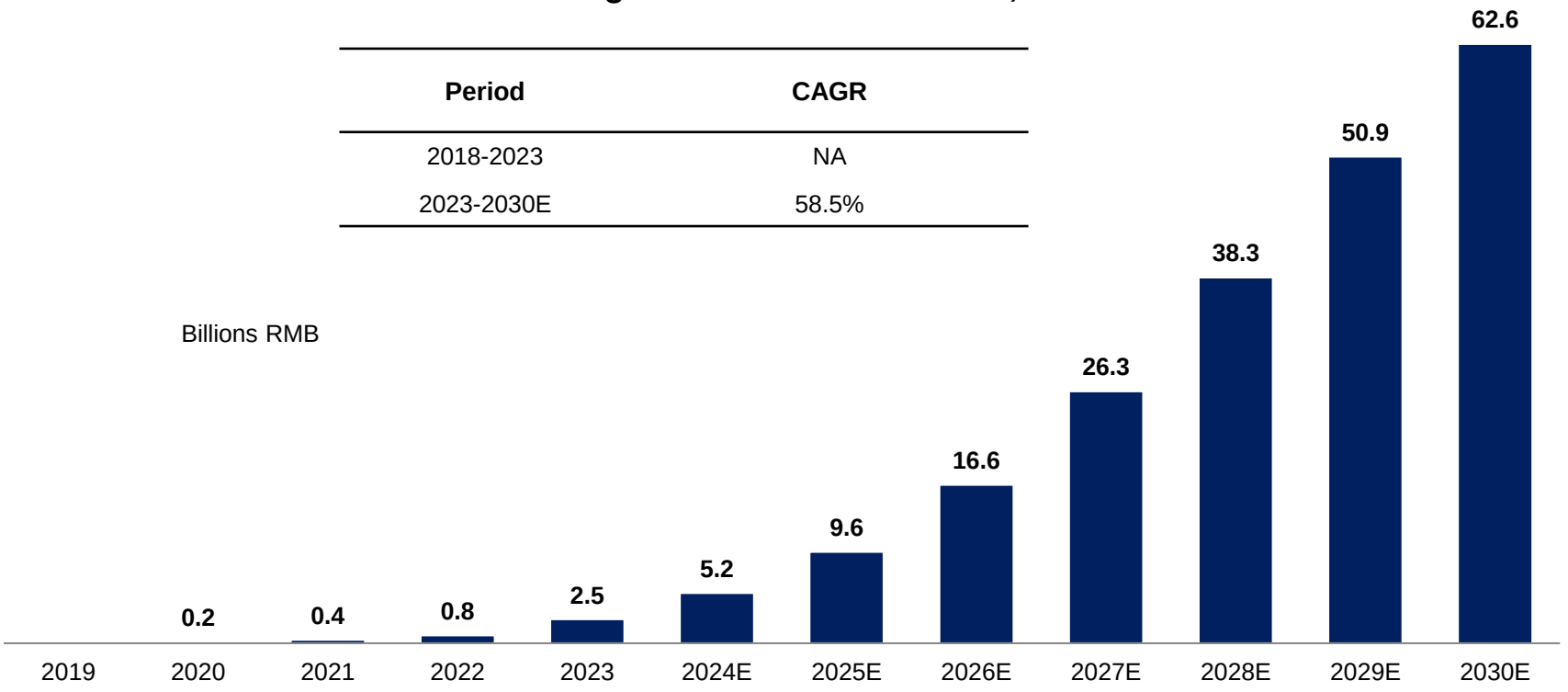
Source: Frost & Sullivan analysis

Historical and Forecasting China ADC Market Size, 2018-2030E

- The China ADC market reach RMB 2.5 billion in 2023. It is expected to reach RMB 26.3 billion in 2027 and RMB 62.6 billion in 2030, with a CAGR of 58.5% from 2027 to 2030 .

Historical and Forecasting China ADC Market Size, 2018-2030E

Period	CAGR
2018-2023	NA
2023-2030E	58.5%



Source: Frost & Sullivan analysis

Analysis of the Advantages of the Main Toxins of ADC Drugs

Microtubule/microtubule inhibitors can be classified into two major categories according to their mechanisms of action: agents promoting microtubule polymerization and stabilizing microtubule structures (e.g., paclitaxel, epothilones, discodermolide and taccalonolides), and agents inhibiting microtubule polymerization and destabilizing microtubule structures (such as maytansinoids, auristatins, vinblastine and vincristine).

Toxins	Mechanism	Advantages	Disadvantages
Maytansinoids	Maytansinoids are anti-mitotic microtubule inhibitors derived from maytansine. Maytansine and maytansinoids bind to the maytansine site, resulting in the suppression of microtubule dynamics and causes cell cycle arrest in the G2/M phase.	Maytansinoid, which demonstrates increased plasma stability, greater therapeutic window, and reduced off-target toxicity compared to that with cleavable linkers	Due to the structural complexity including numerous stereocenters, the total synthesis of maytansine and its analogue can be costly.
Auristatins	Auristatins are derived from the natural product dolastatin-10. Dolastatin-10 and its analogs inhibit microtubule-dependent GTP binding and block the binding of vinca alkaloids to microtubule in a noncompetitive manner.	Both MMAE and MMAF showed no degradation in plasma, in human liver lysosomal environment, or by the action of proteases. As free toxins, the cytotoxicity of MMAE and MMAF are less potent than that of dolastatin 10 in lymphoma cells in vitro.	The potential instabilities and lipophilic MMAE/MMAF-induced bystander effect may increase the toxicity to normal tissues.
Cryptophycins	The cryptophycins are a family of 16-membered cyclic depsipeptides, first isolated from terrestrial blue-green algae. The most abundant component, cryptophycin-1 (10) (Figure 5), has demonstrated excellent activity against a broad spectrum of solid tumors with IC50 values in the picomolar range [96].	Higher potency compare to maytansine and auristatin-based payloads. Not substrate for the P-gp in multiple-drug resistant (MDR) cancer cell lines, potential of induce less drug resistance.	However, the intrinsically low bioavailability of cryptophycin-1 caused by its instability and solubility rendered it inefficacious in vivo.

Source: Frost & Sullivan Analysis

Analysis of the Advantages of the Main Toxins of ADC Drugs

More recently, some potent microtubule inhibitors suitable for payloads of ADCs were discovered and advanced to clinical phase evaluation. These new potential microtubule/microtubule agents for ADC payloads may overcome the current limitations of anticancer therapies. Payloads which are active against drug-resistant tumors and have higher potency and better solubility, stability, tolerability, and therapeutic indices than current payloads, will be beneficial for the success of the next generation of ADC.

Toxins	Mechanism	Advantages	Disadvantages
Paclitaxel and Docetaxel	Paclitaxel and docetaxel represent the taxane family of drugs, which showed remarkable efficacy against advanced solid tumors such as ovarian and breast cancer.	Remarkable efficacy against advanced solid tumors such as ovarian and breast cancer.	Paclitaxel seriously suffered from the lack of tumor specificity, MDR, poor aqueous solubility and dose-limiting toxicities including alopecia, nausea and vomiting, joint and muscle pain, peripheral neuropathy, and bone marrow suppression.
Tubulysins	Tubulysins resembles peptide antimitotics dolastatin-10, phomopsin A, and hemiasterlin, inducing the depletion of cell microtubules, arresting cells in the G2/M phase, and finally triggering cell apoptosis.	The recently developed tubulysin ADCs with a novel quaternary ammonium linker have great stability profiles and potent anticancer activity based on in vitro and in vivo evaluation.	Tubulysins are highly toxic microtubule-targeting agents with a narrow therapeutic window.
Hemiasterlins	Hemiasterlin and its analogs stabilize the binding of colchicines to microtubule. They also inhibit the binding of vinblastine and dolastatin-10 to microtubule in noncompetitive and competitive manners, suggesting that hemiasterlin and dolastatin toxins share common microtubule protein binding sites, which is consistent with recently published structural biologic data	ADC micelle systems using hemiasterlins as payloads showed potent cytotoxicity against a broad range of tumor cells, reduced toxicity, and excellent therapeutic window	HTI-286 is less sensitive to P-gp protein than the current anti-microtubule agents such as paclitaxel, docetaxel, vinorelbine, and vinblastine.

Source: Frost & Sullivan Analysis

Analysis of the advantages and disadvantages of the main linker technology of ADC drugs

- A linker selected must be stable and efficient to release the cytotoxic agent upon internalization of ADC. Linkers for ADCs are categorized into cleavable linkers and non-cleavable linkers. Non-cleavable ones require lysosomal degradation of antibody for releasing cytotoxic agent.
- ADCs with cleavable linkers have broader efficacy and faster rates of activating and releasing cytotoxic drugs for most cell lines. On the contrast, ADCs with non-cleavable linkers can possibly provide increased plasma stability, greater therapeutic window, and reduced off-target toxicity. To reduce aggregation and improve the solubility of some ADCs, hydrophilic linkers such as β-glucuronide linker, Sulfo-SPDB, and Mal-PEG4-NHS were investigated. In conclusion, each type of linker has advantages and disadvantages, and each can be modified to achieve a fine balance between target efficacies and undesired toxicities.

Linker	Linker Type	Pros	Cons
MHH	Chemical labile (acid labile) linker	Cleaving in acidic environment	Poor stability
DSDM	Disulfide-containing reducible linker	Intracelluar release of payload	Potential premature cleavage during circulation
Sulfo-SPDB	Disulfide-containing reducible linker	Intracelluar release of payload	Potential premature cleavage during circulation
MC-VC-PABC	Enzymatically cleavable linker	Stability during circulation	Hydrophobicity
SMCC	Non-cleavable bifunctional linker	Stability during circulation	No “bystander effect”
Mal-PEG-NHS	Non-cleavable spacer linker	Improve water solubility and reduce plasma clearance	No “bystander effect”
GBC	Enzyme-labile beta-Glucuronide linker	Defined DAR hemogeneity	Requires multiple steps

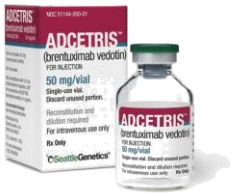
Source: Frost & Sullivan Analysis, literature review

ADCs in combination with chemotherapy drugs

ADC in combination with chemotherapy drugs

- ADCs can be used as in monotherapies, or in combination with other anticancer drugs, such as chemotherapy drugs. Thus, the combination usage of ADCs with other drugs has become an important direction in ADCs drug development.
- The optimal combination of ADCs with chemotherapeutic agents require a better understanding of the unique cell cycle interactions and the regulation of surface antigen expression by cytotoxic chaperones. To date, a growing body of preclinical and clinical data shows promising applications and provides valuable insights to guide further drug development.

Clinical evidence of ADCs in combination with chemotherapy drugs



ADCETRIS® (brentuximab vedotin)

- Brentuximab vedotin (developed by Seagen) combined with chemotherapy was approved by the FDA in 2018 for the use to treated CD30+ PTCL
- An open-label, multicenter, randomized phase 3 trial shown that A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) group had superior efficacy to ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) group in the treatment of patients with advanced-stage Hodgkin ′s lymphoma, with a 4.9% lower combined risk of progression, death, or noncomplete response and use of subsequent anticancer therapy at 2 years

Ib

Thelma Study: Trastuzumab Emtansine (T-DM1) Plus Non-Pegylated Liposomal Doxorubicin (NPLD) in HER2-Positive Metastatic Breast Cancer

- Study results shown that among all evaluable patients, the overall response rate was 40.0% with a median duration of response of 6.9 months. Clinical benefit rate was 66.7% and median progression-free survival was 7.2 months

Source: Frost & Sullivan; Literature Review

Limitations of ADCs

- ADC drugs also face great challenges in clinical development and improvement, common challenges in developing efficacious and safe ADC drugs including in-vivo toxicity of attached cytotoxin agent, dose limiting toxicities (DLTs) in normal cells, difficulties in ensuring production consistency and so on.
- Technology innovations and further studies are yet to be conducted to resolved challenges of ADC drugs.

In vivo toxicity of attached cytotoxin agent

- The toxicity of ADC drugs mainly comes from two aspects, i.e. toxicity produced by antibody molecules and toxicity produced by cytotoxic drug (payload), among which the toxicity produced by cytotoxic drug is mainly manifested in the damage to rapidly proliferating healthy cells, such as reduction of lymphocytes, alopecia, gastrointestinal tract reaction and so on
- Neutropenia, anaemia, alopecia are the common side effects of ADCs

Dose limiting toxicities (DLTs) in normal cells

- Mechanisms of ADC toxicity in normal cells/tissues are not clearly understood, but the majority of DLTs are considered to be target-independent, including linker-drug instability contributing to the premature release of cytotoxic drug (payload) in circulation, uptake/trafficking of intact ADCs by both receptor-dependent (FcγRs, FcRn and C-type lectin receptors), and-independent (non-specific endocytosis) mechanisms may contribute to off-target toxicity in normal cells

Difficulty in ensuring production consistency

- A central difficulty within ADC development lies in the linker technology. The traditional linker technique usually couples drugs through an antibody disulfide bond utilizing cysteine or lysine residues. The approximately 20 potential joinable lysine residues and random conjugation lead to production of millions of different ADC forms. The PK properties of the heterogeneous ADCs in vivo vary greatly and as a result, industrial production faces great challenges to ensure sample consistency between batches

Source: Frost & Sullivan, Literature Review

Entry Barrier for Development and Manufacturing of ADCs Drugs

- The unique targeting capabilities and promising clinical trial results of ADCs have made them an exciting and promising treatment in the fight against cancer. However, despite this tremendous growth, drugmakers still face a number of challenges in the development and manufacturing process for ADCs.

Challenges on Development of ADCs

Selection of specific antibody	The ADCs must be able to target cell-surface proteins with tumor-specific membrane expression.
Development of stable linker	The ADCs must be stabilized by a linker that keeps the cytotoxic payload attached during circulation but permits release of the load after cellular internalization.
Selection of efficient cytotoxin	The ADCs must contain a cytotoxin that effectively kills tumor cells

Challenges on Manufacturing of ADCs

Analytical method and conjugation technology	It is important to keep the drug-to-antibody ratio during the whole manufacturing process, which requires advanced and accurate analytical methods to minimize the variability caused by conjugation chemistries and assay methods, ensuring the drug will fall within the necessary specifications. In addition, the conjugation technology makes the manufacturer not only faced with challenges associated with the biologic itself, but also brings the high containment to handle highly potent chemical molecules.
Scale-UP	One of the most notable challenges of scaling up ADCs is the process variation caused by changes in equipment, scale, and raw materials.
Facility	Facility must be designed with proper engineering controls to provide product and personnel protection from highly potent compounds. Also, most smaller companies, and even some larger companies, do not have enough of a pipeline to justify the level of facility investment needed for ADCs and/or cannot keep the facility fully utilized.

Source: Frost & Sullivan Analysis

Entry Barrier for Development and Manufacturing of ADCs Drugs

- Critical to the clinical efficacy of an ADC are the target site-specificity and binding properties of the antibody, the in vitro and in vivo stability of the linker and drug species, the potency of the drug and both the distribution and average number of drug species on the antibody. Therefore, in ADC therapy development, the selection of targeted antigen, chemical linker, the payload drug and the choice of attachment sites are the key technical barriers and areas of improvement to reduce adverse events.

ADC Technical Barriers

Linker Stability

- Linker stability engineering is a key challenge since linkers may break and release drug prematurely, killing normal cells.
- Conventional bioconjugation chemistries suffer from premature loss of payload cargo in the bloodstream, which translates to loss of efficacy and off-site toxicity.

Payload Selection

- Drug selection is a technical challenge as it can affect internalization, ADC polarity and immunogenicity, and therapeutic efficacy.
- The selected drug needs to have the following characteristics: high cytotoxicity, affinity, low hydrophobicity and sensitivity. This makes few molecules suitable as the drug. Currently, most molecules derivatives from the auristatins and maytansinoids families.

Optimal DAR

- DAR is critical in determining efficacy, but designing ADCs with optimal drug-to-antibody ratio (DAR) is a key technical barrier.
- DAR varies within a single product and controlling this heterogeneity is difficult.
- Low DAR may not provide an adequate cytotoxic response while high DAR can become unstable and cause increased aggregation.

Target Selection and Antibody Reconstruction

- Selection of targeted antigen is a technical barrier. Challenges include low expression and low rate of internalization of the complex.
- IgG reconstruction is a key technical barrier in order to connect to linker with the drug and have high homogeneity. In conventional ADC therapy, TDC (THIOMAB drug conjugates) technique is adopted but has risk for dissociation in bloodstream.

Source: Frost & Sullivan Analysis

Key Elements for Successful Development of ADCs Agent

- To develop a successful ADCs agent, four key elements should be put into consideration, including tumor antigen, antibody, linker, and cytotoxic drug.

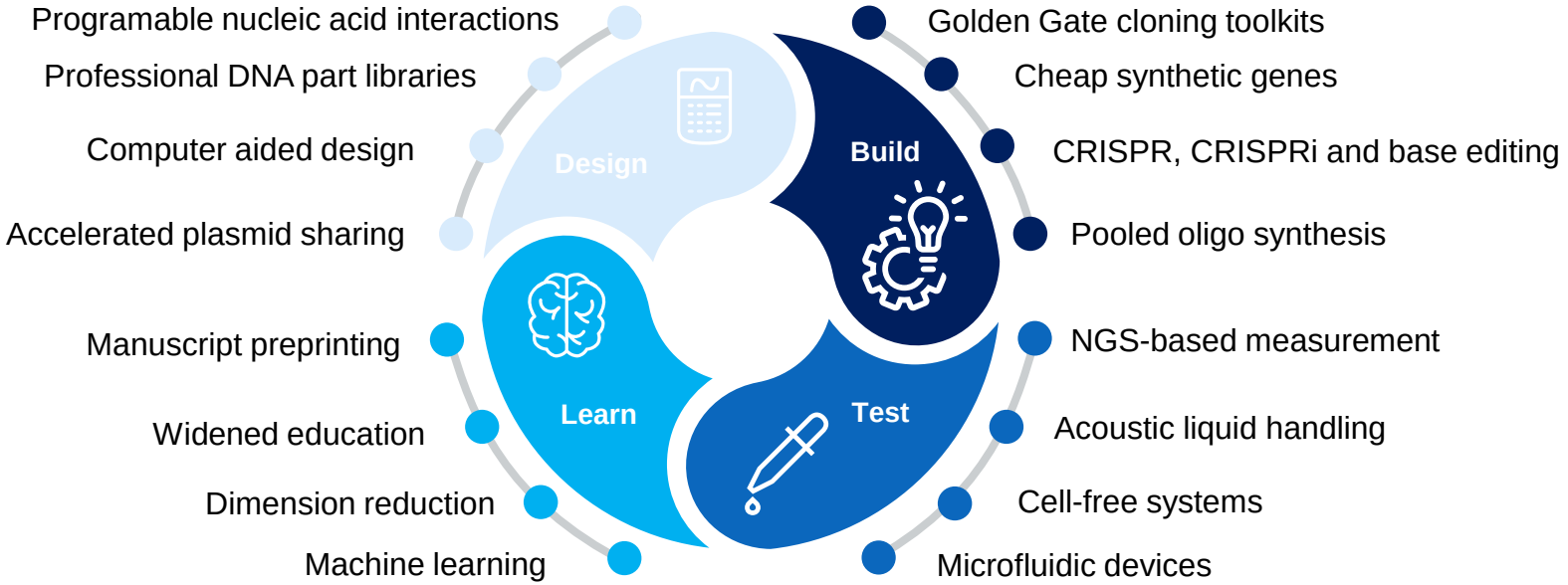
Element	Description
Tumor Antigen	• ADCs agents are mainly used for anti-tumor effects. An ideal target antigen should be overexpressed on the surface of tumor cells, but has little or none of expression in normal tissues. • When the tumor antigen is bound by the antibody of the ADCs agent, they can be effectively internalized and the cytotoxic drug can be released within the tumor cells.
Antibody	• Specificity, affinity and pharmacokinetics are important indexes to characterize an antibody. • The high affinity of antibody to tumor antigen is considered to be the core of killing target cells. Generally, the binding affinity index $K_D < 10^{-3}$ M is the basic requirement for the antibody. Based on the high affinity, the antibody is expected to have low immunogenicity, a long half-life, and to be stable in the blood.
Linker	• An ideal linker should maintain stability in the blood while effectively release the drug in target cells. In addition, linkers can be modified to be appropriate for different modes of metabolism or activation. • There are two types of linkers: cleavable linkers and non-cleavable linkers. The greatest advantage of non-cleavable linkers compared to cleavable linkers is their increased plasma stability, which offers reduced off-target toxicity. However, cleavable linkers can maintain better potency by allowing a faster rate of activation and release of the cytotoxic drugs.
Cytotoxic Drug	• The percent of an injected antibody that localize to a tumor is very small (0.003-0.08% injected does per gram of tumor). For this reason, it is necessary to use cytotoxic drug of high efficiency and high sensitivity (free drug IC_{50}: 10^{-11}-10^{-9} M) of killing target cells. • There are two common categories of drugs used for ADCs: microtubule inhibitors and DNA-damaging agents.

Source: Frost & Sullivan Analysis

Overview of Synthetic Biology

- Synthetic biology was first proposed by Hobom B. in 1980. However, with the continuous advancement of technology and technology, synthetic biology has gradually developed in recent years. Scientists can design components and modules according to specific needs, transform and optimize biological systems, and ultimately produce new, non-natural substances with unique structures. Through targeted editing of the genome and regulation of cellular metabolic pathways, synthetic biology technology can effectively increase the expression of major products. It also inhibits side metabolic pathways, increases production while reducing the generation of by-products, and has the advantages of less environmental pollution and low cost. Different from traditional chemical synthesis, biosynthetic products are more complex and diverse in chemical structure and can synthesize some substances that are difficult to chemically synthesize. The unique chemical structure of its products provides good targeting and biological activity. Therefore, it is of great significance in the drug development and production process.

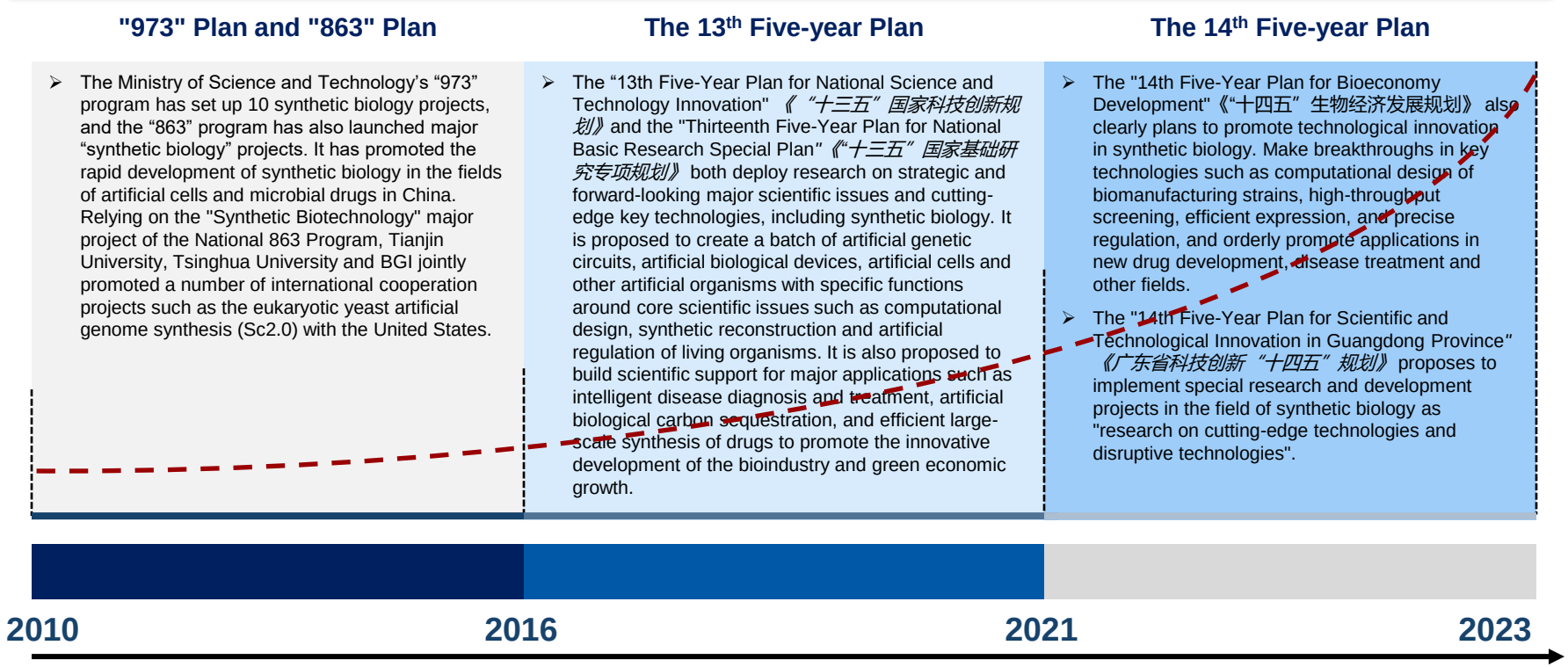
New Enabling Technologies and Ways of Working Accelerate Synthetic Biology's Design-build-test-learn Cycle



Source: Literature Review, Frost & Sullivan Analysis

Favorable Policies for Synthetic Biology

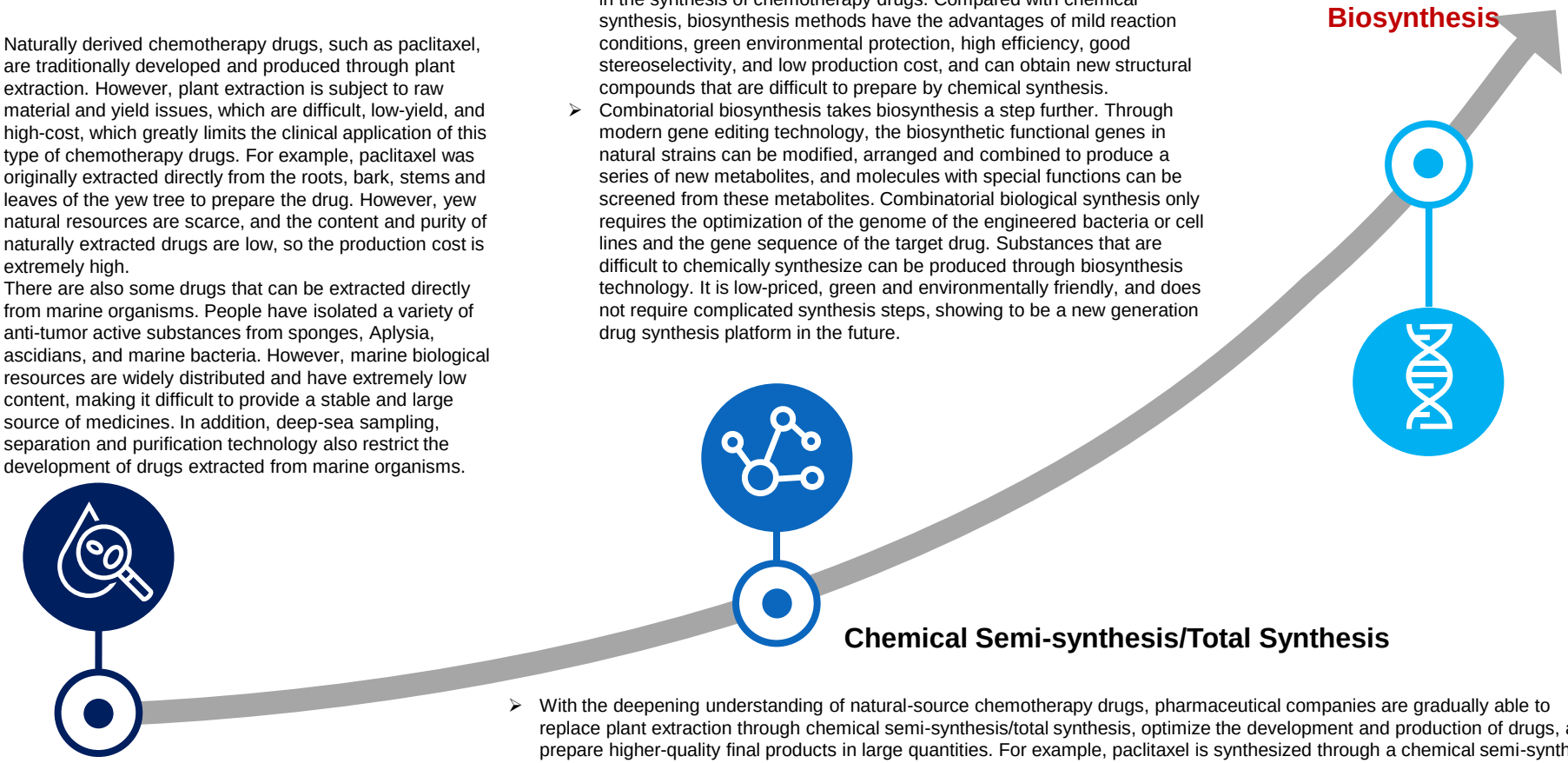
- In the healthcare field, most biopharmaceutical companies have established complete monoclonal antibody production systems, using mice or cell lines to mass-produce monoclonal antibody drugs with reliable quality. However, due to the high technical barriers of combinatorial biosynthesis, only a few companies are currently able to produce drugs through combinatorial biology platforms.
- In recent years, the Chinese government has vigorously supported innovation, continuously introduced relevant incentive policies, and continued to plan and deploy cutting-edge fields. As a result, synthetic biology has developed rapidly.



Source: Frost & Sullivan Analysis

Development History of Chemotherapy Drug Manufacturing Platform

- Naturally derived chemotherapy drugs, such as paclitaxel, are traditionally developed and produced through plant extraction. However, plant extraction is subject to raw material and yield issues, which are difficult, low-yield, and high-cost, which greatly limits the clinical application of this type of chemotherapy drugs. For example, paclitaxel was originally extracted directly from the roots, bark, stems and leaves of the yew tree to prepare the drug. However, yew natural resources are scarce, and the content and purity of naturally extracted drugs are low, so the production cost is extremely high.
- There are also some drugs that can be extracted directly from marine organisms. People have isolated a variety of anti-tumor active substances from sponges, Aplysia, ascidians, and marine bacteria. However, marine biological resources are widely distributed and have extremely low content, making it difficult to provide a stable and large source of medicines. In addition, deep-sea sampling, separation and purification technology also restrict the development of drugs extracted from marine organisms.



- As there are still many limitations in the production of naturally derived chemotherapy drugs, the exploration of innovative production methods is still ongoing. With the continuous deepening of the understanding of the structure of chemotherapy drugs from natural sources and the continuous development of biotechnology, biosynthetic methods are gradually used in the synthesis of chemotherapy drugs. Compared with chemical synthesis, biosynthesis methods have the advantages of mild reaction conditions, green environmental protection, high efficiency, good stereoselectivity, and low production cost, and can obtain new structural compounds that are difficult to prepare by chemical synthesis.
- Combinatorial biosynthesis takes biosynthesis a step further. Through modern gene editing technology, the biosynthetic functional genes in natural strains can be modified, arranged and combined to produce a series of new metabolites, and molecules with special functions can be screened from these metabolites. Combinatorial biological synthesis only requires the optimization of the genome of the engineered bacteria or cell lines and the gene sequence of the target drug. Substances that are difficult to chemically synthesize can be produced through biosynthesis technology. It is low-priced, green and environmentally friendly, and does not require complicated synthesis steps, showing to be a new generation drug synthesis platform in the future.

- With the deepening understanding of natural-source chemotherapy drugs, pharmaceutical companies are gradually able to replace plant extraction through chemical semi-synthesis/total synthesis, optimize the development and production of drugs, and prepare higher-quality final products in large quantities. For example, paclitaxel is synthesized through a chemical semi-synthetic method using 10-DAB in yew as raw material, because the content of 10-DAB in yew is three times that of paclitaxel. Therefore, chemical semi-synthesis can significantly increase the yield, while making the side chain of the group highly variable, effectively reducing the production cost of paclitaxel.

Source: Literature Review, Frost & Sullivan Analysis

Chemotherapy Drug Development Platform Comparison

	Direct Extraction	Chemical Semi-synthesis/Total Synthesis	Biosynthesis	Combinatorial Biosynthesis
Technology Requirements	• No special technical requirements, easy to get started and universally applicable	• It has a complete industrial chain and clear synthesis route, and its existing experimental equipment and industrial equipment are very mature.	• Through methods such as gene editing, the required genes can be transferred into engineered bacteria or cell lines to produce drugs in large quantities.	• On the basis of biosynthesis, through the modification and recombination of foreign genes, the structure of the compound is modified in a targeted manner, the expression level of the product is optimized, and the metabolites are controlled, so as to synthesize a large number of new complex substances.
Raw Materials/Cost	• Extracted from plants, roots, stems and leaves. • High cost.	• A large number of semi-synthetic precursor substances exist in plants, and the cost is greatly reduced.	• The starting raw materials are all from readily available raw materials such as amino acids, sugars, and inorganic salts. No toxic low-boiling point organic solvents are involved, and the cost of raw materials is low.	
Purity	• The purity is low, there are a lot of impurities, and it takes a lot of time to detect and purify.	• Through chemical synthesis, the purity of the synthetic products is consistent and the types of impurities are limited, making it easy to control trace impurities and reducing inspection time.	• With the development of biotechnology, purification and separation efficiency are higher and high-purity products can be provided.	
Activity	• Lower purity and complex purification processes will affect the biological activity of the product.	• There is insufficient control over the spatial structure of the product, and the biological activity is moderate.	• Its unique chemical structure confers diverse biological activities and the ability to specifically combine with specific targets.	
Environmentally Friendly /Renewable	• Over-exploitation will cause irreversible damage to the environment.	• Although synthetic precursor substances exist in large quantities, overexploitation can also endanger ecology and species.	• Usually using renewable biological resources as raw materials, it has the advantages of high efficiency, green and sustainable. Most of the reaction steps in biosynthesis are carried out under the action of microorganisms or enzymes, and the reaction conditions are milder and the process is simpler.	

Source: Literature Review, Frost & Sullivan Analysis

Analysis of Technological Advantages, Disadvantages and Barriers of Chemotherapy Drug Manufacturing Platform

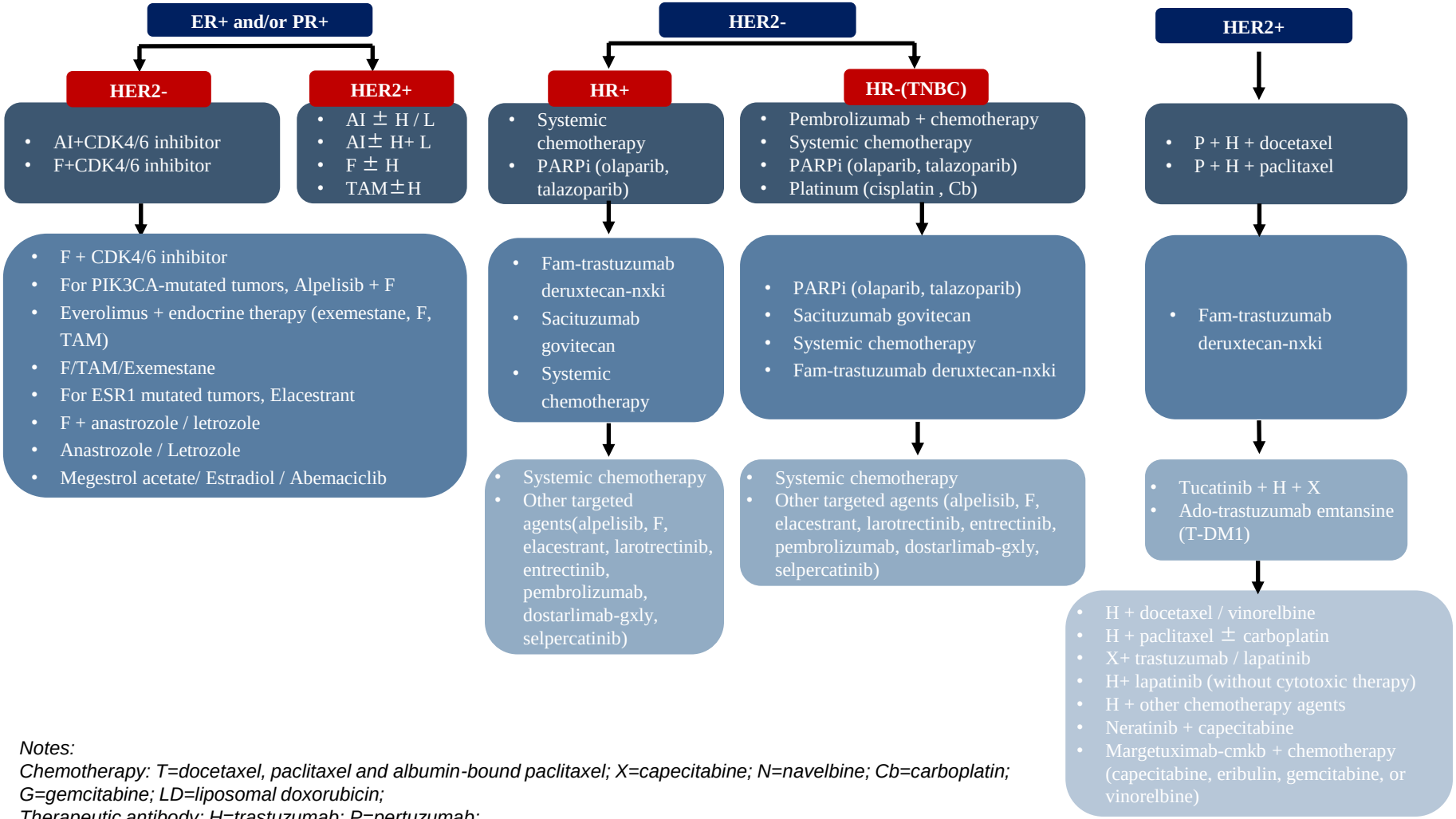
- Drug manufacturing methods use different platforms depending on the type of drug. Direct extraction is now rarely used in drug production due to its low yield, high impurities, and unfriendly environment.
- At present, the main drug synthesis methods are chemical semi-synthesis/total synthesis, which are widely used in the manufacture of most drugs. However, chemical synthesis still has many disadvantages, such as more complex synthesis steps, harsh reaction conditions, and greater environmental pollution.
- In recent years, biopharmaceuticals have developed rapidly, and biosynthetic platforms have gradually emerged and are widely used in the manufacture of biopharmaceuticals. Biosynthesis has the advantages of being green, environmentally friendly, and having mild reaction conditions, and is a new drug manufacturing method with great potential. The current development of combinatorial biosynthesis technology is still in its early stages, and there are still many bottlenecks. Only one innovative anti-tumor drug synthesized using combinatorial biology has been launched in China, and no overseas innovative anti-tumor drug synthesized using combinatorial biology has entered the Chinese market.

	Direct Extraction	Chemical Semi-synthesis/Total Synthesis	Biosynthesis	Combinatorial Biosynthesis
Advantages	• Due to the availability of raw materials, the purity of the product is low, requiring a lot of time to detect impurities and purify.	• High output and high manufacturing efficiency.	• It has high yield and can synthesize biological macromolecules with complex structures. Moreover, the synthesis method is low-cost, environmentally friendly, and has mild reaction conditions.	
Disadvantages	• Due to the availability of raw materials, the purity of the product is low, requiring a lot of time to detect impurities and purify.	• The synthesis steps are complicated and steric hindrance problems are prominent, making it difficult to produce complex biomacromolecule drugs. Moreover, the reaction conditions are violent and the environment is polluted.	• All production processes are completed by microorganisms, and the controllability of the production process is lower than that of chemical synthesis.	
Technical Barriers	• Technical barriers are low.	• The barriers are lower for drugs with simple structures and higher for drugs with complex structures.	• Involving genetic engineering, microbial culture and other technologies, the technical barriers are relatively high	• It not only involves genetic engineering and microbial culture, but also involves the recombination of gene clusters and the regulation of metabolic processes and signaling pathways. The technical barriers are extremely high.

Source: Literature Review, Frost & Sullivan Analysis

Treatment Paradigm of of Breast Cancer from NCCN

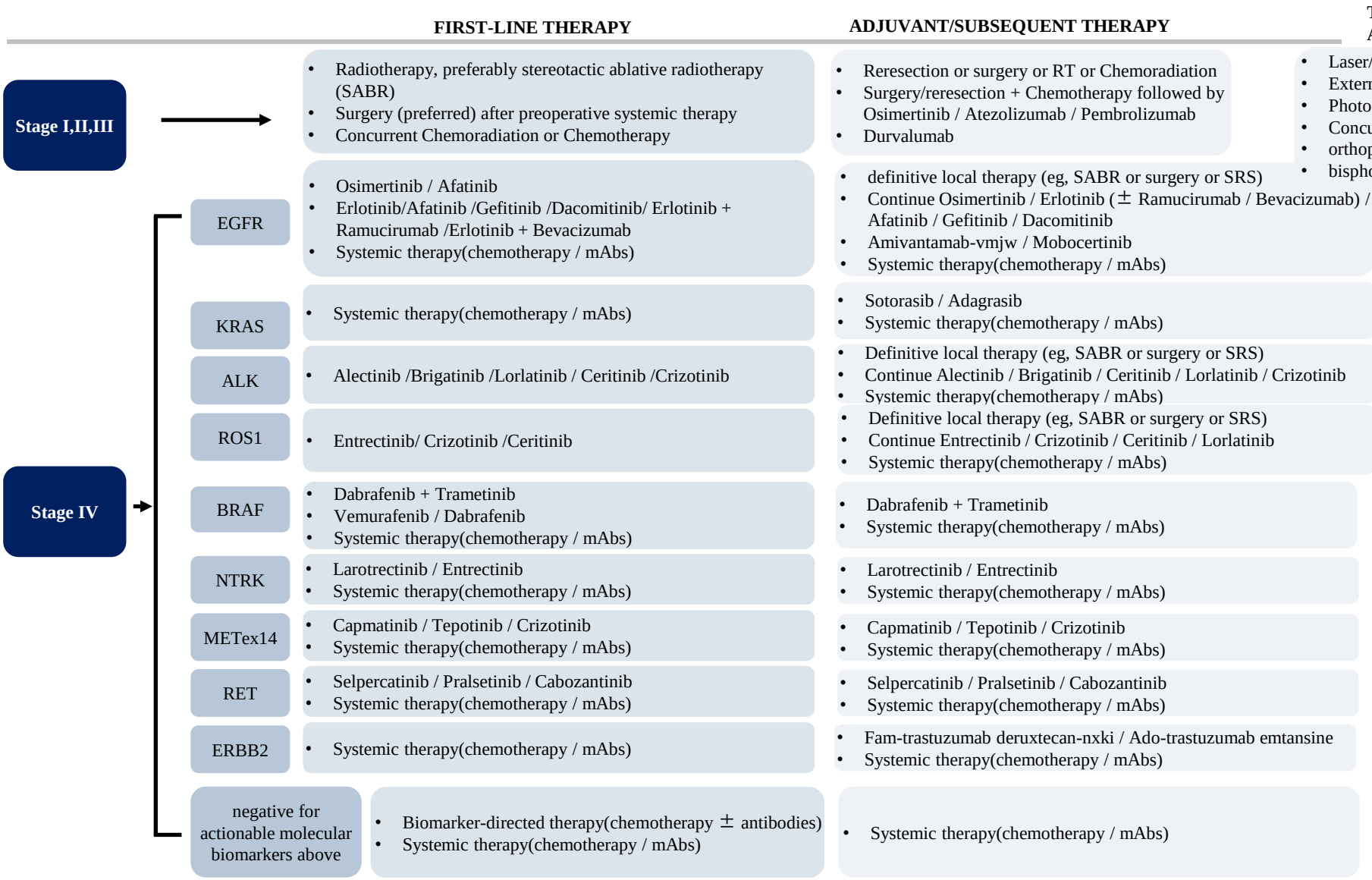
Treatment of Recurrent or Stage IV Disease



Notes:
Chemotherapy: T=docetaxel, paclitaxel and albumin-bound paclitaxel; X=capecitabine; N=navelbine; Cb=carboplatin; G=gemcitabine; LD=liposomal doxorubicin;
Therapeutic antibody: H=trastuzumab; P=pertuzumab;
Endocrine Therapy: AI=Aromatase inhibitor; F=fulvestrant; TAM=tamoxifen;
Small molecule targeted drug: CDK4/6 inhibitor includes ribociclib, abemaciclib, palbociclib; L=lapatinib.

Source: NCCN 2023, Frost & Sullivan Analysis

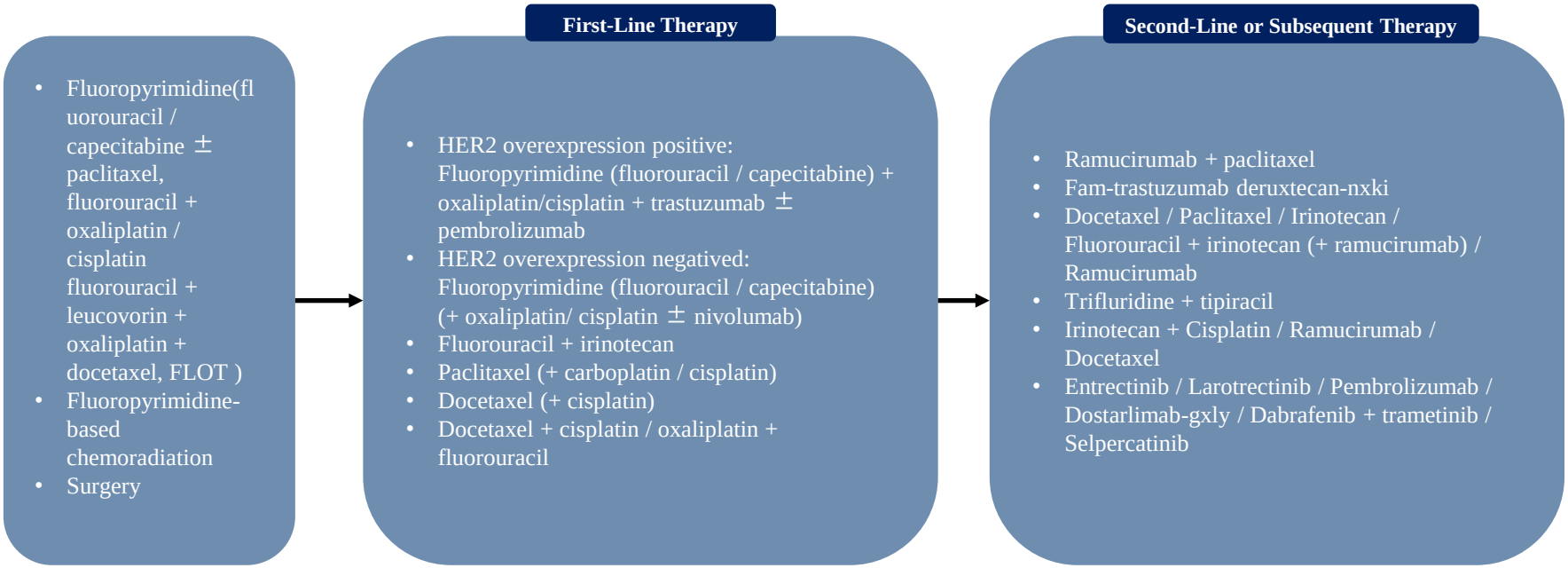
Treatment Paradigm of of NSCLC from NCCN



Source: NCCN 2023, Frost & Sullivan Analysis

Treatment Paradigm of of Gastric Cancer from NCCN

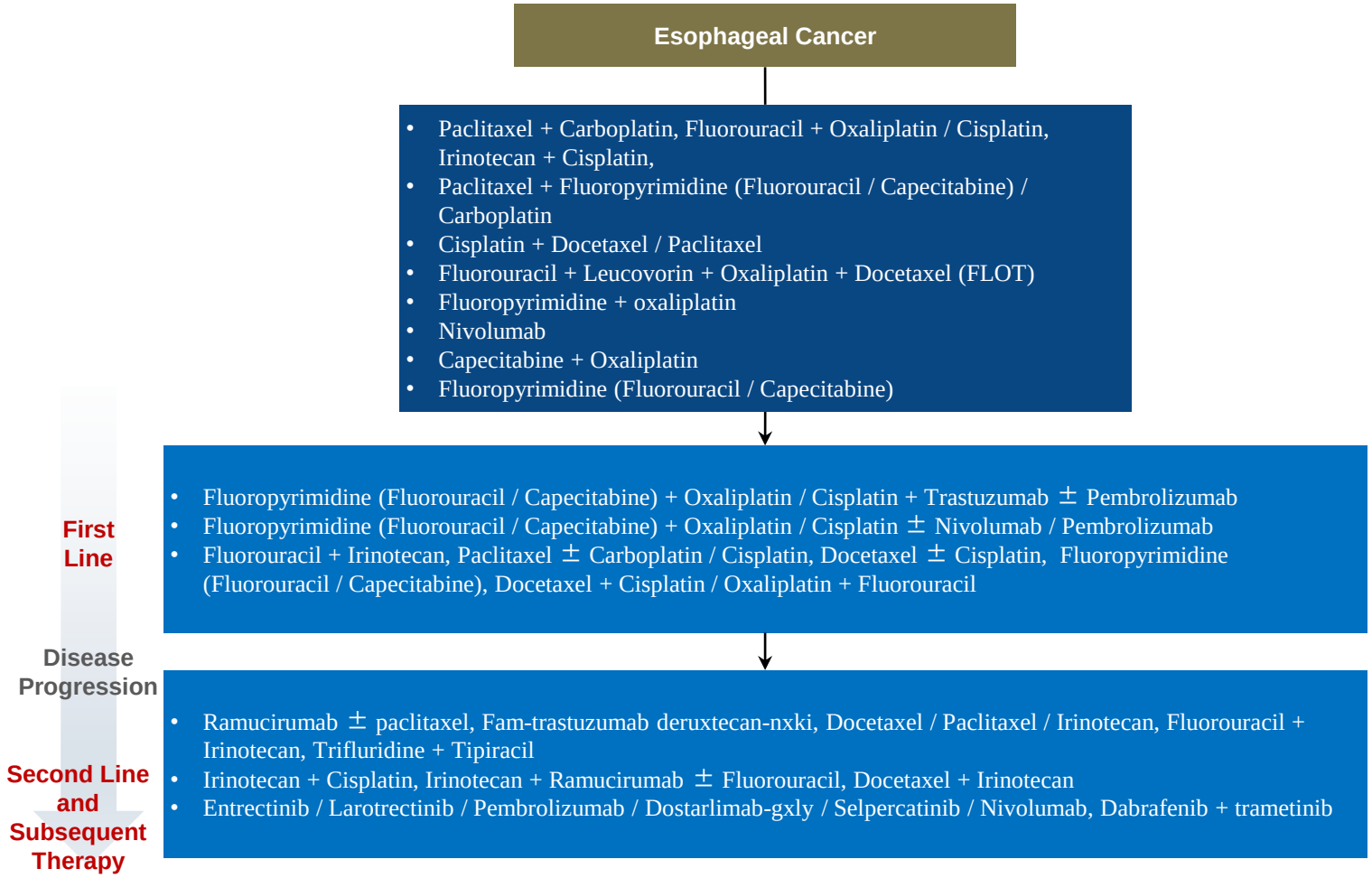
Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease



Notes:
Chemotherapy: T=docetaxel, paclitaxel and albumin-bound paclitaxel; X=capecitabine; N=navelbine; Cb=carboplatin; G=gemcitabine; LD=liposomal doxorubicin;
Therapeutic antibody: H=trastuzumab; P=pertuzumab;
Endocrine Therapy: AI=Aromatase inhibitor; F=fulvestrant;
Small molecule targeted drug: L=lapatinib.

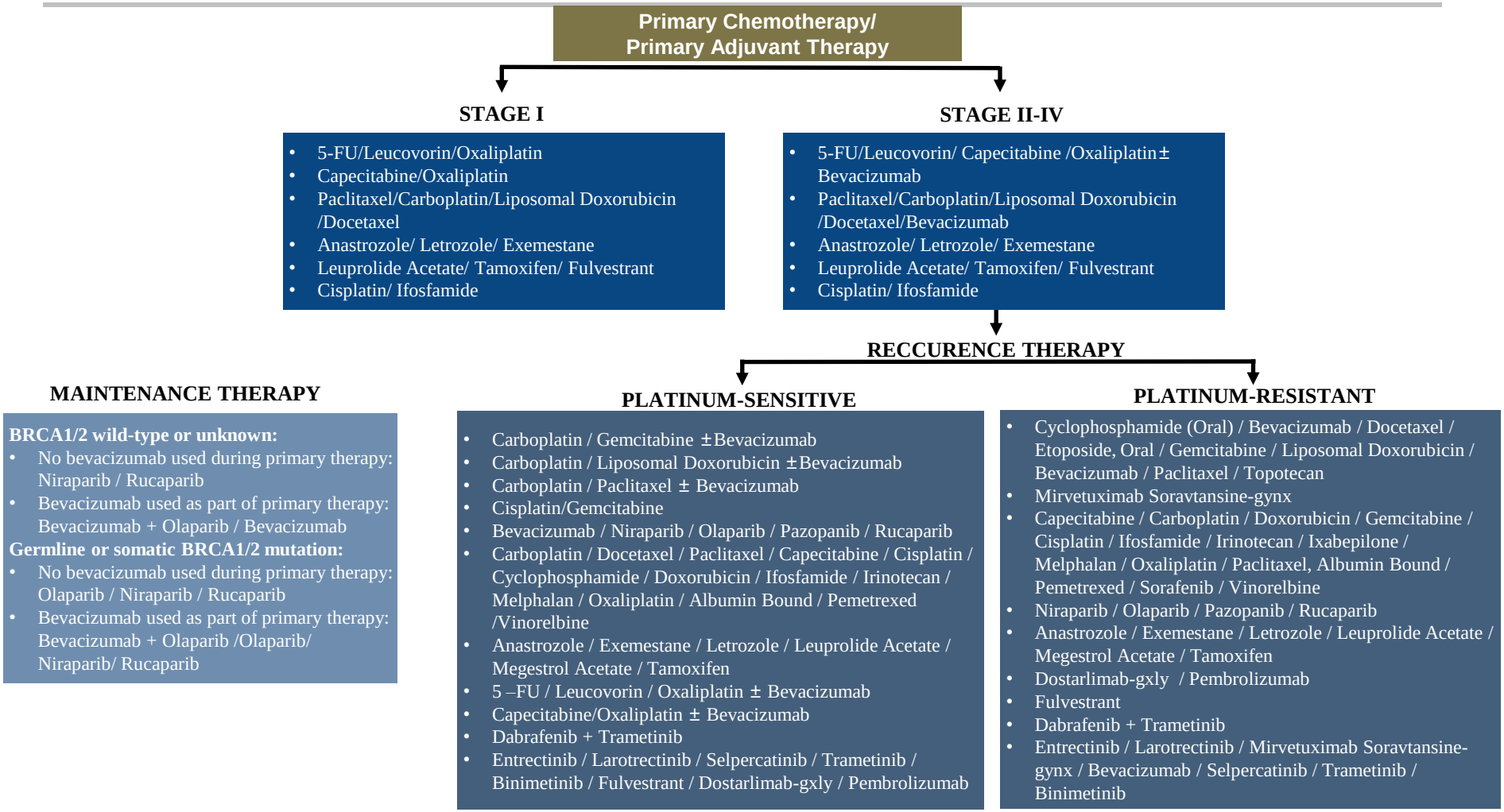
Source: NCCN 2023, Frost & Sullivan Analysis

Treatment Paradigm of Esophageal Cancer from NCCN



Source: NCCN 2023, Frost & Sullivan Analysis

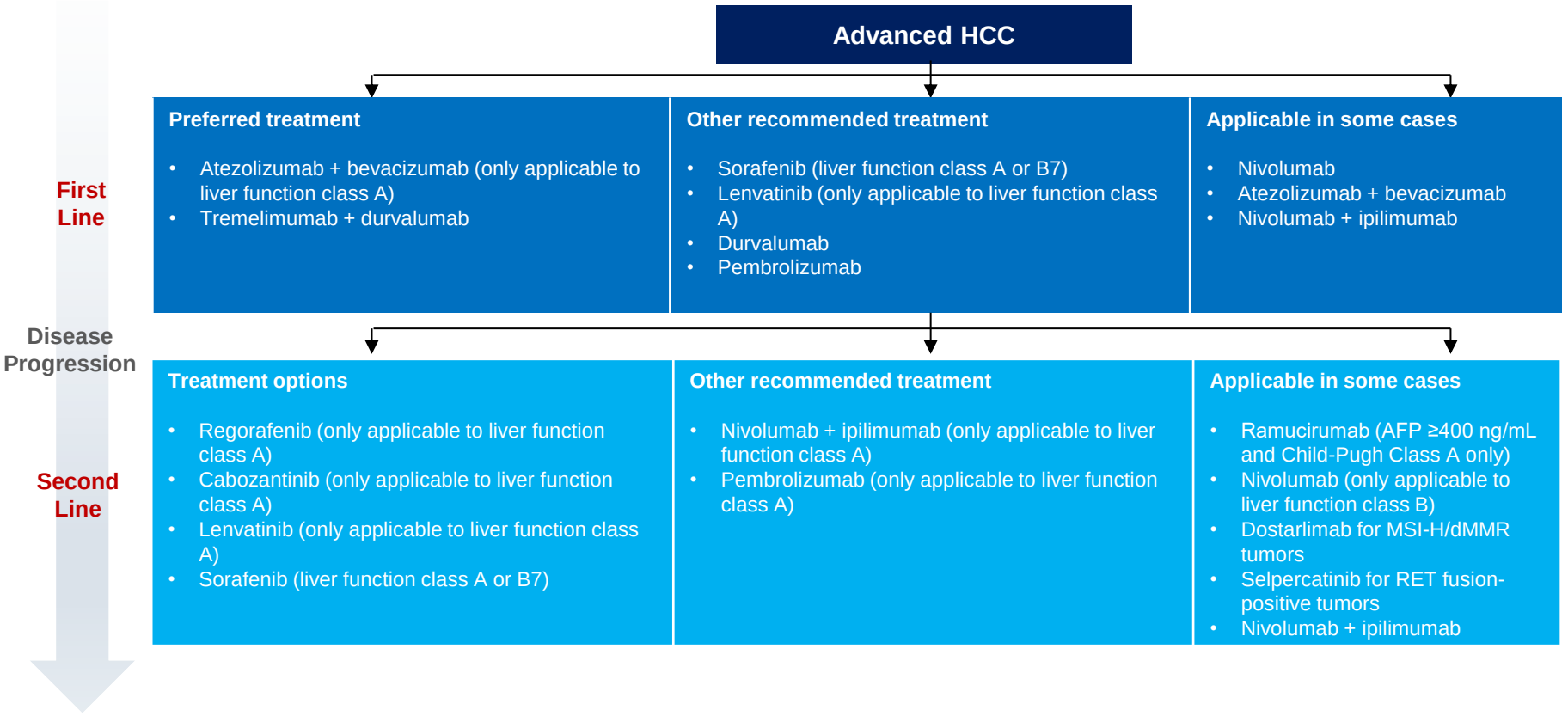
Treatment Paradigm of Ovarian Cancer from NCCN



Source: NCCN 2023, Frost & Sullivan Analysis

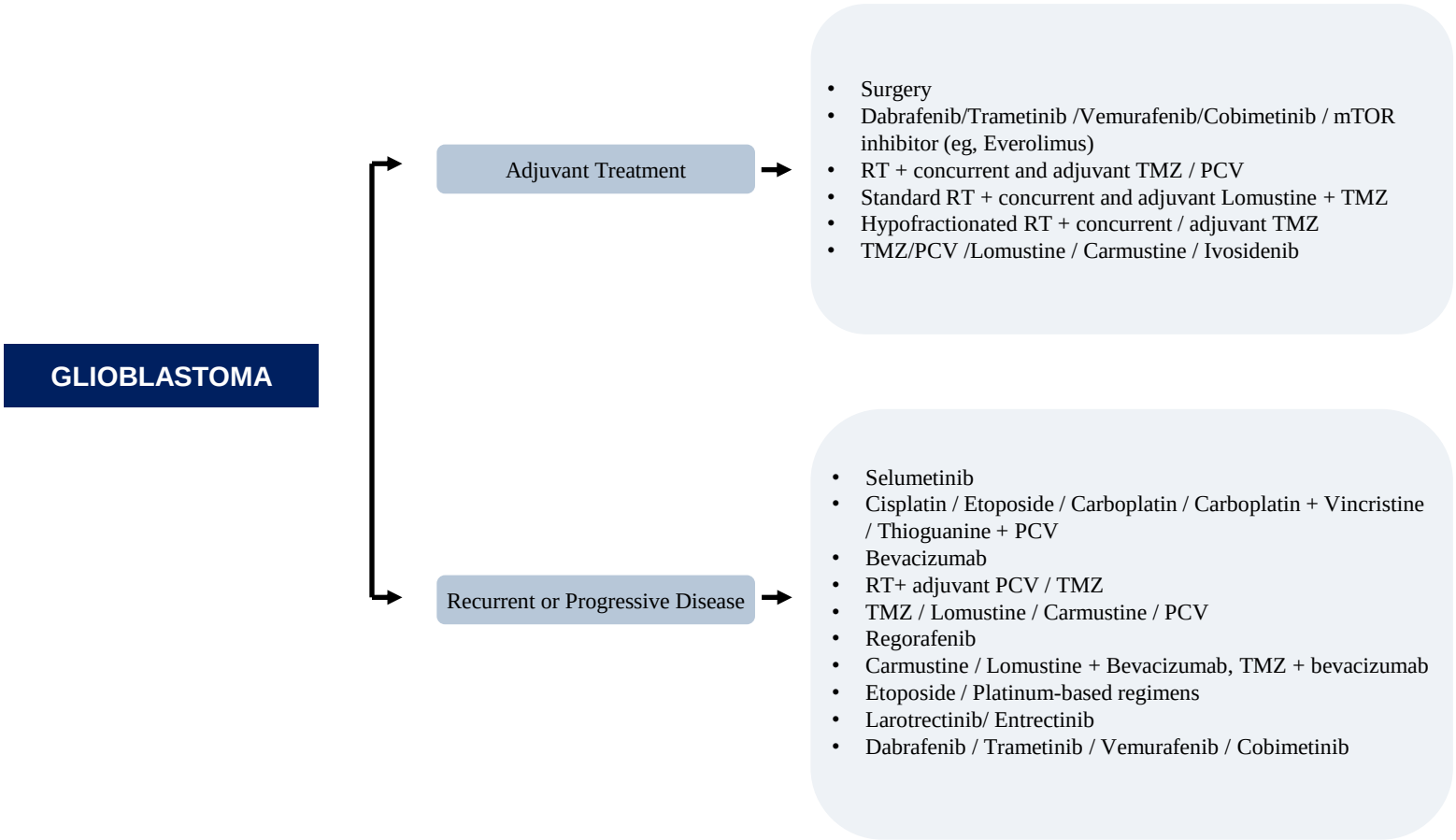
Treatment Paradigm of HCC from NCCN

- The treatment of hepatocellular carcinoma is characterized by the participation of multiple disciplines and the coexistence of multiple treatment methods. Common treatment methods include liver resection, liver transplantation, ablation therapy, TACE, radiation therapy, systemic anti-tumor therapy and other methods. Choosing reasonable treatment methods for patients with liver cancer at different stages can maximize the efficacy. Antibody drugs suitable for the treatment of hepatocellular carcinoma mainly include atezolizumab, bevacizumab, tremelimumab, durvalumab, etc.



Source: NCCN 2023, Frost & Sullivan analysis

Treatment Paradigm of Glioblastoma from NCCN



Notes: TMZ:temozolomide, PCV: procarbazine/lomustine/vincristine

Source: NCCN 2023, Frost & Sullivan analysis

Comparison of Different Treatment Therapies - I

Category	Features	Advantages	Shortcomings	Indication Examples
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	Chemotherapy is a systemic treatment that can treat both primary and metastatic lesions. Chemotherapy, as the main treatment modality for tumors, can be used to treat almost all tumors, including various types of solid tumors and hematological tumors, and the cost of treatment for patients is relatively low.	Chemotherapy also can damage the immune system by reducing the number of infection-fighting white blood cells. It can cause some side effects, which are generally attributed to non-specific drug exposure to off-target tissues.	• Utidelone plus capecitabine as the emerging t advanced breast cancer shown both efficacy a Utidelone combination regimen can significant PFS and OS, meet the actual clinical needs, a of disease survival and death in advanced pat • Temozolomide is a first-line chemotherapy dru and has broad-spectrum anti-tumor activity. It blood-brain barrier and is an important option to extend their progression-free survival.
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs). By targeting specific antigens on the surface of target cells and relying on mechanisms such as antibody-dependent cytotoxicity (ADCC), it can achieve the goals of regulating signaling pathways and killing tumor cells.	The main advantages of mAbs are their mechanism of action, which could promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells. monoclonal antibodies (mAbs) showed therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms.	Therapeutic antibodies treatment usually costs a relatively high price, and can issue risks, including tissue accessibility, poor pharmacokinetics, lame interactions with the immune system, and off-target effects.	• Trastuzumab can significantly reduce the risk patients with HER2-positive breast cancer, so in combination with trastuzumab and taxanes, main treatment for HER2-positive breast canc • Bevacizumab is a humanized monoclonal anti against circulating vascular endothelial growth which has been approved as therapy for many metastatic colorectal cancer (CRC), non-small (NSCLC), glioblastoma therapy, and metastati carcinoma (RCC), etc. However, this treatmer the number of white blood cells and cause oth effects.

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies - II

Category	Features	Advantages	Shortcomings	Indication Examples
ADC	ADCs are composed of an antibody linked to a toxic payload, allowing precise killing of tumor cells.	ADCs combine both the advantages of highly specific targeting ability and highly potent killing effect to achieve accurate and efficient elimination of cancer cells.	There remain many challenges in the use of anti-cancer ADCs, including off-target effects, complexity in pharmacokinetics, insufficient tumor targeting and payload release, as well as drug resistance.	• Trastuzumab deruxtecan is the most significant second-line therapy for HER2 positive breast cancer for its precise targeting, high efficacy and highly stability in blood with low off-target rate and good safety.
Targeted small-molecule therapy	Small molecule targeted drugs are chemical drugs that can specifically block the signaling pathways necessary for tumor growth and proliferation to produce anti-tumor effects. Because of their small molecular weight, a small number of small molecule targeted drugs can penetrate the blood-brain barrier.	Targeted small-molecule cancer therapy has several benefits. Most small molecule drugs are stable and can be administered orally, which enhances patient compliance. Some small molecule drugs can pass through the blood-brain barrier and can be used to treat brain diseases.	The major challenge includes drug resistance and limited number of users (are effective only in a limited number of patients, who are positive for a specific gene or mutation).	• Small molecule drugs play an important role in lung cancer and liver cancer. Osimertinib is the preferred first-line treatment for patients with EGFR-mutated advanced NSCLC, and it significantly extended patients' survival.

Source: Literature review, Frost & Sullivan analysis

Summary of Indication Market

- The types of drugs approved for each indication, the marketing status of generics/biosimilars of each drug, NRDL inclusion status, and VBP status vary greatly. Therefore, in the treatment of different indications, the range of annual treatment costs for different therapies is also large.
- In addition, according to the drug instructions, because the same drug has different usage periods for different indications, and the patient's compliance with medication during treatment is also extremely complex, the actual annual treatment cost will vary even further.

Indication	2022 China Market /Billion RMB	2022 Incidence /Thousand	Treatment Rate	Annual Treatment Cost/Thousand RMB
Breast cancer	54.8	341.0	~90%	16~570
NSCLC	54.0	836.8	~90%	2~360
Gastric cancer	33.8	498.6	~90%	2~470
Esophageal cancer	3.7	308.6	~90%	2~360
Ovarian cancer	4.3	57.0	~90%	2~160
Liver cancer	10.3	441.7	~90%	2~140
Glioblastoma	0.9	42.4	80%-90%	74~130

Note: In the treatment of different indications and different stages, the treatment methods (chemotherapy, small molecule targeted drugs, antibodies, etc.) that patients can choose vary greatly according to the guidelines and approved drugs. Moreover, the gap in medication compliance between different patients is also significant, so it is difficult to calculate the penetration rate of a certain overall indication.

Source: Frost & Sullivan analysis

Incidence of cancer stage of Core Product's indications

Incidence of indication stage(2023, China)/Thousand	Incidence of indication stage(2027, China)/Thousand	Incidence of indication stage(2030, China)/Thousand	Incidence of indication stage(2023, Global)/Thousand	Incidence of indication stage(2027, Global)/Thousand	Incidence of indication stage(2030, Global)/Thousand	
85.0	93.3	99.3	560.4	634.7	704.9	~23% of to
588.4	652.1	698.5	1,377.6	1,537.0	1,660.1	Advance
75.9	89.3	99.6	500.9	607.0	706.9	Early s nec Chemo
45.6	49.8	52.7	301.0	338.7	374.4	Breast cance rat
185.3	205.4	220.0	433.9	484.1	522.9	Lung cance rat
43.7	48.9	52.5	311.2	339.1	360.4	
78.9	86.1	91.1	520.1	585.4	647.0	Advance
225.1	250.6	269.5	607.2	674.7	727.0	Advance
164.0	184.2	199.1	373.1	415.2	447.6	Advance
46.2	48.2	49.4	250.5	272.3	287.6	Advance
295.5	321.8	341.2	698.9	773.7	831.4	Advance

Notes: As of date: 2024.5.31

1. *There is no chemotherapy drug that is completely consistent with the approved indications of the company's products, so the focused indication is advanced breast cancer.*
2. *Neoadjuvant therapy was developed later than most of the early approved chemotherapy drugs, so the drug label does not specify whether it is suitable for neoadjuvant the used for neoadjuvant therapy are derived from CSCO guideline recommendations.*

SOC of Indications

Indication	Standard of Care
Breast Cancer	Neo adjuvant treatment / Adjuvant treatment: Her2+: Trastuzumab, pertuzumab, taxane Her2-: Anthracycline combined with taxane Advanced breast cancer: HER2+: taxane and trastuzumab combined with pertuzumab/pyrotinib HER2-: taxane alone or taxane combined with capecitabine/gemcitabine/platinum or combination with pd-1 inhibitors ER+ and/or PR+: chemotherapy(as salvage therapy), CDK4/6i combined with endocrine therapy (aromatase inhibitor or fulvestrant)
NSCLC	Stage I-III: Surgery plus/or chemoradiotherapy Stage IV: TKI or chemotherapy (Platinum-based chemotherapy, taxane, etc.) or antibody drugs. (Different drugs are used according to different mutations)
Gastric Cancer	HER2-positive advanced or metastatic gastric cancer: trastuzumab combine with chemotherapy (xaliplatin/cisplatin+ Fluorouracil /capecitabine)
Liver Cancer	Advanced liver cancer: single agent TKI or PD-L1 inhibitor combined with VEGFR monoclonal antibody
Esophagus Cancer	Advanced esophageal cancer: immunotherapy combined with chemotherapy
Ovarian Cancer	Surgery with postoperative adjuvant chemotherapy (platinum, paclitaxel, docetaxel, etc.) Maintenance therapy: PARP inhibitors
Glioblastoma	Surgery, postoperative temozolomide (TMZ) combined with radiotherapy, and temozolomide adjuvant chemotherapy are the current standard treatment options for glioma.

Note: As of Apr 29, 2024.

Source: CSCO, Literature review, Frost & Sullivan Analysis

Appendix III: Number of peer products/ programs chemical drugs that are in more advanced or similar development stages as compared to the programs/treatment lines of the Core Product

Indication	Region	No. of approved chemical drugs	No. of developing chemical drugs in phase III or later	No. of developing chemical drugs in phase II	No. of developing chemical drugs in phase I
BC	Global	22	/	/	/
	China	18	/	/	/
NSCLC	Global	8	9	/	/
	China	6	5	/	/
Gastric	Global	14	2	10	/
	China	8	0	4	/
EC	Global	16	2	12	6
	China	8	0	4	4
GBM	Global	3	5	5	1
	China	1	1	1	0

Note:
1. As of 2024/05/31
2. Only new molecule drugs are included

Source: NMPA, FDA, EMA, CDE, Clinical Trials, Frost & Sullivan Analysis

Comparison of Different Treatment Therapies – Breast Cancer

Category	Features	Advantages	Shortcomings	
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can treat both primary and metastatic lesions • can be used as the neo adjuvant treatment, adjuvant treatment, or the treatment for advanced breast cancer • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues	• Chemo (Doxor based of adva
Microtubule inhibitor	*Microtubule inhibitors can inhibit tumor proliferation by inhibiting the polymerization or depolymerization of microtubules.*	• *for cancer cells that proliferate faster than most normal cells, microtubule inhibitors can preferentially kill cancer cells.* • *effective in the treatment of various tumors at different stages* • *has broad-spectrum anti-cancer potential*	• *Lack of targeting* • *Toxic side effects* • *Usually require injection*	• *Microtu (albur Doceta utidelon advanc*
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Treatm include inhibito
ADC	ADCs are composed of an antibody linked to a toxic payload, allowing precise killing of tumor cells.	• highly specific targeting ability • highly potent killing effect to achieve accurate and efficient elimination of cancer cells	• Off-target effects and complexity in pharmacokinetic • Usually cost a relatively high price • Usually require injection	• Trastuz trastuz ADC th cancer
Targeted small-molecule therapy	Small molecule targeted drugs are chemical drugs that can specifically block the signaling pathways necessary for tumor growth and proliferation to produce anti-tumor	• Most are stable and can be administered orally • Some small molecule drugs can pass through the blood-brain barrier and can be used to treat brain diseases	• Drug resistance	• Pyrotin the rec positive

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies – NSCLC

Category	Features	Advantages	Shortcomings	Indication Ex
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can treat both primary and metastatic lesions. • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues	• Platinum-based chem are widely used in the NSCLC.
Microtubule inhibitor	*Microtubule inhibitors can inhibit tumor proliferation by inhibiting the polymerization or depolymerization of microtubules.*	• *for cancer cells that proliferate faster than most normal cells, microtubule inhibitors can preferentially kill cancer cells.* • *effective in the treatment of various tumors at different stages* • *has broad-spectrum anti-cancer potential*	• *Lack of targeting* • *Toxic side effects* • *Usually require injection*	• *Microtubule inhibitors (paclitaxel, paclitaxe liposome/polymer mic vinorelbine are widely treatment of NSCLC.*
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Bevacizumab, PD-1(N Pembrolizuma) , and (Atezolizumab, Durva are used for non-sma (NSCLC) treatment.
Targeted small-molecule therapy	Small molecule targeted drugs are chemical drugs that can specifically block the signaling pathways necessary for tumor growth and proliferation to produce anti-tumor effects.	• Most are stable and can be administered orally. • Some small molecule drugs can pass through the blood-brain barrier and can be used to treat brain diseases.	• Drug resistance	• Small molecule drugs role in lung cancer, su Gefitinib, Crizotinib, C

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies – Gastric Cancer

Category	Features	Advantages	Shortcomings	Indication Examp
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can be used before surgery, after surgery, and for advanced gastric cancer. • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues.	• Carboplatin combination paclitaxel is the recomme treatment for unresectabl cancer. Other chemother include capecitabine, etc
Microtubule inhibitor	*Microtubule inhibitors can inhibit tumor proliferation by inhibiting the polymerization or depolymerization of microtubules.*	• *for cancer cells that proliferate faster than most normal cells, microtubule inhibitors can preferentially kill cancer cells.* • *effective in the treatment of various tumors at different stages* • *has broad-spectrum anti-cancer potential*	• *Lack of targeting* • *Toxic side effects* • *Usually require injection.*	• *Docetaxel are widely use treatment of gastric canc*
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Trastuzumab can signific reduce the risk of recurre patients with HER2-positi cancer. Sintilimab and Ni are also used to treat adv gastric cancer.
ADC	ADCs are composed of an antibody linked to a toxic payload, allowing precise killing of tumor cells.	• highly specific targeting ability • highly potent killing effect to achieve accurate and efficient elimination of cancer cells.	• Off-target effects and complexity in pharmacokinetic • Usually cost a relatively high price • Usually require injection	• Disitamab vedotin can be second-line treatment for gastric cancer.
	Small molecule targeted drugs	• Most are stable and can be		

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies –Esophageal Cancer

Category	Features	Advantages	Shortcomings	Indication Examp
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can be used before surgery, after surgery, and for advanced esophageal cancer • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues	• Chemotherapy drugs such platinum-based drugs and p are widely used in the treat metastatic esophageal canc
Microtubule inhibitor	*Microtubule inhibitors can inhibit tumor proliferation by inhibiting the polymerization or depolymerization of microtubules.*	• *for cancer cells that proliferate faster than most normal cells, microtubule inhibitors can preferentially kill cancer cells.* • *effective in the treatment of various tumors at different stages* • *has broad-spectrum anti-cancer potential*	• *Lack of targeting* • *Toxic side effects* • *Usually require injection*	• *Docetaxel are widely used treatment of gastroesophag junction adenocarcinoma.*
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Trastuzumab can significan the risk of recurrence in pat HER2-positive esophageal
ADC	ADCs are composed of an antibody linked to a toxic payload, allowing precise killing of tumor cells.	• highly specific targeting ability • highly potent killing effect to achieve accurate and efficient elimination of cancer cells.	• Off-target effects and complexity in pharmacokinetic • Usually cost a relatively high price • Usually require injection	• Disitamab vedotin can be u second-line treatment for ad esophageal cancer.
	Small molecule targeted drugs	• Most are stable and can be		

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies –Ovarian Cancer

Category	Features	Advantages	Shortcomings	Indication Examples
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can treat both primary and metastatic stages • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues.	• Chemotherapy drugs for ovarian cancer includes platinum-based drugs, paclitaxel, docetaxel, doxorubicin, etc.
Microtubule inhibitor	*Microtubule inhibitors can inhibit tumor proliferation by inhibiting the polymerization or depolymerization of microtubules.*	• *for cancer cells that proliferate faster than most normal cells, microtubule inhibitors can preferentially kill cancer cells.* • *effective in the treatment of various tumors at different stages* • *has broad-spectrum anti-cancer potential*	• *Lack of targeting* • *Toxic side effects* • *Usually require injection.*	• *Paclitaxel is widely used in the treatment of ovarian cancer.*
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Bevacizumab can be used in combination with platinum drugs for patients with platinum-sensitive recurrent ovarian cancer.
ADC	ADCs are composed of an antibody linked to a toxic payload, allowing precise killing of tumor cells.	• highly specific targeting ability • highly potent killing effect to achieve accurate and efficient elimination of cancer cells.	• Off-target effects and complexity in pharmacokinetic • Usually cost a relatively high price • Usually require	• Mirvetuximab soravtansine is the world's first ADC for the treatment of platinum-resistant ovarian cancer, receives full approval from FDA.

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies – Liver Cancer

Category	Features	Advantages	Shortcomings	Indication Examples
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can treat both primary and metastatic stages • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues.	• Oxaliplatin can be used in the treatment of advanced HCC.
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Tislelizumab can be used as first-line treatment for patients with unresectable or metastatic hepatocellular carcinoma (HCC)
Targeted small-molecule therapy	Small molecule targeted drugs are chemical drugs that can specifically block the signaling pathways necessary for tumor growth and proliferation to produce anti-tumor effects.	• Most are stable and can be administered orally • Some small molecule drugs can pass through the blood-brain barrier and can be used to treat brain diseases.	• Drug resistance	• Small molecule drugs play an important role in liver cancer, such as Sorafenib, Lenvatinib and Apatinib, etc., which are the preferred treatment for patients with advanced HCC.

Source: Literature review, Frost & Sullivan analysis

Comparison of Different Treatment Therapies – GBM

Category	Features	Advantages	Shortcomings	Indication Examples
Chemotherapy	Chemotherapy uses cytotoxic chemicals to treat diseases, affecting the formation of cancer cells by interfering with DNA, RNA or protein synthesis in cells.	• can treat both primary and metastatic stages • the cost of chemotherapy for patients is relatively low	• Side effects • Non-specific drug exposure to off-target tissues	• Temozolomide is a first-line chemotherapy drug for brain glioma and has broad-spectrum anti-tumor activity. It can penetrate the blood-brain barrier and is an important option for many patients to extend their progression-free survival.
Therapeutic antibodies	Therapeutic antibodies are important effector molecules that can specifically bind to antigens and mediate immune responses. Currently, the main therapeutic antibodies include monoclonal antibodies (mAbs) and bispecific antibodies (Bsabs).	• promote the death of tumor cells by recognizing the tumor-associated antigens (TAA) and the stimulation of long-lasting antitumoral activities with less effect on healthy cells • have therapeutic and safety benefits in both hematologic malignancies and solid tumors by selectively targeting cancer cells and by activating direct and/or indirect killing mechanisms	• Usually cost a relatively high price • Usually require injection • Potential resistance and mutation	• Bevacizumab is a humanized monoclonal antibody directed against circulating vascular endothelial growth factor (VEGF), which has been approved as therapy for glioblastoma therapy.
Targeted small-molecule therapy	Small molecule targeted drugs are chemical drugs that can specifically block the signaling pathways necessary for tumor growth and proliferation to produce anti-tumor effects.	• Most are stable and can be administered orally • Some small molecule drugs can pass through the blood-brain barrier and can be used to treat brain diseases.	• Drug resistance	• Bozitinib can penetrate the blood-brain barrier and significantly prolong the survival time for GBM patients.

Source: Literature review, Frost & Sullivan analysis

Appendix for Verification - I

- Utidelone Injection stands out as the only newly approved chemotherapy drug developed using synthetic biology technology, and it is also the sole microtubule inhibitor drug with a novel molecular structure to have received approval in the past decade worldwide as of 2024.01.22.
- Microtubule inhibitor have been used as cornerstone in cancer treatments for over 30 years.
- Utidelone distinguishes itself from taxanes as it has different tubulin binding sites and chemical structures.
- As recommended by domestic and the NCCN guidelines, AC in combination with taxanes (TAC regimen) is currently a neoadjuvant standard treatment for patients with HER2-breast cancer, nevertheless its efficacy and safety profile are limited.
- Given the promising performance of ADCs in indications like breast cancer, and the clinical exploration involving microtubule inhibitor drugs as effective payloads.
- Studies have shown that the presence of ~cancer stem cells in malignant tumors such as breast cancer, lung cancer, liver cancer, and pancreatic cancer, is considered to be one of the causes of tumor development, invasion, metastasis, and resistance to radiotherapy and chemotherapy.
- Studies have shown that this natural compound demonstrates significant inhibitory effects on human cancer cell lines such as leukemia, colorectal cancer, lung cancer, breast cancer, and ovarian cancer in vitro, and also displays promising anti-tumor effects ~in vivo.
- The development of improved drug formulations typically involves lower investment and a shorter research cycle, benefiting from favorable policies and market conditions.
- As of 2024.01.22, no oral formulation of paclitaxel had been successfully launched in China and the United States.
- Taxanes still face challenges such as drug resistance and safety concerns. Taxanes is the top-selling chemotherapy and anti-tumor drug in the country.
- Clinical trials showed that, in terms of grade three or four neutropenia, the incidences of Utidelone monotherapy and combination therapy were significantly lower than other treatments, demonstrating a unique advantage in low hematological toxicity.
- The overexpressed P-glycoprotein induced by drugs will decrease the concentration of drugs in tumor cells. In addition, tubulin mutation can cause paclitaxel resistance.
- As of 2024.01.22, there was no approved drugs for the treatment of breast and lung cancer brain metastases in China.
- The scarcity of yew trees, the primary source of taxanes, constrains the production of taxanes and impedes the expansion of their market prospects.

Appendix for Verification - II

- Chemotherapy is one of the most widely used treatments for indications such as breast cancer, NSCLC, gastric cancer, and esophageal cancer. However, as no new molecular innovative microtubule inhibitor drug with clinical value has been launched over the years, patients face limited options for treatment.
- In cancer treatment, compared with injectable formulation, oral formulation shows better convenience and compliance in clinical practice. It not only helps in adjuvant and maintenance therapies for cancer patients but also reduces the economic burden on patients as there is no need for hospitalization, suggesting potential for wide application around the world. However, developing oral formulations of chemotherapy drugs poses challenges. To be developed into oral formulations, these drug molecules generally must have appropriate solubility, permeability, good metabolic stability, and are not susceptible to P-glycoprotein mediated efflux. As of 2024.01.22, paclitaxel oral liquid and vinorelbine tartrate soft capsule were the only approved oral microtubule inhibitor drugs worldwide, with approval and availability restricted to a very limited number of countries.
- Taxanes have been crucial chemotherapy drugs for about 30 years for treating solid tumors since their launch. However, their considerable side effects, such as bone marrow suppression, and inevitable drug resistance limit their clinical efficacy.
- Neoadjuvant treatment for breast cancer can help patients in reducing distant recurrence, allowing patients to start systemic treatment earlier and reducing their tumor stages. Neoadjuvant treatment for HER2+ breast cancer typically consists combination of chemotherapy with monoclonal antibodies (trastuzumab and pertuzumab) or targeted therapy (pyrotinib). Neoadjuvant treatment for TNBC consists of chemotherapy or a combination of chemotherapy (paclitaxel, docetaxel, paclitaxel albumin, carboplatin, doxorubicin) or a combination of chemotherapy with monoclonal antibodies (pembrolizumab). For HR+ patients, chemotherapy (paclitaxel, docetaxel, paclitaxel albumin, doxorubicin) is the primary option for neoadjuvant treatment. Since only about 20% of breast cancer cases are HER2+, the remaining 80% of breast cancer patients primarily receive chemotherapy drugs as the main modality for neoadjuvant treatment.
- As 2024.01.22, although there had been no head-to-head comparison of Utidelone with taxane.
- As 2024.01.22, although there had been no head-to-head comparison of Utidelone with non-taxane drugs such as vinorelbine, gemcitabine, and ixabepilone, a study published in the SCI journal BMC Cancer carried out a meta-analysis to compare the efficacy of eribulin with other chemotherapy regimens, including Utidelone in combination with capecitabine.
- Chemotherapy drugs kill tumor cells but also inadvertently damage normal tissues and organs, resulting in various types of toxicities, such as hematological toxicity, gastrointestinal toxicity, hepatorenal toxicity, and peripheral neuropathy. Hematological toxicity often leads to bone marrow suppression, manifesting as neutropenia, leukopenia, and eosinopenia.
- For example, such use can lead to antibiotic resistance, where bacteria evolve to resist the effects of these drugs, making future infections harder to treat. Additionally, antibiotics can disrupt the natural balance of the gut microbiome, leading to digestive issues. They might also cause allergic reactions in some individuals. These side effects underscore the importance of careful antibiotic management in medical treatments.

Appendix for Verification – III

- Chemotherapy is one of the primary means of treating tumors. Although chemotherapy drugs may initially be developed for particular tumors, they are often effective in the treatment of other tumors due to the common characteristics of tumors. In comparison, although targeted therapy and immunotherapy show significant efficacy in treating cancer patients with high expression of particular targets, their applicability is limited to these patients. For example, PD-1 or PD-L1 inhibitors are effective for only 20%–40% of patients with solid tumors, indicating a limited patient response rate.
- The increase in P-glycoprotein expression level in tumor cells can pump out various antitumor drugs, such as anthracycline, vinblastine, taxane, and eribulin.
- The clinical treatment cycle of taxane generally ranges from four to six cycles.
- Brain metastasis is a significant challenge in cancer treatment, as P-glycoprotein in endothelial cells prevents drugs from crossing blood-brain barrier. Additionally, a majority of molecules larger than 500Da and small molecules cannot cross the barrier, making brain metastasis virtually untreatable. Normal dosages of taxane and eribulin are unable to reach effective concentrations in brain tissues, hence they are ineffective in crossing the blood-brain barrier.
- The production process of chemotherapy drugs, such as eribulin and paclitaxel, typically involves either chemical synthesis or semi-chemical synthesis approach. However, the harsh conditions required for chemical reactions often result in the production of various toxic substances, leading to serious environmental pollution. Biosynthesis, which uses bacteria or cells to produce chemotherapy drugs, offers a mild reaction environment, simple and quick steps, and is environmentally friendly. It effectively addresses many of the shortcomings of chemical synthesis. Additionally, the scarcity of yew trees, the primary source of taxane drugs, limits the production of taxane drugs and hindering the overall development of the industry.
- In the current trend of chemotherapy drug, the pursuit of developing oral formulation is a prominent yet challenging endeavor, and the global landscape features only a limited number of approved oral microtubule inhibitors, each exhibiting moderate performance.
- Compared to injections, orally administered microtubule inhibitors exhibit greater convenience and patient adherence, allowing patients to take medication at home and reducing the need for inperson care, thereby optimizing healthcare resources.
- Esophageal cancer is cancer that occurs in the esophagus — a long, hollow tube that runs from your throat to your stomach.
- As a basic chemotherapy drug, microtubule inhibitor has been widely used in clinical practice in injectable formulation. Since the main microtubule inhibitors on the market, such as anthracycline, vinblastine, taxane, and eribulin ~lack the aforementioned characteristics, it is difficult to develop their oral formulations. For instance, taxane has poor water solubility, resulting in low absorption amount. Moreover, as P-glycoprotein substrates, once drug molecules enter the gastrointestinal mucosal cells, they are often effluxed back into the intestinal lumen by P-glycoprotein, resulting in a lower bioavailability of the oral formulation. There have also been attempts in the market to explore the development of oral formulations of microtubule inhibitors. However, due to issues related to bioavailability and safety, these attempts have not made significant progress. As of 2024.01.11, no oral taxane had been approved for marketing in China and the United States.

Appendix for Verification – IV

- Bioavailability reflects the proportion of a drug that enters the human circulatory system, and there is a certain correlation between a drug's bioavailability and its safety. Specifically, the higher the bioavailability of a drug, the fewer the dose required for patients to achieve the same efficacy, which brings fewer toxicity to patients, thereby enhancing the drug's safety profile.
- Currently, most chemotherapy drugs are administered via injection and are associated with severe adverse events. For instance, organic solvents like polyoxyethylene castor oil and surfactants in paclitaxel injection can cause intense allergic reactions, exhibiting poor safety profile.
- The microbial fermentation production level primarily depends on the genetic characteristics and culture conditions of bacterial strains. In most cases, the limited production capacity of genetically engineering bacterial strains is the main reason that hinders their industrialization.
- The fundamental technology behind oral formulations lies in the design of drug formulations based on the physical and chemical properties of the drugs, ensuring that the drugs maintain quality stability throughout their lifecycle.
- The launch of Utidelone marked a significant milestone, ending a nearly twodecade absence of independently developed Class I innovative chemotherapy drugs in China, and is the only non-taxane microtubule inhibitor drug that has achieved dual benefits in both PFS and OS, compared to capecitabine monotherapy.
- Chemotherapy is one of the most important treatments for advanced NSCLC. Chemotherapy in combination with PD-1 has been gradually becoming the preferred option for frontline treatment of advanced gastric and esophageal cancers.
- Chemotherapy drug industry is highly competitive and subject to rapid and significant change.
- Biostar biopharma face potential competition from many others working to develop therapies targeting the same indications. These include major biopharmaceutical companies, specialty pharmaceutical and biotechnology companies, and academic institutions, government agencies and research institutions.
- With advancements in diagnosis and treatment, the overall survival of patients has significantly improved, transforming cancer into a chronic disease. In this context, oral formulations offer greater convenience and compliance than injectable formulations in long-term cancer treatment. This favors their use in adjuvant and maintenance therapies for cancer patients, suggesting a great potential for wide application around the world. However, developing oral formulations poses significant challenges. This is primarily because oral drug molecules must pass through the gastrointestinal epithelial cell layer and overcome various physiological, biochemical, and chemical barriers to be absorbed into the bloodstream and reach the target site.
- Oral microtubule inhibitors approved for marketing included paclitaxel oral liquid, which was only approved in South Korea, and vinorelbine tartrate soft capsule, the only oral microtubule inhibitor approved in China. The bioavailabilities of them were 23% and 33%, respectively, which were relatively low. Besides, the incidence of grade ¾ neutropenia of vinorelbine is about 47.7%, with a relatively poor safety profile. Additionally, Utidelone Capsule is a hard capsule. Compared to oral liquid or soft capsules, its hard form can prevent the drug from irritating esophagus and skin and also protect it from being destroyed by stomach acid.

Appendix for Verification –V

- The technologies developed on the basis of Biostar's three platforms have evolved into Biostar's proprietary technologies, distinguished by their high technical barriers, being unique in the industry.