The information and statistics set out in this section and other sections of this document were extracted from the report prepared by Frost & Sullivan, which was commissioned by us, and from various official government publications and other publicly available publications. We engaged Frost & Sullivan to prepare the Frost & Sullivan Report, an independent industry report, in connection with the [**REDACTED**]. *The information from official government sources has not been independently verified by us, the Sole Sponsor, the* [**REDACTED**], *the* [**REDACTED**], *the* [**REDACTED**], *the* [**REDACTED**], *the* [**REDACTED**], *any of their respective directors and advisers, or any other persons or parties involved in the* [**REDACTED**], *and no representation is given as to its accuracy.*

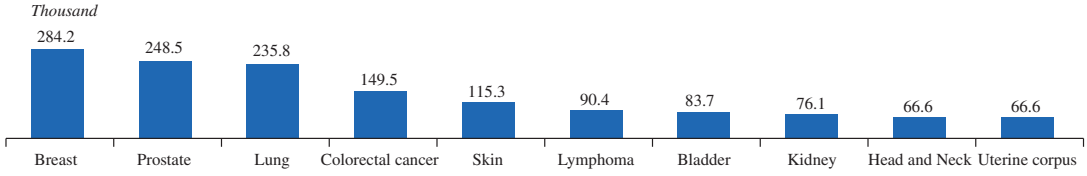
ONCOLOGY DRUG MARKET

Most Common Cancers by Incidence

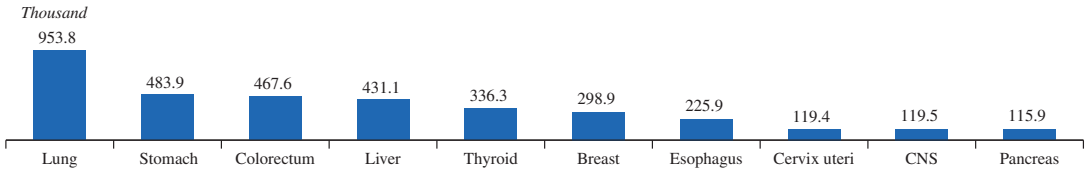
Due to the differences in dietary structure, environment and other factors such as lifestyle, smoking habits, age, and vaccination programs, the most prevalent cancer types in China differ from those of the U.S. In China, lung cancer accounted for the highest incidence in 2021, while breast cancer accounted for the highest in the U.S. The number of gastric cancer and liver cancer patients ranked the second and fourth out of all cancer patients in China in 2021, respectively, whereas their incidence in the U.S. ranked much lower. The cancer types that are prevalent in China but have lower incidence in other more developed markets generally have much more limited treatment options, suggesting significant unmet medical needs and market opportunities to further tap in China.

The following charts show the top 10 cancer types by incidence in the U.S. and China in 2021, respectively:

Top 10 Cancers by Incidence in the U.S., 2021



Top 10 Cancers by Incidence in China, 2021

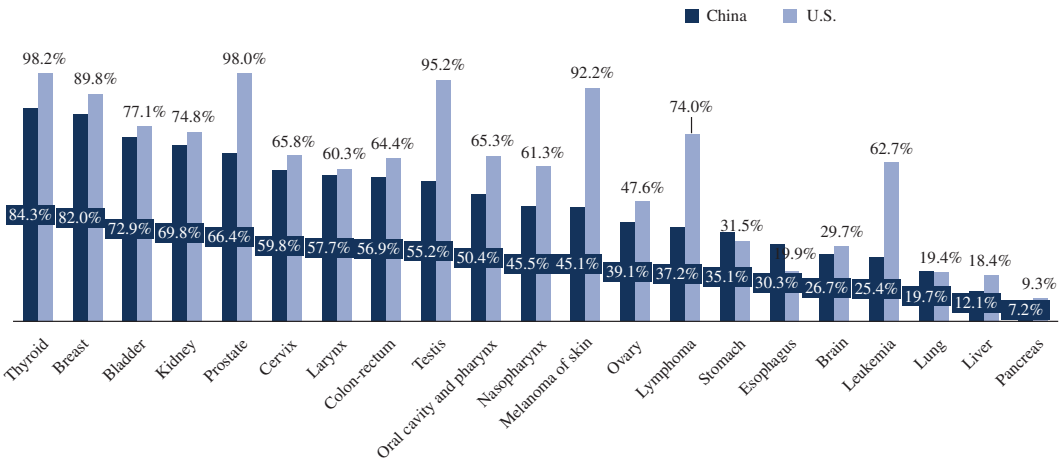


Source: IARC, ACS, NCCR, Globocan, Frost & Sullivan analysis

As illustrated below, China has much lower five-year survival rates on some of the most common cancers than those of in the U.S., which indicates a great market opportunity for cancer treatment in China.

The following chart sets forth the five-year survival rate of cancers in China and the U.S., respectively:

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



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

Cancer Treatment

Research and development on cancer treatment has seen major advancements over the past 20 years and is expected to sustain growth with continued innovation. There are currently several major therapy options to treat a variety of cancers, including surgery, radiotherapy, chemotherapy, targeted therapy, and immuno-oncology therapy according to Frost & Sullivan.

With continued progress in the understanding of cancer biology and advancement of modern biotechnology, it is expected that more cutting-edge technologies will be devised and deployed for oncology drug development in the future, and an increasing number of innovative treatment options are expected to be brought to oncology patients in dire needs. The following diagram illustrates a paradigm shift from conventional cancer treatments to novel cancer treatments:

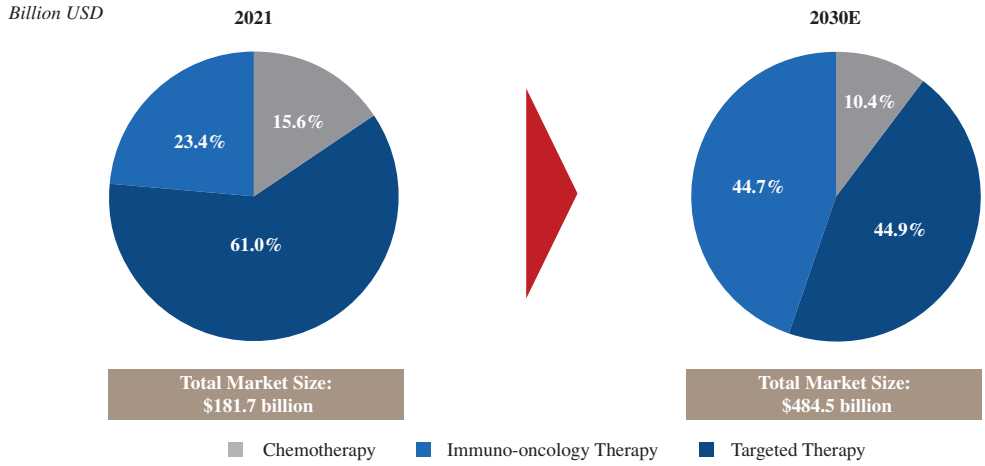
	Conventional Cancer Treatments			Novel Cancer Treatments	
	Surgery	Radiotherapy	Chemotherapy	Targeted Therapy	Immuno-oncology
Description	A procedure in which a surgeon removes cancer from a patient's body	High doses of radiation to kill cancer cells and shrink tumors	Use single or combinations of anti-cancer drugs to stop or slow tumor growth	Act on specific targets that are associated with cancer development	Harness the patient's own immune system to fight cancer
Features	Foundation of solid tumor treatment. More effective for early stage, while relatively limited for most late stage	Affects surrounding normal cells causing side effects such as fatigue, hair loss	Targets all fast growing cells, causing side effects such as hair loss, easy bruising/bleeding	Includes both small-molecule drugs and mAbs, less harmful to healthy cells	Includes cytokines, mAbs, checkpoint inhibitors, immune cell therapies
Examples	Liver resection	3D-CRT, IMRT, SBRT	Taxanes, fluorouracil, chlorambucil	AKT inhibitor	PD-1 inhibitor, CAR-T cell therapy

Source: Literature research, Frost & Sullivan analysis

Targeted and Immuno-Oncology Therapies

Compared with conventional cancer treatments, targeted therapy and immune-oncology therapy are expected to further propel the growth of the global oncology drug markets. Immuno-oncology therapy is designed to stimulate the patient's own immune system to generate or augment an anti-tumor immune response in order to control or eradicate cancer cells. Major types of immuno-oncology therapies include checkpoint inhibitors, cytokines and cellular immunotherapies. Targeted therapy accounted for the largest share of the global oncology drug market in 2021, representing 61% of the total market share based on revenue. The market size of each type of therapy is expected to grow in absolute amounts from 2021 to 2030, and targeted and immuno-oncology therapies together are expected to account for approximately 90% of the global oncology drug market by 2030, according to Frost & Sullivan.

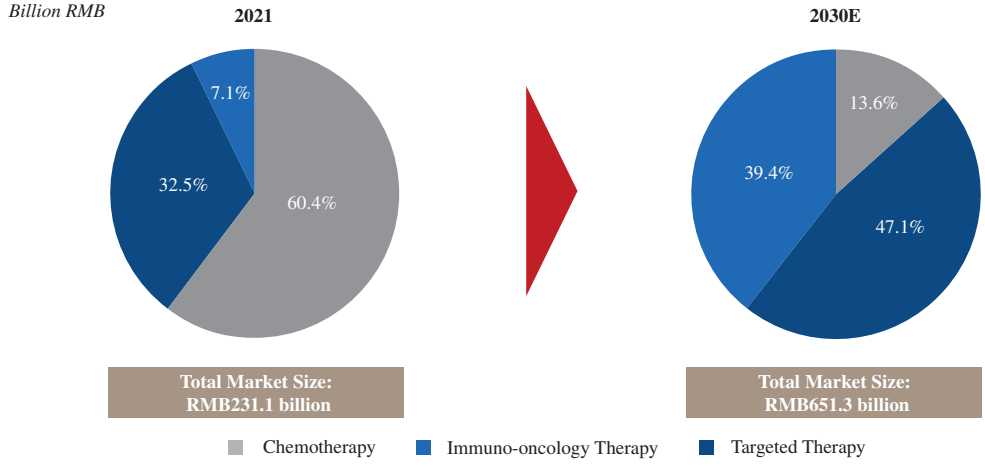
Breakdown of the Global Oncology Drug Market by Therapy, 2021 and 2030E



Source: Annual Reports of Listed Medical Companies, NMPA, CDE, NRDL, MOHRSS, FDA, IARC, GLOBOCAN, Frost & Sullivan analysis

The following charts set forth the actual and expected total market sizes for chemotherapy, immuno-oncology therapy and targeted therapy in China's oncology drug market during the years indicated, showing a much more considerable growth in China's novel oncology drug market as compared to the global market:

Breakdown of the Oncology Drug Market by Therapy in China, 2021 and 2030E



Source: Annual Reports of Listed Medical Companies, NMPA, CDE, NRDL, MOHRSS, NCCR, Frost & Sullivan analysis

Increasing Trend of Combination Therapies

The emergence of combination therapies, a treatment modality that combines two or more therapeutic agents, represents an increasing trend in the treatment of oncology. As a result of targeting multiple key pathways in a synergistic or additive manner, the adoption of oncology drugs in combination therapies could have the potential to improve efficacy, treatment response rate and durability as compared to monotherapies.

Both pre-clinical and clinical studies in therapeutic combination have exhibited better efficacy, which in turn leads to more combination trials and the potential to penetrate the untapped market. Studies also show that the combination therapies of multiple small-molecule targeted oncology therapies significantly improve the overall survival rate of patients. Specifically, although the modalities of targeted therapy and immuno-oncology therapy differ in nature, in many cases, the combination of these therapies has generated synergic effects, typically with one therapeutic agent complementing the other, unleashing the anti-tumor immunity of patients and thereby leading to enhanced efficacy. Such combinations have been improved to result in better outcomes in clinical practice, demonstrating a promising strategy of cancer treatment.

SMALL-MOLECULE TARGETED ONCOLOGY THERAPY

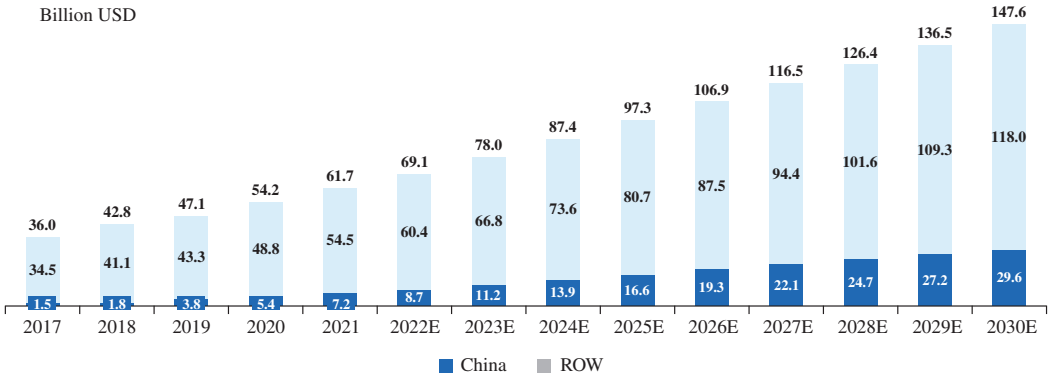
Overview

Targeted oncology drug therapies can be roughly classified into two categories: small molecules and biologics (e.g. antibodies, recombinant proteins). Compared with biologics, small-molecule drugs have advantages in aspects such as the pharmacokinetic (PK) properties, manufacturing costs, patient compliance, drug storage and transportation.

The following chart shows the historical market size breakdown of global and China small-molecule targeted oncology therapy market from 2017 to 2021, and the estimated market size in these markets from 2022 to 2030, as well as CAGRs during the periods indicated:

Global Small-Molecule Targeted Oncology Drug Therapy Market, 2017-2030E

CAGR	ROW	China	Global
2016-2021	12.1%	49.3%	14.4%
2021-2025E	10.3%	23.1%	12.0%
2025E-2030E	7.9%	12.3%	8.7%



Note: ROW refers to rest of the world excluding China

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

Growth Drivers and Future Trends

The key growth drivers of the global and China small-molecule targeted oncology therapy market include the following:

- Safety and patient compliance. Safety is one of the major causes of failure of small molecule drug development at early clinical stage. Besides, some of the marketed drugs need specific administration regimen to limit the potential sides effects. For instance, despite its significant role in prostate cancer treatment, abiraterone needs to be co-administered with prednisone, and has specific risks of hypertension, fluid retention and hypokalemia. LAE001 may eliminate the need for long-term prednisone use under abiraterone acetate regimens for mHSPC as a first-line treatment, thereby reducing the risk of the related potential cardiovascular toxicity and hepatotoxicity. Drugs with improved safety profile and fewer side effects would have better patient compliance and often represents growth opportunities once marketed.

- Advancement of biology and translational science. With the development of molecular biology, proteomics, and translational science, more drug targets and mechanism of actions are unveiled. Small molecule drugs, which can penetrate cell membrane and cell sub-compartments, are able to access a much larger number of drug targets. The discovery of new target and protein structure would provide more information regarding drug interactions, thus leading to more efficient identification of lead compounds. With the development of small-molecule discovery technology, for instance, bioinformatics data mining, it is expected that the discovery process would become more efficient and make more candidates to enter the development timeline, thus driving the market growth.

- Combination therapies. The emergence of combination therapies represents an increasing trend in cancer treatment. Small-molecule drugs offer complementary mechanisms to potentially combine with other small-molecule drugs and biologics, to enhance efficacy profile and expand clinical adoptions. As a result of targeting multiple key pathways in a synergistic or additive manner, the adoption of oncology drugs in combination therapies could have the potential to improve efficacy, treatment response rate and durability as compared to monotherapies, and have the potential to penetrate untapped markets. Studies also show that the combination of multiple small-molecule targeted oncology therapies significantly improve the overall survival rate of patients, which also increases the patient pool. For example, studies have shown that combinatory use of new generation anti-androgen agents tend to provide better survival benefit to mHSPC patients compared with using single anti-androgen agent for treatment. Additionally, an increasing number of biotech companies are exploring the combination potentials of their drug candidates, which would further enrich the treatment options for patients. This also includes LAE002 and other drug candidates which are being developed in a variety of combination therapies. The increasing availability of combination therapies will further enrich the varieties of combinations and expand the oncology drug market globally.

Barriers to Research and Development

The entry barriers of global and China small-molecule targeted oncology therapy market include the following:

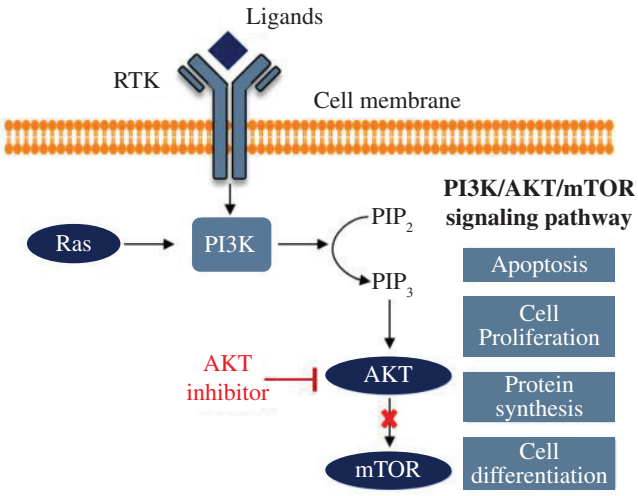
- Target selection capability. The selection of targets requires a detailed understanding of molecular mechanisms and strong research capability, which represents a technical barrier for small-molecule targeted oncology therapy.

- Clinical development capability. Antitumor drugs have different requirements compared to non-oncology drugs in terms of clinical trial design, selection of clinical endpoints, patient enrollment criteria, patient recruitment process, and patient follow-up. The adverse events also need to be carefully monitored and resolved. Therefore, a clinical trial team with professional strength and rich experience is required, representing another entry barrier to the small-molecule targeted oncology therapy market.

AKT INHIBITORS

Overview

The serine/threonine kinase AKT is a key component of the PI3K intracellular pathway that plays a pivotal role in regulating cell proliferation, survival, and metabolism. Three AKT isoforms (namely AKT1, AKT2, and AKT3) are encoded by different genes with high sequence homology and display a conserved protein structure. While AKT1 and AKT2 present a ubiquitous distribution, AKT3 is prevalently expressed in neural cells. Enhanced activation of all the isoforms can be related to tumor growth and progression in certain types of cancer, including in breast, ovarian, pancreatic, and prostate cancers. In cancer cells, AKT1 is involved in proliferation and growth, promoting tumor initiation and suppressing apoptosis, whereas AKT2 regulates cytoskeleton dynamics, favoring tumor invasiveness and metastasis. The role of AKT3 hyperactivation in cancer is still controversial, although a possible stimulation of cell proliferation has been hypothesized. Activation of AKT can be inhibited by two different direct classes (allosteric or ATP-competitive) of AKT inhibitors. The allosteric AKT inhibitors lock AKT in an auto-inhibited conformation and interfere with PH-domain mediated-membrane recruitment, thus preventing AKT kinase activation and AKT phosphorylation. The ATP-competitive AKT inhibitor attenuates AKT activity by preventing ATP from binding to kinases.



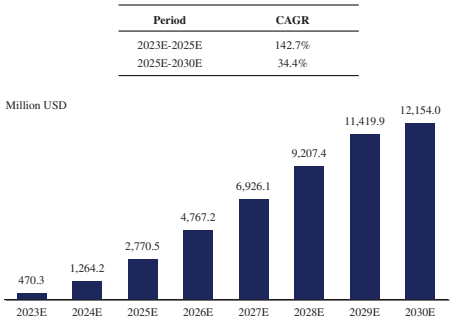
Notes: RTK receptor protein tyrosine kinase; mTOR: mammalian target of rapamycin; PIP_2: phosphatidylinositol(4,5) bisphosphate; PIP_3: phosphatidylinositol-3,4,5-triphosphate

Source: Frost & Sullivan analysis

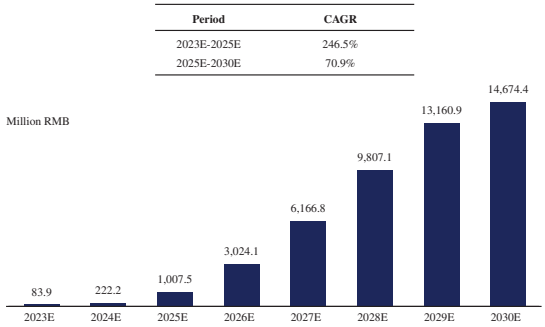
Market Size

The following chart shows the forecasted market size of the global and China AKT inhibitor drug market from 2023 to 2030, as well as CAGRs for the periods indicated:

Forecasted Global AKT Targeting Drug Market Size, 2023E-2030E



Forecasted China AKT Targeting Drug Market Size, 2023E-2030E



Source: Expert interview, Frost & Sullivan analysis

Notes: It is expected that the market size of AKT inhibitors will see significant growth as:

(i) AKT inhibitors are expanding their indications for more solid tumors such as TNBC, mCRPC and PROC, which will further contribute to the growth of the AKT inhibitor drug market. The incidences of those indications are expected to experience significant growth in the next decade. The AKT inhibitor drug market is expected to expand significantly in correspondence to the growth of the market of AKT inhibitors' key indications;

(ii) Currently, there are a number of companies developing AKT inhibitors. A number of AKT inhibitors are expected to be approved and commercialized in China in the next decade with additional indications. Multiple candidates are being developed for different indications, and the indications for future commercial approval will be diversified, thus contributing to market expansion and growth. Multiple competitors will conduct various clinical trials, and the evidence-based data out of such trials will further facilitate academic development, which in turn will lay the foundation for future market growth; and

(iii) AKT inhibitors may be included in NRDL. NRDL inclusion and marketing promotion by companies for AKT inhibitors will further contribute to the growth of AKT inhibitors.

AKT Overexpression in Various Tumor Types

AKT activation has been shown to correlate with advanced disease and/or poor prognosis in some tumor types. For example, one study examining the role of AKT kinase signaling networks in cancers reported that approximately 40% of breast and ovarian cancers and more than 50% of prostate carcinomas exhibited increased AKT1 kinase activity; and nearly 80% of tumors with activated AKT1 were high grade and stage III/IV carcinomas (Song M. et al., AKT as a Therapeutic Target for Cancer. Cancer Res. 2019; 79(6):1019-1031). Among other studies, activation of the AKT2 kinase was observed in around 40% of ovarian cancers. Moreover, elevated AKT3 activity has been reported in estrogen receptor-deficient breast cancer and androgen-insensitive prostate cancer cell lines, suggesting that AKT3 may contribute to the aggressiveness of steroid hormone-insensitive carcinomas.

AKT Phosphorylation in Inducing Drug Resistance

AKT is one of the most commonly dysregulated pathways in all of the cancers. Dysregulation of AKT-dependent pathways is associated with the development and maintenance of a range of solid tumors. AKT/NF-κB and AKT/mTOR are the two main mutated pathways, where mutations lead to inhibition of apoptosis, stimulation of cell growth, and modulation of cellular metabolism such as overexpression of drug efflux pumps. These mechanisms are related to the development of drug resistance in cancer treatment. Therefore, targeting AKT represents a potential strategy to overcome drug resistance.

Studies have shown that the phosphorylated AKT (pAKT) level is correlated with higher rates of chemo-resistance. For instance, cisplatin-resistant ovarian cancer cell line exhibited higher AKT expression levels than its cisplatin sensitive isotype. The cell lines expressing higher levels of pAKT were more resistant to paclitaxel. AKT inhibition has been shown to overcome oncology drug resistance in a number of pre-clinical scenarios. For example, AKT inhibition can increase chemo-sensitivity in TNBC in pre-clinical settings, eventually overcoming chemo-resistance in this disease subset.

AKT Combination Therapies

Cancer cells may become resistant to previously effective treatments, including chemotherapy and targeted therapy. Drug resistance is one of the major/primary causes of cancer recurrence and death in many cancer patients and has become a major factor limiting their survival and quality of life. For patients with cancer that has progressed to an advanced stage, treatment options may become limited with poor outcome. Thus, there is a significant unmet need for therapies to overcome drug resistance.

Solid tumors are heterogeneous neoplasms composed of different types of cancer cells, with heterogeneousness in their molecular signatures; this is referred to as intra-tumor heterogeneity. There is a strong pre-clinical rationale for the combination therapies of AKT inhibitors with other molecules to treat the drug-resistant cancer, including acquired resistance to other anticancer agents and adaptive resistance to chemotherapy and targeted therapy. AKT activation is reported to correlate with drug resistance.

AKT combination therapies have demonstrated clinical benefits. For instance, for the treatment of metastatic castration-resistant prostate cancer (mCRPC), a Phase II trial sponsored by AstraZeneca demonstrated significantly longer median overall survival (31.2 months in treatment group vs. 20.3 months in the placebo group) in the AKT inhibitor combined with chemotherapy treatment group compared to chemotherapy control group. In a Phase II randomized controlled trial, combination therapy of an AKT inhibitor capivasertib with fulvestrant significantly prolonged progression-free survival in patients with aromatase inhibitor-resistant HR+/HER2- locally advanced or metastatic breast cancer (10.3 months in capivasertib group vs. 4.8 months in the placebo group). AKT inhibitors are also being evaluated in combination with fulvestrant in multiple targeted therapies, including PD-1/PD-L1, CDK4/6, poly (ADP-ribose) polymerase (PARP) inhibitors, anti-hormone and other therapies.

Competitive Landscape

Currently, there is no AKT inhibitor approved for global commercialization, according to Frost & Sullivan. There are seven AKT inhibitor candidates under clinical development for the treatment of cancer globally.

Pipeline Globally

INN/Drug Code	Company	Phase*	First Post Date**	Indication***
Capivasertib	AstraZeneca	III	2019/6/25	Prostate Cancer (III, HSPC), locally advanced or metastatic breast cancer (III), triple negative breast neoplasms (III), Non-Hodgkin Lymphoma (II), endometrial cancer (II), meningioma (II)
LAE002 (Afuresertib)	**Laekna**	**II (Registrational)**	**2020/5/5**	**PROC (II), mCRPC(II), Locally advanced or metastatic HR+/HER2-breast cancer (Ib/III), PD-1/PD-L1 inhibitor resistant solid tumor (I/II)**
Ipatasertib	Roche	II	2020/07/13	NSCLC (II), gastric cancer (II), ovarian cancer (II, R/R epithelial OC), glioblastoma multiforme (I/II), endometrial cancer (I/II)
TAS-117	Taiho Oncology	II	2021/2/25	Advanced or metastatic solid tumors (excluding primary brain tumors) harboring germline PTEN inactivating mutations
M2698	EMD Serono	I	2013/10/29	Solid tumors
TAS0612	Taiho Oncology	I	2020/10/14	Advanced or metastatic solid tumors
WGI-0301	HaichangBiotech	I	2022/3/07	Advanced Solid Tumors

Notes:

* Phase refers to the drug's most advanced phase stage of all ongoing studies.

** First posted date denotes the date when the most advanced clinical stage of a clinical trial for an indication is first publicly announced. Information as of April 30, 2023.

*** The chart shows cancer indications only.

Source: ClinicalTrials.gov, Frost & Sullivan analysis

Currently, there are three AKT inhibitor candidates under clinical development in China, according to Frost & Sullivan.

Pipeline in China

INN/Drug Code	Company	Phase*	First Post Date**	Indication***
Capivasertib	AstraZeneca	III	2020/10/9	Metastatic HSPC (III), Metastatic CRPC (III), TNBC (III), HR+/HER2-Locally Advanced or Metastatic Breast Cancer (III)
LAE002 (Afuresertib)	**Laekna**	**II (Registrational)**	**2020/11/19**	**PROC (including fallopian tube carcinoma and primary peritoneal carcinoma) (II), TNBC (I/II), HR+/HER2-Locally Advanced or Metastatic Breast Cancer (Ib/III), PD-1/P1-L1 resistant solid tumor (I/II)**
NTQ1062	Chia Tai Tianqing	I	2021-08-18	Advanced solid tumor

Notes:

* Phase refers to the drug's most advanced phase of all ongoing clinical trials.

** First posted date denotes the date when the most advanced clinical stage of a clinical trial for an indication is first publicly announced. Information as of April 30, 2023.

*** The chart shows cancer indications only.

Source: CDE, Frost & Sullivan analysis

Therapeutic Areas of Interest

Ovarian Cancer

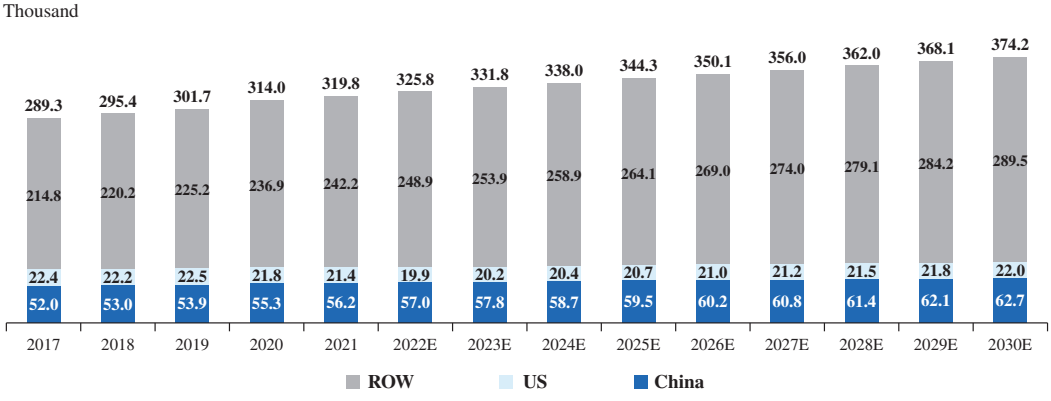
Ovarian cancer is a group of diseases that originates in the ovaries, or in the related areas of the fallopian tubes and the peritoneum. In the early stages, there may be few or even no symptoms. If symptoms occur, they can resemble those of other conditions, such as premenstrual syndrome, irritable bowel syndrome, or a temporary bladder problem. However, in ovarian cancer, the symptoms will persist and worsen.

Ovarian cancer risk factors include age, nulliparity or first pregnancy after age of 35 years old, postmenopausal hormone therapy, and pelvic inflammatory disease. There is an association with women who develop early-onset ovarian cancer (about 15% of ovarian cancer patients) with family history of ovarian cancer and BRCA1/2 mutations, and with Lynch syndrome. About 70% of ovarian cancer patients present with advanced disease. No regular screenings are available.

The following chart shows the historical incidence breakdown of global ovarian cancer from 2017 to 2021, and the estimated incidence from 2022 to 2030, as well as CAGRs during the periods indicated:

Incidence Breakdown of Global Ovarian Cancer, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	3.1%	-1.2%	1.9%	2.5%
2021-2025E	2.2%	-0.8%	1.5%	1.9%
2025E-2030E	1.9%	1.2%	1.0%	1.7%



Note: ROW refers to rest of the world excluding China and US

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

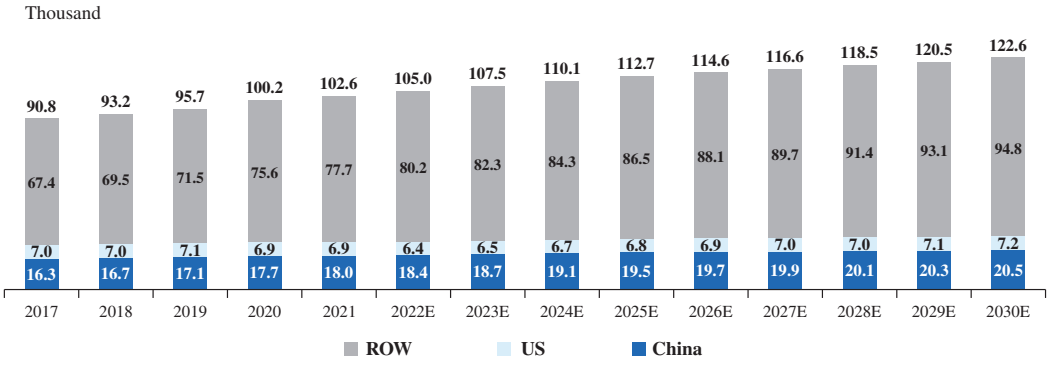
Platinum Resistant Ovarian Cancer (PROC)

PROC is broadly defined as primary ovarian cancer recurrence within six months of completing platinum-based chemotherapy, either in the primary or recurrent setting. Although there is significant heterogeneity, PROC is generally associated with poor outcomes and low response rates to standard chemotherapy.

The following chart shows the historical incidence breakdown of global PROC from 2017 to 2021, and the estimated incidence from 2022 to 2030, as well as CAGRs during the periods indicated:

Incidence Breakdown of Global PROC, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	3.6%	-0.6%	2.5%	3.1%
2021-2025E	2.7%	-0.3%	2.0%	2.4%
2025E-2030E	1.9%	1.2%	1.0%	1.7%



Note: ROW refers to rest of the world excluding China and US

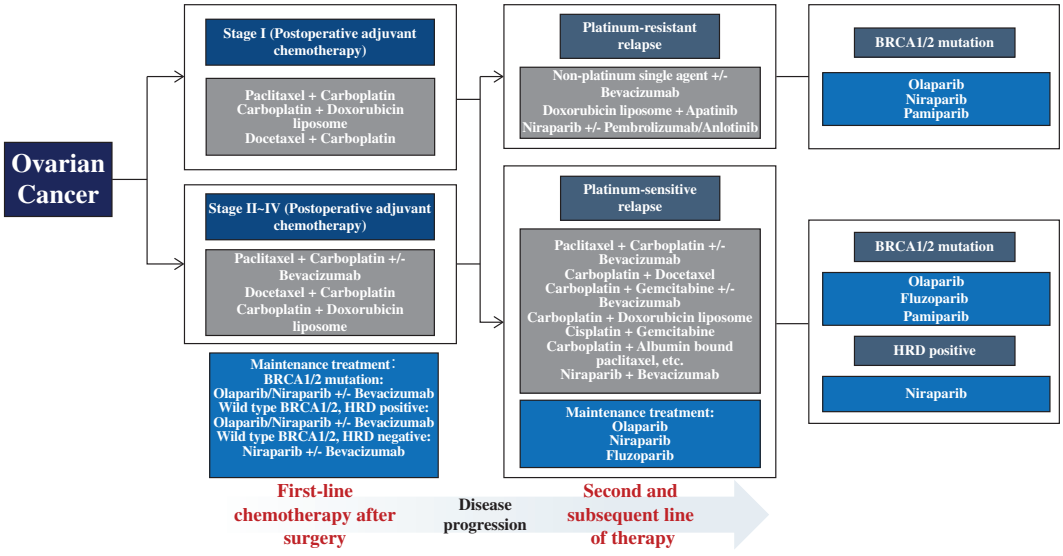
Source: Globocan, IARC, NCCR, Frost & Sullivan analysis

Treatment Paradigm and Unmet Medical Needs

The current standard of care (SOC) of ovarian cancer in China mainly consists of debulking surgery and platinum-based chemotherapy (cisplatin, carboplatin or oxaliplatin) with or without bevacizumab or PARP inhibitor. The American National Comprehensive Cancer Network Guideline ("**NCCN Guideline**") recommends platinum-based chemotherapy with or without bevacizumab as a first-line treatment for a recurrence of platinum-sensitive ovarian cancer. Compared with cisplatin and oxaliplatin, carboplatin exhibits a lower hydration rate and has higher biosafety with reduced systemic toxicity. Thus, carboplatin chemotherapy is recommended as a preferred regimen for the treatment of ovarian cancer in the NCCN Guideline, and other platinum-based chemotherapies are recommended as alternative options in the first-line treatment. PARP inhibitor is also recommended for patients with platinum-sensitive ovarian cancer. Once the ovarian cancer becomes platinum-resistant, only limited, less-effective options, such as the sequential use of single-agent nonplatinum cytotoxic therapy, are available. Immunotherapies and targeted therapies, including bevacizumab and PARP inhibitors, are also only useful in certain subtypes of ovarian cancer patients. Although platinum-based chemotherapy with or without bevacizumab or PARP inhibitor as an initial treatment is effective, ovarian cancer in more than 80% of the patients will recur, and the patients will eventually become resistant to platinum-based therapy (Pignata S. et al., Treatment of Recurrent Ovarian Cancer, Annals of Oncology, 2017, Volume 28, Supplement 8, viii51-viii56; Garzon S. et al., Secondary and Tertiary Ovarian Cancer Recurrence: What is the Best Management? Gland Surgery, 2020, 9(4): 1118–V1129; Keener A., Innovative Therapies

to Tackle Platinum-Resistant Ovarian Cancer, Nature, 2021, 600, S45-S47). The high recurrence rate of more than 80% are mainly because the high likelihood of patients developing drug resistance to chemotherapy and the accompanying targeted drugs which would lead to treatment failure. Such high probability of developing drug resistance is contributed by a number of factors, including but not limited to the fact that continued drug treatment may lead to (i) increased drug excretion through renal or hepatic metabolism before they are able to reach cancer cells, (ii) activation or increase of the cell-membrane transport proteins which could export drug molecules from cancer cells before they take effect and (iii) activation or enhancement of DNA damage repair mechanism which would prevent cancer cell apoptosis that drug treatment is designed to achieve. The five-year survival rate of ovarian cancer is less than 40%. However, PROC has a poor prognosis compared to PSOC that its overall survival is only 12-14 months under the current SOC. There are limited treatment options, such as non-platinum-based chemotherapy, for relapsed ovarian cancer patients. Moreover, the interval between recurrences decreases and the rate of tumor relapse jumps with the increase in the number of recurrences.

The below table sets forth maintenance and treatment options for ovarian cancer under the clinical guidelines in China:



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

NCCN Guideline with respect to the standard of care and treatment guidelines for ovarian cancer in the U.S. is largely consistent with the standard of care and treatment guidelines recognized in China described above. However, the current PROC treatment paradigm is facing challenges.

As the first-line treatment for ovarian cancer after surgery, platinum-based chemotherapy in combination with paclitaxel, has been successful in initially shrinking and killing the remaining tumors left in most patients. However, it is observed that about 10-15% of patients do not respond to platinum-based chemotherapy. In addition, more than 80% of tumors that have initially responded relapse and eventually develop resistance to platinum-based therapy. The cause of platinum resistance is not fully clear given that there can be many mechanisms by which tumor cells acquire platinum resistance, including enhanced DNA repair, improved cell survival, increased drug efflux processes, or production of proteins that protect the genome from the effects of platinum, and cancer cells may develop as a result of any combination of these mechanisms.

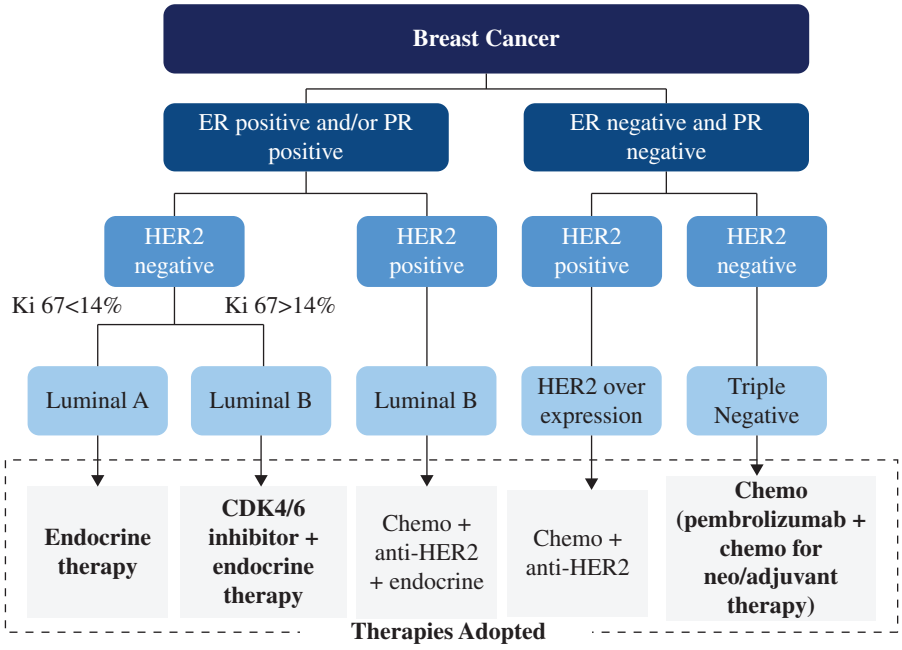
In the U.S. and China, a combination of non-platinum monotherapy and bevacizumab (a vascular endothelial growth factor inhibitor) is recommended as the first and second lines of therapy for patients with PROC according to guidelines. However, 66% to 84% of treated patients may develop primary resistance and almost all patients who initially responded may develop acquired resistance to bevacizumab. In addition, PARP inhibitors are recommended for patients with BRCA1/2 mutations. However, studies have shown that ovarian cancer patients carrying BRCA mutations represent less than 30% of the ovarian cancer patients. While the time interval of recurrence becomes shorter after each relapse, effective treatment options for subsequent lines of treatments are limited. Those with BRCA1/2 mutations have a high probability of failing PARP inhibitors of about 70%. The rest of the 70% patients without BRCA mutations and the 30% ovarian cancer patients with BRAC mutations who failed PARP inhibitor treatment have limited treatment options, such as non-platinum-based chemotherapies, and usually have poor outcome. In 2022, three approved PARP inhibitors, including niraparib, olaparib and rucaparib (not approved in China yet), voluntarily withdrawn their FDA's approvals for late-line ovarian cancer treatment because of safety concerns. The FDA also restricted the use of niraparib to the second-line maintenance treatment for BRCA mutation cancer patients. Because of PARP inhibitors' safety issues and limited clinical benefits there exists great unmet medical needs for late line ovarian cancer treatment.

Breast Cancer

Overview

Breast cancer was one of the most common types of cancer in women globally in 2021 and occurs most frequently in women aged 50 and over. Factors that may increase the risk of developing breast cancer include: genetic predisposition (BRCA1 or BRCA2 mutations), estrogen and progesterone exposure, oral contraceptives or birth control drugs, atypical hyperplasia of the breast, lobular carcinoma *in situ*, lifestyle factors (such as weight, food, alcohol or physical activity), breast density (dense breast tissue) and family history of breast cancer.

Breast cancer can be classified into four genotypes based on the expression level of hormone receptor (HR) and epidermal growth factor receptor-2 (HER2), and HR includes estrogen receptor (ER) and progesterone receptor (PR). The below table sets forth the genotypes of the breast cancer and the therapy adopted:

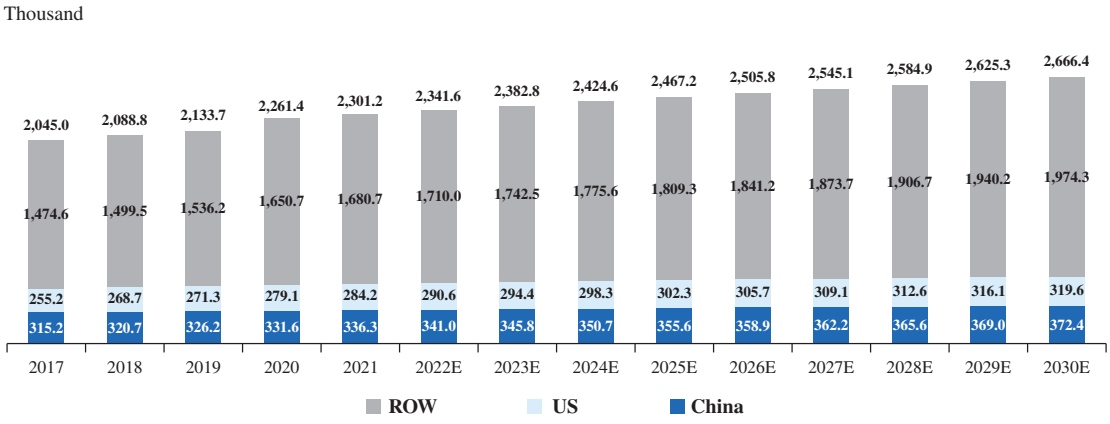


Source: NCCN Breast Cancer Guideline (2021 V8), Frost & Sullivan analysis

The following chart shows the historical incidence breakdown of the breast cancer from 2017 to 2021, and the estimated incidence from 2022 to 2030, as well as CAGRs during the periods indicated. The incidence of TNBC, HR+/HER2- breast cancer, HR+/HER2+ breast cancer and HR-/HER2+ breast cancer account for 15%, 60%, 10% and 15% of breast cancers in China, respectively.

Incidence Breakdown of Global Breast Cancer, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	3.3%	2.7%	1.6%	3.0%
2021-2025E	1.9%	1.6%	1.4%	1.8%
2025E-2030E	1.8%	1.1%	0.9%	1.6%



Note: ROW refers to rest of the world excluding China and US

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

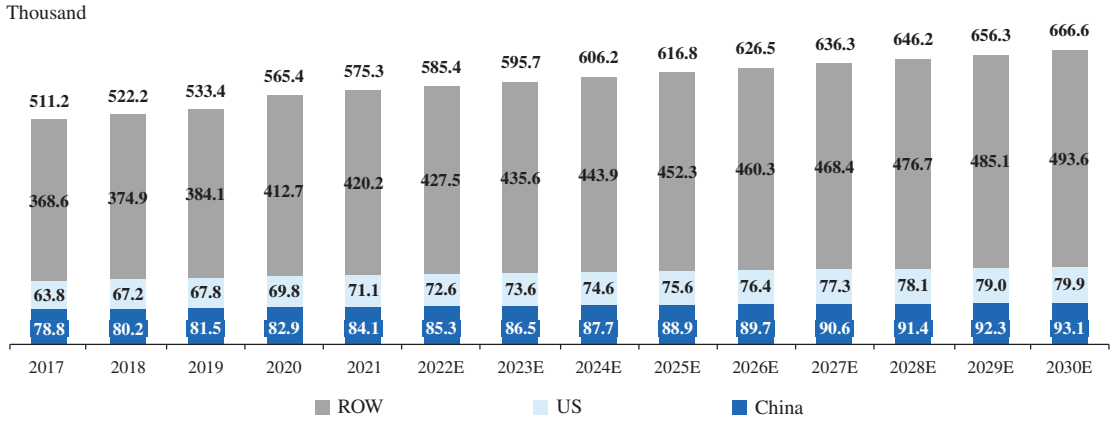
HR+/HER2- Metastatic Breast Cancer (HR+/HER2- mBC)

The status of the HR and HER2 in a breast cancer defines the four most common types of breast cancer. HR and HER2 can be either present, or positive (HR+, HER2+), or absent, or negative (HR-, HER2-), in the tumor. HR+/HER2- is the most common subtype among the four.

The following chart shows the historical incidence breakdown of global HR+/HER2- mBC from 2017 to 2021, and the estimated incidence from 2022 to 2030, as well as CAGRs during the periods indicated:

Incidence Breakdown of Global HR+/HER2- mBC, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	3.3%	2.7%	1.6%	3.0%
2021-2025E	1.9%	1.6%	1.4%	1.8%
2025E-2030E	1.8%	1.1%	0.9%	1.6%



Note: ROW refers to rest of the world excluding China and US

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

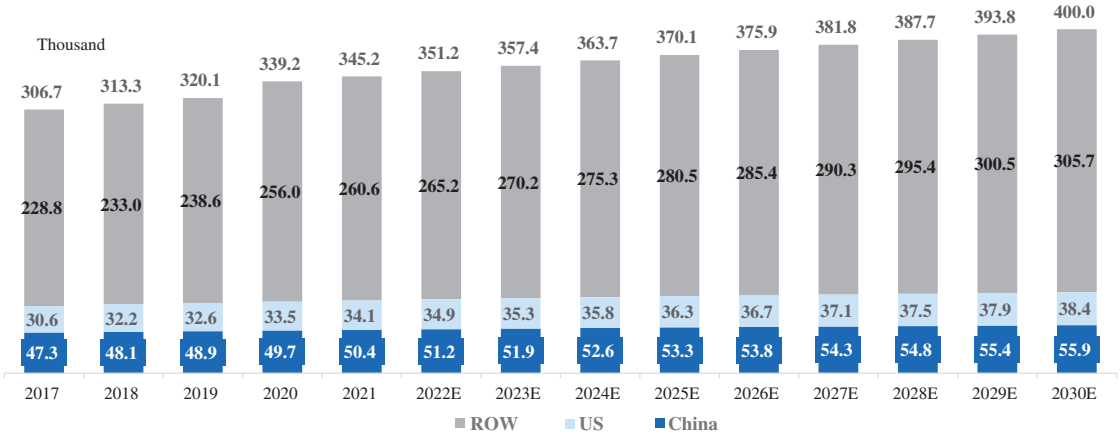
Triple Negative Breast Cancer (TNBC)

TNBC is a type of breast cancer that does not have any of the receptors that are commonly identified in breast cancer, including ER, PR, and HER2. TNBC is characterized by a shorter overall survival rate and an early peak in distant recurrences three years after diagnosis. In 2020, TNBC accounted for approximately 15% and 15% of the total breast cancer population globally and in China, respectively.

The following chart shows the historical incidence breakdown of global TNBC from 2017 to 2021, and the estimated incidence from 2022 to 2030, as well as CAGRs during the periods indicated:

Incidence Breakdown of Global TNBC, 2017-2030E

CAGR	ROW	US	China	Global
2017 -2021	3.3%	2.7%	1.6%	3.0%
2021 -2025E	1.9%	1.6%	1.4%	1.8%
2025E -2030E	1.7%	1.1%	0.9%	1.6%



Note: ROW refers to rest of the world excluding China and US

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

Treatment Paradigm and Unmet Medical Needs

In the U.S., according to the NCCN Guideline on HR+/HER2- breast cancer, the anti-cancer therapy of resectable breast cancer is surgery plus systemic therapies as listed in the following table. Once the disease progresses, the locally advanced or metastatic breast cancer will be treated by multiple endocrine therapy, CDK4/6 inhibitors and targeted therapy as listed in the following table. NCCN Guideline recommends sacituzumab govitecan-hziy (an antibody-drug conjugate composed of an antibody targeting the human trophoblast cell surface antigen 2 coupled to SN-38, a topoisomerase I inhibitor) after patients failed the prior line of therapy of chemotherapy plus pembrolizumab (an anti-PD-1 antibody), in a systemic treatment of recurrent or stage IV TNBC.

The below table sets forth the treatment paradigm of HR+/HER2- mBC and TNBC in the U.S.:

Indication	Treatment			
ER^+ and/or PR^+; $HER2^-$	Visceral crisis	• Initial systemic therapy (*Chemotherapy*[1])		
	No visceral crisis	Prior endocrine therapy within 1y	Premenopausal	• Ovarian ablation or suppression + Systemic therapy[2] • Continue Endocrine therapy
			Postmenopausal	• Systemic therapy[2] • Continue Endocrine therapy
		No prior endocrine therapy within 1y	Premenopausal	• Ovarian ablation or suppression + Systemic therapy • Selective ER modulators[4] • Continue Endocrine therapy
			Postmenopausal	• Systemic therapy[2] • Continue Endocrine therapy
ER^- and PR^-, $HER2^-$ (Triple Negative)	• Chemotherapy[1] + PD-1 (pembrolizumab) as neo/adjuvant therapy • Chemotherapy + pembrolizumab/sacituzumab govitecan for advanced TNBC • PARP inhibitors for BRCA mutation TNBC			

Notes:

1. Chemotherapy (Preferred Regimens + Other Recommended Regimens) = Anthracyclines, taxanes, anthracyclines, anti-metabolites, microtubule inhibitors, platinum, cyclophosphamide, docetaxel, albumin-bound paclitaxel, epirubicin, ixabepilone;

2. Systemic therapy (Preferred Regimens - First-Line) = Aromatase inhibitor + CDK4/6 inhibitor, Selective ER down-regulator ± non-steroidal aromatase inhibitor, Fulvestrant + CDK4/6 inhibitor, Non-steroidal aromatase inhibitor, Selective estrogen receptors modulator, Steroidal aromatase inactivator.

Source: NCCN 2020, Frost & Sullivan analysis

According to Chinese Society of Clinical Oncology Guideline ("**CSCO Guideline**"), the below table sets forth the treatment paradigm of HR+/HER2- mBC and TNBC in China:

Indication	Treatment		
$HER2^-$	After First Line Treatment Systemic therapies	Sensitive to taxane therapy	• Paclitaxel-albumin/ docetaxel/paclitaxel • TP • Paclitaxel-albumin+ PD-1 inhibitor • Paclitaxel Liposome • TX • X • T+Bevacizumab • Olaparib • GT • N • LD • Chemo+ PD-1 inhibitor • G • Etoposide
		After the treatment failure of taxane	• Alibrin/X/N/G • Sacituzumab govitecan-hziy/Paclitaxel-albumin/Etoposide • LD • NP • Bevacizumab +X • Paclitaxel Liposome • GP • Paclitaxel-albumin + Chemotherapeutic drug • Olaparib • NX • Chemo+ PD-1 inhibitor • UTD1+X
ER^+ and/or PR^+	Without prior endocrine therapy		• AI+Abemaciclib/Palbociclib • F • TAM • AI • F+CDK4/6 inhibitor
	After the treatment failure of TAM		• AI+Abemaciclib/Palbociclib /Chidamide • AI • F+CDK4/6 inhibitor • F
	After the treatment failure of NSAI		• F+Abemaciclib/Palbociclib/ Dalpicilib • SAI+Chidamide/CDK4/6 inhibitor/F/Everolimus • F/SAI • Progestogen • TAM/toremifene
	After the treatment failure of SAI		• F+Abemaciclib/Dalpicilib/ Palbociclib • F/NSAI • TAM/toremifene • NSAI+CDK4/6 inhibitor • Progestogen
	After the treatment failure of CDK4/6 i		• Chidamide+Endocrine therapy • Toremifene • Progestogen • Another CDK4/6 inhibitor+ Endocrine therapy

Notes: H=trastuzumab; L=lapatinib; P=pertuzumab; T=docetaxel; paclitaxel and albumin-bound paclitaxel; X=capecitabine; N=navelbine; Cb=carboplatin; G=gemcitabine; LD=liposomal doxorubicin; F=fulvestrant; AI=Aromatase inhibitor; TAM=tamoxifen.

Source: CSCO 2022, Frost & Sullivan analysis

According to Frost & Sullivan, the current HR+/HER2- mBC treatment is facing multiple major challenges, including:

- Low penetration of endocrine therapy. Different from the recommendations of the CSCO guidelines, the proportion of Chinese HR+/HER2- mBC patients currently receiving first-line chemotherapy is high, while the penetration rate of the recommended endocrine therapy is low. Due to the influence of family income level and regional medical insurance reimbursement level, HR+/HER2- mBC patients have differences in endocrine therapy affordability, and there are still unmet clinical needs.

- Endocrine + CDK4/6 therapy resistance in HR+/HER2- mBC. The endocrine/anti-estrogen therapies in combination with CDK4/6 inhibitors has emerged as the first- and second-line treatment for patients with HR+/HER2- mBC. However, most patients will develop drug resistance over time.

According to Frost & Sullivan, the current TNBC treatment is facing multiple major challenges, including:

- Lack of therapies for treatment. Because TNBC is ER negative, PR negative and HER2 negative, hormonal therapy and HER2 receptor target therapy cannot be effective for TNBC patients.

- Limitations of current therapies. Currently, TNBC is primarily treated with systemic therapies (chemotherapies), PD-1 (pembrolizumab plus chemotherapies) as neo/adjuvant therapy or first line therapy and antibody-drug conjugate therapies as the second-line therapy for TNBC have been approved by FDA recently. However, current treatments for patients with immunotherapy- and/or chemotherapy-resistant TNBC are limited in clinical practice and have relatively poor prognosis, high risk of recurrence, and no significant survival benefit, indicating huge unmet medical needs for the treatment of TNBC.

ANTI-CYP17A1 ANDROGEN DRUG

Overview

Androgens are closely related to the growth of the prostate and the occurrence of prostate cancer. Therefore, endocrine therapy has become an effective treatment for prostate cancer. Endocrine therapy includes androgen deprivation therapy (ADT) with estrogen therapy, gonadotropin-releasing hormone analog therapy, gonadotropin-releasing hormone antagonist therapy, and androgen suppressive. Androgen suppressive therapy can be used on top of ADT for the treatment of early-stage prostate cancer or combined with surgery for adjuvant therapy.

Androgen suppressive therapy is one of the major methods of clinical treatment of prostate cancer, which involves intervention of the androgen signaling pathway. The main categories of androgen suppressive drugs are anti-CYP17A1 drugs and AR inhibitors. Anti-CYP17A1 drugs inhibit the synthesis of androgen, the best known drug of which is abiraterone. AR inhibitor represented by enzalutamide inhibits binding of androgen and receptor.

Competitive Landscape and Market Size

Currently, there are seven anti-androgen drugs approved for commercialization globally (ex-China) and there are seven anti-androgen drugs approved in China.

Marketed Anti -androgen Drug in the US and China

Approved drug	Flutamide	Bicalutamide	Nilutamide	Abiraterone	Enzalutamide	Apalutamide	Darolutamide	Rezvilutamide
Commercial name	Fugerel	Casodex	Nilandron	Zytiga	Xtandi	Erleada	Nubeqa	艾瑞恩
Mechanism	AR inhibitor	AR inhibitor	AR inhibitor	CYP17A1 inhibitor	AR inhibitor	AR inhibitor	AR inhibitor	AR inhibitor
Company	Ferring	Astra Zeneca	Concordia	Janssen Biotech	Astellas	Janssen Biotech	Bayer	Hengrui Medicine
US approval time	1989*	1995	1996	2011	2012	2018	2019	Not approved
2020 global revenue (million US dollar)	NA	388.3	NA	2,767.6	5,134.3	760.0	317.0	NA
2022 US market price (US dollar)	NA	115.0 (50mg)	285.8 (150mg)	94.8 (250mg)	113.8 (40mg)	117.8 (60mg)	106.7 (300mg)	NA
2022 US monthly treatment cost (thousand US dollar)	NA	3.5 (PFS:NA)	3.5 (PFS:21.1)	11.4 (PFS:NA)	13.6 (mCRPC PFS:19.5 nmCRPC PFS:36.6 mHSPC PFS:NA)	14.1 (mHSPC PFS:NA nmCRPC PFS:40.5)	12.8 (PFS:40.4)	NA
FDA approved indications	B2-C stage prostate cancer, D2 stage metastasis prostate cancer	Metastatic prostate cancer	Metastatic prostate cancer	mCRPC, HSPC	CRPC, mHSPC	mHSPC, nmCRPC	nmCRPC, mHSPC	NA
China approval time	2003	1999	Not approved	2015	2019	2019	2021	2022
NMPA approved indications	Prostate cancer	Late stage Prostate cancer	NA	mCRPC, mHSPC	mCRPC, nmCRPC	nmCRPC, mHSPC	nmCRPC, mHSPC	mHSPC
China NRDL inclusion	Category B	Category B	NA	Category B	Category B	Category B	Category B	Category B
China generic drug approval status	Y	Y	NA	Y	Y	N	N	N
2020 China revenue (million RMB)	20.5	776.6	NA	1,614.3	141.5	38.9	NA	NA
2021 China market price (RMB)	NA	31.0 (50mg)	NA	108.5 (250mg)	69.6 (40mg)	332.5 (60mg)	196.7 (300mg)	NA
2021 China generic drug market price (RMB)	3.8 (250mg)	25.0 (50mg)	NA	30.0 (250mg)	48.2 (40mg)	NA	NA	NA
2021 China monthly treatment cost (thousand RMB)	NA	0.9 (PFS:NA)	NA	13.0 (PFS:NA)	8.4 (mCRPC PFS:19.5 nmCRPC PFS:36.6)	39.9 (mHSPC PFS:NA nmCRPC PFS:40.5)	23.6 (PFS:40.4)	NA
2021 China generic drug monthly treatment cost (thousand RMB)	0.3 (PFS:NA)	0.8 (PFS:NA)	NA	3.6 (PFS:NA)	5.8 (mCRPC PFS:19.5 nmCRPC PFS:36.6)	NA	NA	NA

Notes:

1. There were over 15 generic competitors of the approved anti-androgen drugs as of April 30, 2023. If the generic name of a drug is listed in the NRDL, both the original drug and the generics under such generic name will be included in the NRDL and available for reimbursement. Once a drug is included in the NRDL, it will be subject to volume-based purchasing in China.

2. The revenue refers to the overall sales under the generic name.

3. The chart does not include androgen deprivation therapy (ADT) drugs. Flutamide original drug has been withdrawn from China and the US market.

4. Information as of April 30, 2023.

Source: NMPA, FDA, Frost & Sullivan analysis.

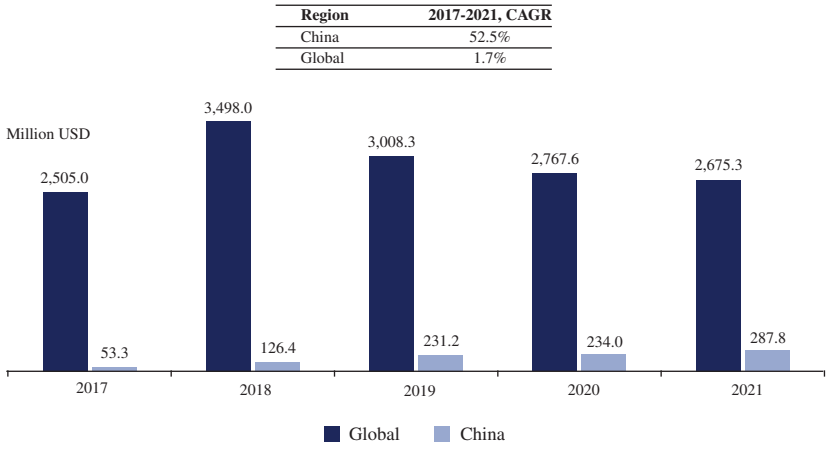
Currently, there is only one CYP17A1 inhibitor approved for commercialization globally including China, namely abiraterone, according to Frost & Sullivan.

Marketed Anti-CYP17A1 Drug in the US and China	
Approved drug	Abiraterone
Commercial name	Zytiga
Mechanism	CYP17A1 inhibitor
Company	Janssen Biotech
US approval time	2011
2020 global revenue (million US dollar)	2,767.6
2022 US market price (US dollar)	94.8 (250 mg)
2022 US monthly treatment cost (thousand US dollar)	11.4 (PFS: NA)
FDA approved indications	mCRPC, mHSPC
China approval time	2015
NMPA approved indications	mCRPC, mHSPC
China NRDL inclusion	Category B
2020 China revenue (million RMB)	1,614.3
2021 China market price (RMB)	108.5 (250 mg)
2021 China monthly treatment cost (thousand RMB)	13.0 (PFS:NA)

Source: NMPA, FDA, Frost & Sullivan analysis

The market size of anti-CYP17A1 drug from 2017 to 2021 is thus equivalent to the historical sale of abiraterone. The following chart shows the historical market size (sale) of the global and China anti-CYP17A1 drug market from 2017 to 2021, as well as CAGRs for the periods indicated:

Historical sale of Abiraterone globally and in China, 2017-2021



Notes: Global revenues for abiraterone declined in 2019, 2020 and 2021 due to (i) patent expiration and generic entry in 2018, (ii) entry of new AR antagonists in 2019, including dalotamide and apalutamide, and (iii) an increased proportion of AR antagonists, particularly enzalutamide.

Source: Annual reports published by the relevant market players, Expert interview, Frost & Sullivan analysis

There are 11 anti-androgen drugs in clinical trials globally and LAE001 is the only CYP17A1 and CYP11B2 dual inhibitor candidate under development. In China, there are five anti-androgen drugs in clinical trials and LAE001 is also the only CYP17A1 and CYP11B2 dual inhibitor candidate in clinical trial stage.

Pipeline global

Drug name	Target	Company	Indication	Phase	First posted date
SHR3680	AR inhibitor	Hengrui Medicine	HSPC, mCRPC, advanced breast cancer	III	2018-05-09
HC-1119	AR inhibitor	Hinova Pharmaceuticals	mCRPC	III	2019-02-22
Seviteronel/VT-464	Dual CYP17A1 and AR inhibitor	Innocrin Pharmaceuticals	CRPC, HR+ breast cancer, TNBC	II	2013-12-17
Proxalutamide/GT0918	AR inhibitor	Kintor Pharma	mCRPC	II	2019-04-02
TRC253	AR inhibitor	Tracon	mCRPC	I/II	2016-12-09
ODM-208	CYP11A1	Orion Corporation/Merck	mCRPC	I/II	2018-02-19
LAE001	**Dual CYP17A1 and CYP11B2 inhibitor**	**Laekna**	**mHSPC***	II	**2019-02-18**
ODM-209	CYP11A1	Orion Corporation	Metastatic/advanced prostate cancer, metastatic/advanced breast cancer	I/II	2019-03-18
EPI-7386	AR inhibitor	ESSA Pharmaceuticals	mCRPC	I/II	2021-10-13
TAS3681	AR inhibitor	Taiho Oncology	mCRPC	I	2015-10-02
ONC1-0013B	AR inhibitor	Avionco LLC	mCRPC	I	2017-03-03

Notes: Only includes oncology drugs. The chart does not include androgen deprivation therapy (ADT) drugs or PROTAC. First posted date denotes the date when the most advanced clinical stage of a clinical trial for an indication is first publicly announced. Information as of April 30, 2023.

* We are currently conducting a Phase II clinical trial of LAE001 monotherapy on mCRPC. As part of our clinical development strategy for LAE001 in prostate cancer and based on the clinical data from trials on mCRPC, we plan to initiate a Phase III MRCT registrational trial for mHSPC in the fourth quarter of 2023 in China and the U.S. and apply the NDA for mHSPC.

Pipeline in China

Drug name	Mechanism/Target	Company	Indication	Phase	First posted date
Proxalutamide	AR inhibitor	Kintor Pharma	mCRPC	III	2018-07-02
HC-1119	AR inhibitor	Hinova Pharmaceuticals	mCRPC	III	2019-03-01
ISIS560131/AZD5312	AR inhibitor	Pyramid Laboratories	AR-V7 positive mCRPC	II	2021-04-29
LAE001	**Dual CYP17A1 and CYP11B2 inhibitor**	**Laekna**	**mHSPC***	**II**	**2019-04-25**
TQB3720	AR inhibitor	Chia Tai-Tianqing Pharmaceutical	mCRPC	I	2021-01-26

Notes: Only includes oncology drugs. First posted date denotes the date when the most advanced clinical stage of a clinical trial for an indication is first publicly announced. The chart does not include ADT drugs or PROTAC. Information as of April 30, 2023.

* We are currently conducting a Phase II clinical trial of LAE001 monotherapy on mCRPC. As part of our clinical development strategy for LAE001 in prostate cancer and based on the clinical data from trials on mCRPC, we plan to initiate a Phase III MRCT registrational trial for mHSPC in the fourth quarter of 2023 in China and the U.S. and apply the NDA for mHSPC.

Source: ClinicalTrials.gov, CDE, Frost & Sullivan analysis

Growth Drivers and Further Trends

The anti-CYP17A1 androgen drug market is largely driven by the following key growth drivers:

- Increasing patient pool and clinical adoptions. With the growing aging population and increasing prostate cancer screening rate, the patient pool (including mHSPC and mCRPC) will continue to expand. Globally, the mHSPC prevalence has increased from 1.6 million in 2017 to 1.9 million in 2021, and is expected to continue to grow and reach 2.4 million in 2030. As for mCRPC, it is expected that the global prevalence will reach 2.1 million in 2030, representing great clinical needs. Abiraterone is currently listed as the Class I recommendation in the CSCO guideline for mCRPC. This is primarily attributed to its better safety profile than that of other chemotherapy drugs and proven efficacy in androgen inhibition. With the growing patient pool and buildup of clinical knowledge, it is estimated that the China anti-CYP17A1 drug market will continue to grow.

- Drug candidates with less side effects are under development. Despite its important role in prostate cancer treatment, abiraterone needs to be co-administered with prednisone for both mHSPC and mCRPC treatment, and has specific risks of hypertension, fluid retention and hypokalemia. To overcome the issue, drugs with improved safety profile and fewer side effects are being developed to drive the market growth.

- Novel therapy or combination therapies. For mCRPC patients, there are only limited treatment options other than chemotherapy, including abiraterone and enzalutamide. With disease progression, almost all patients will become resistant to currently available treatment. Therefore, novel therapies are being developed to overcome the issue. For example, studies have shown that combinatory use of new generation anti-androgen agents tend to provide better survival benefit to mHSPC patients compared with using single anti-androgen agent for treatment. Furthermore, combination of anti-CYP17A1 drugs with other treatment represents a future trend and will further drive the anti-CYP17A1 market growth.

Therapeutic Areas of Interest

Prostate Cancer

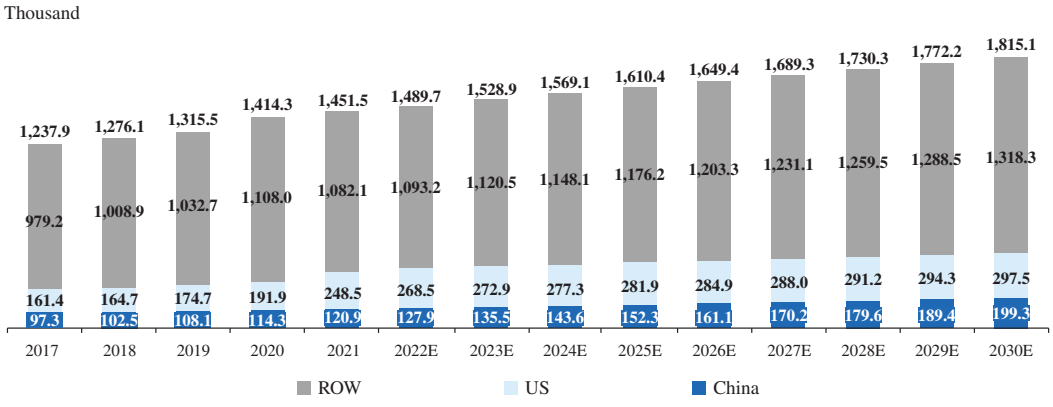
Prostate cancer begins when healthy cells in the prostate change and grow out of control, eventually developing into a tumor. The risk factors that may lead to prostate cancer include: mutations in the BRCA1 and/or BRCA2 genes, other genetic changes (HPC1, HPC2, HPCX, CAPB, ATM and FANCA), family history and eating habits. The overall five-year survival rate in the U.S. for prostate cancer was 97.5%, as compared to 69.2% in China.

Localized prostate cancer is the stage the tumor cells have not spread beyond the prostate. As the disease progresses and treatment is administered, prostate cancer may develop into two stages: (i) become metastatic but remain sensitive to ADT treatment (mHSPC); and (ii) remain in the localized stage but are resistant to ADT treatment (nmCRPC). Approximately 45% of patients with localized prostate cancer will progress to mHSPC. As treatment continues, almost all mHSPC patients will become resistant to ADT therapy, which is known as mCRPC.

The following chart shows the historical incidence breakdown of global prostate cancer from 2017 to 2021, and the estimated incidence from 2022 to 2030, as well as CAGRs during the periods indicated:

Incidence Breakdown of Global Prostate Cancer, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	2.5%	11.4%	5.6%	4.1%
2021-2025E	2.1%	3.2%	5.9%	2.6%
2025E-2030E	2.3%	1.1%	5.5%	2.4%



Note: ROW refers to rest of the world excluding China and US

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

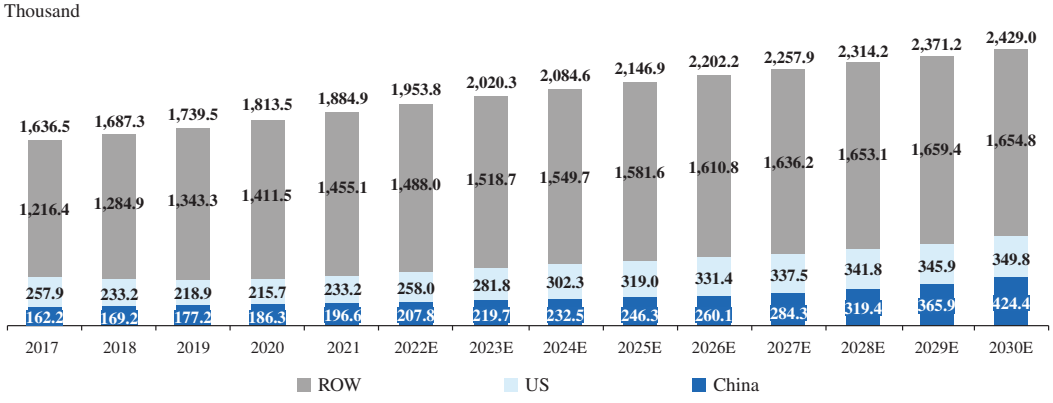
Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Hormone-sensitive prostate cancer (HSPC) is the stage of prostate cancer where the patients effectively respond to hormone therapies, typically androgen deprivation therapy (ADT). mHSPC is a prostate cancer that has spread to other parts of the body.

The following chart shows the historical prevalence breakdown of global mHSPC from 2017 to 2021, and the estimated prevalence from 2022 to 2030, as well as CAGRs during the periods indicated:

Prevalence Breakdown of Global mHSPC, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	4.6%	-2.5%	4.9%	3.6%
2021-2025E	2.1%	8.1%	5.8%	3.3%
2025E-2030E	0.9%	1.9%	11.5%	2.5%



Note: ROW refers to rest of the world excluding China and US

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

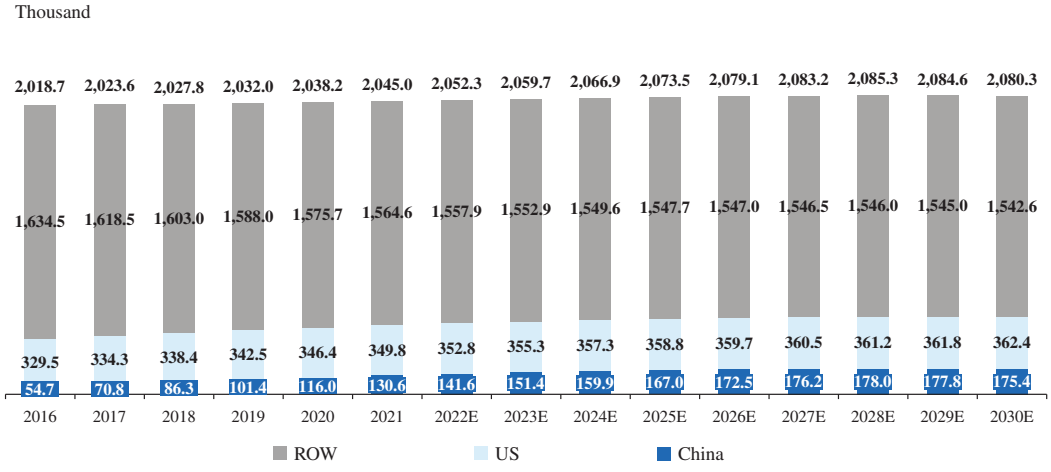
Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Castration-resistant prostate cancer (CRPC) is a prostate cancer that progresses clinically, radiographically or biochemically, despite castrate levels of serum testosterone (<50 ng/dL) in a patient. Patients with prostate cancer that have relapsed after local therapy or that have distant metastasis usually respond to ADT. However, despite receiving ADT, most of these patients eventually experience disease progression and develop CRPC within a median of 18 to 24 months from receiving ADT. A substantial majority of CRPC will be developed into mCRPC.

The following chart shows the historical prevalence breakdown of global mCRPC from 2016 to 2021, and the estimated prevalence from 2022 to 2030, as well as CAGRs during the periods indicated:

Prevalence Breakdown of Global mCRPC, 2016-2030E

CAGR	ROW	US	China	Global
2016-2020	-0.9%	1.3%	20.7%	0.2%
2020-2025E	-0.4%	0.7%	7.6%	0.3%
2025E-2030E	-0.1%	0.2%	1.0%	0.1%



Note: ROW refers to rest of the world excluding China and US

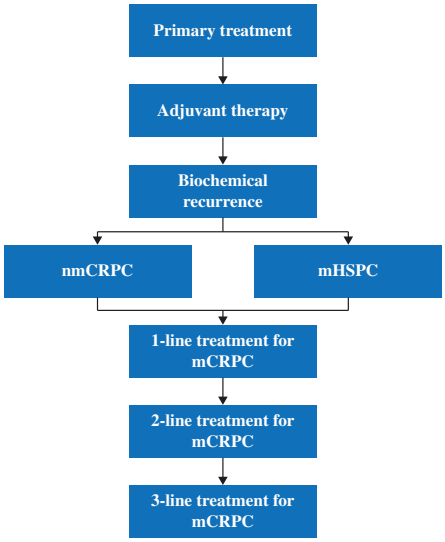
Source: Globocan, IARC, NCCR, Frost & Sullivan analysis

Treatment Paradigm and Unmet Medical Needs

The treatment of prostate cancer can be categorized into primary treatment, adjuvant therapy, mHSPC treatment, non-mCRPC and mCRPC treatment based on the disease stages. Since the 1940s, endocrine therapy and chemotherapy have been the optimized option for first-line therapies of prostate cancer. According to the latest NCCN Guideline for the treatment of prostate cancer, several combination therapies, which are all endocrine-based therapies, are also recommended for the treatment of the early stage of prostate cancer.

The following chart sets forth the treatment process for prostate cancer in the national and international guidelines.

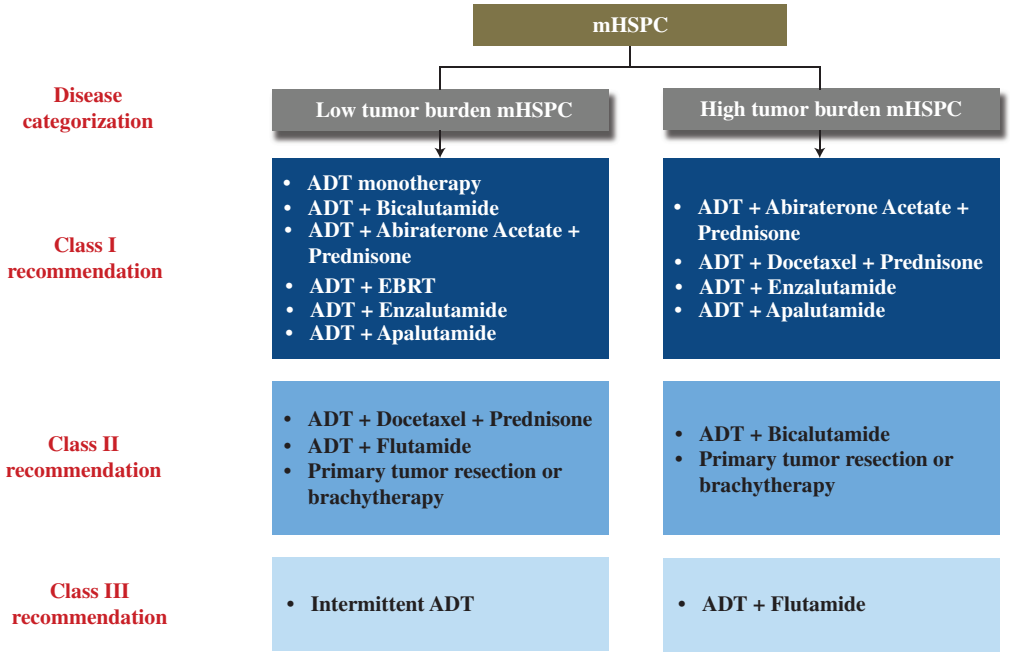
Treatment Process for Prostate Cancer



Notes: nmCRPC: nonmetastatic castration-resistant prostate cancer.

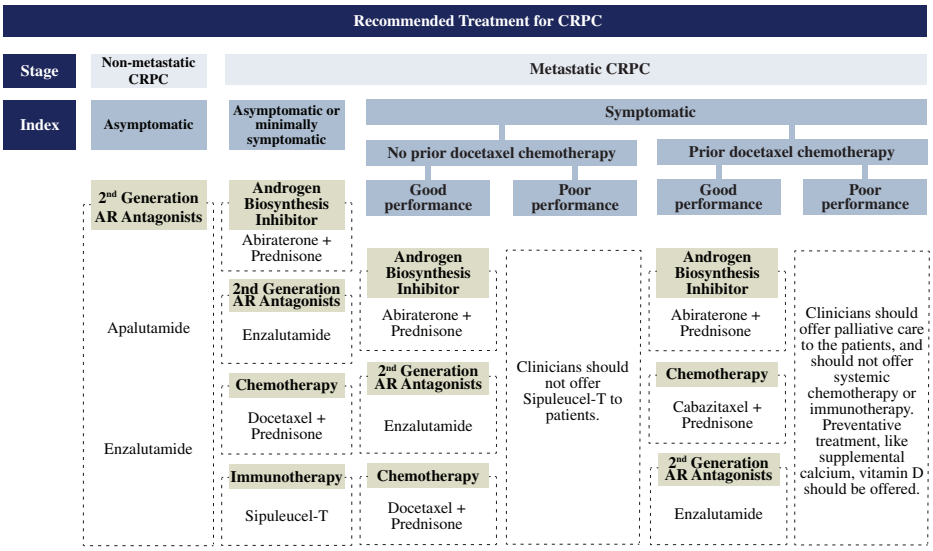
Source: NCCN Guideline, CSCO 2020, Frost & Sullivan analysis

The following chart sets forth the recommended mHSPC treatment in the national and international guidelines:



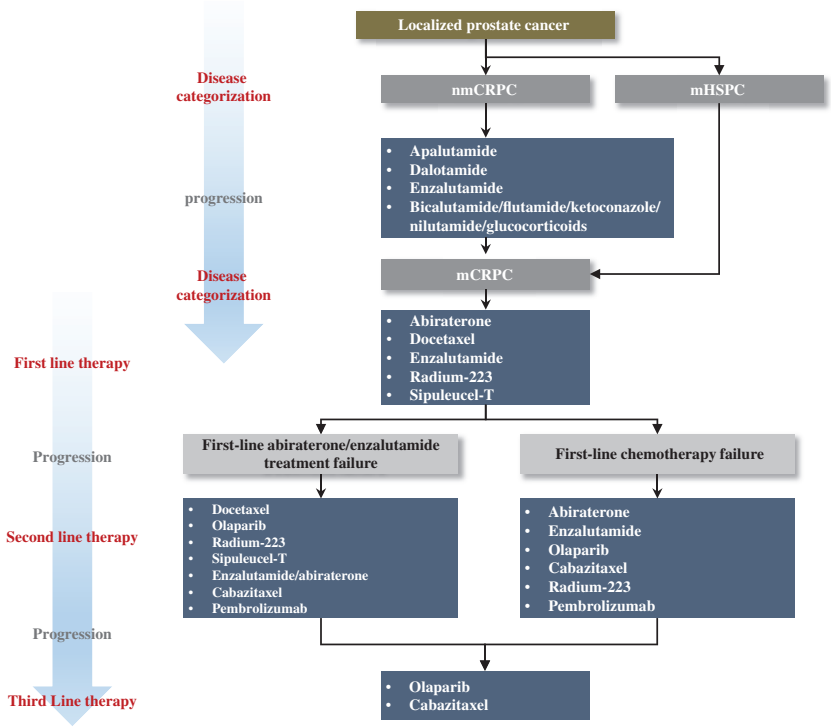
Source: NCCN Guideline, CSCO 2020, Frost & Sullivan analysis

The following chart sets forth the recommended CRPC treatment according to the international guideline, the NCCN Guideline:



Source: Castration-Resistant Prostate Cancer: America Urological Association Guideline, Frost & Sullivan analysis

The following chart sets forth the recommended CRPC treatment in the national guideline, the CSCO Guideline:



Source: CSCO 2020, Frost & Sullivan analysis

According to Frost & Sullivan, the current prostate cancer treatment paradigm is facing multiple major challenges, including:

- Lack of early diagnosis in China. Most prostate cancer patients are diagnosed at an advanced stage, mainly due to the lack of awareness and limited diagnostic techniques for regular prostate examinations in China. Only approximately 30% of new prostate cancer cases are diagnosed at an early stage in China, while more than 70% new prostate cancer patients are diagnosed at an early stage in the U.S.

- Unsatisfied prognosis. Radical treatment is not suitable for patients with locally advanced or metastatic prostate cancer, so the prognosis for these patients is usually relatively poor compared to the patients who were diagnosed in local stages. ADT is a primary treatment for metastatic prostate cancer. However, CRPC patients have developed resistance to ADT and have limited treatment options. The median survival duration for CRPC patients is less than two years due to the rapid progress of disease and lack of effective treatment.

- Limited treatment for drug-resistant mCRPC patients. Currently, there are limited treatment options for CRPC, mainly including chemotherapy, abiraterone and enzalutamide. However, these patients will most likely develop drug resistance within two years. For most drug-resistant mCRPC patients, there are limited effective treatments when they become resistant to first to third lines of SOCs, such as abiraterone, A/AR inhibitors and chemotherapies. However, the prognosis is poor in these drug-resistant mCRPC patients.

LIVER FIBROSIS DRUG

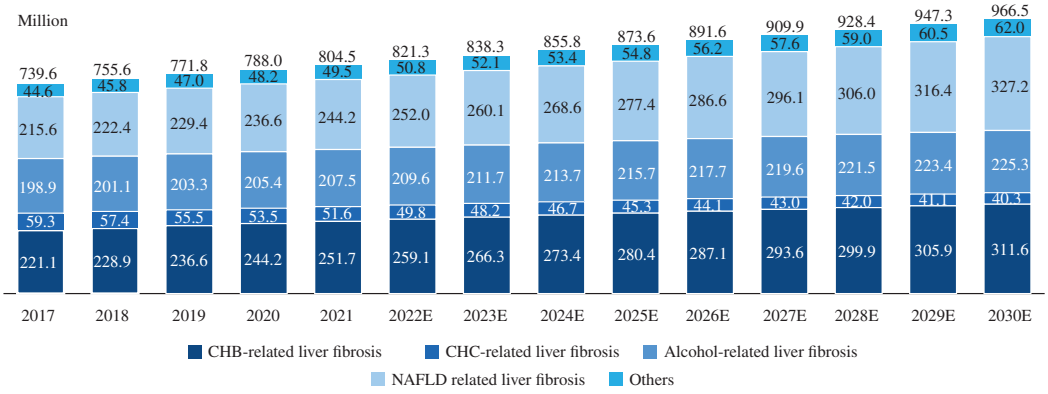
Liver Fibrosis

Liver fibrosis is a pathological change in most chronic liver diseases, such as chronic hepatitis B (CHB), chronic hepatitis C (CHC), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) and others. Liver fibrosis is a reversible over-repair reaction of liver tissue injury and is an important process in the progression from chronic liver disease to cirrhosis. In the course of fibrosis progression, the extracellular matrix (ECM) such as collagen, glycoprotein and proteoglycan, in liver tissue develops diffuse hyperplasia and deposition, while normal liver parenchymal cells undergo necrosis and apoptosis. As this process continues, the scar tissue formed by ECM gradually replaces normal liver parenchyma cells, leading to abnormal changes in liver tissue structure, which eventually leads to cirrhosis and liver cancer, furthering to liver failure. Liver fibrosis can be caused by not only chronic liver diseases, but also etiologies such as genetic and metabolic diseases.

The following chart shows the historical prevalence breakdown of liver fibrosis globally and in China from 2017 to 2021, and the estimated prevalence from 2022 to 2030, as well as CAGRs during the periods indicated:

Prevalence of Liver Fibrosis Globally, 2017-2030E

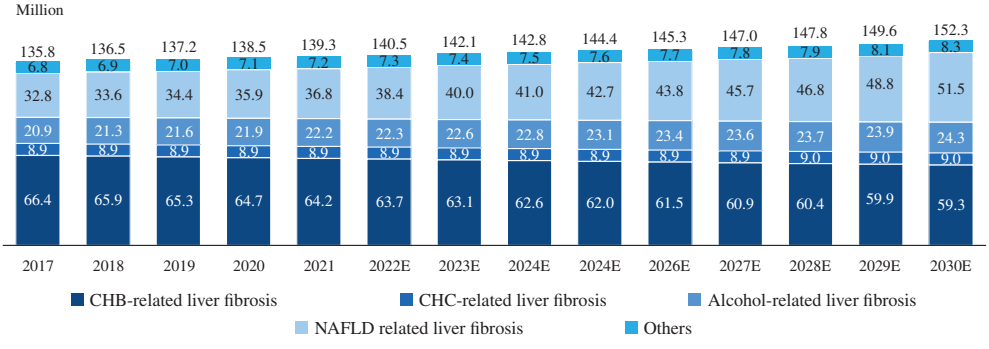
CAGR	CHB-related liver fibrosis	CHC-related liver fibrosis	Alcohol-related liver fibrosis	NAFLD-related liver fibrosis	Total liver fibrosis
2017-2021	3.3%	-3.4%	1.1%	3.2%	2.1%
2021-2025E	2.7%	-3.2%	1.0%	3.2%	2.1%
2025E-2030E	2.1%	-2.3%	0.9%	3.4%	2.0%



Source: Frost & Sullivan Analysis

Prevalence of Liver Fibrosis in China, 2017-2030E

CAGR	CHB-related liver fibrosis	CHC-related liver fibrosis	Alcohol-related liver fibrosis	NAFLD-related liver fibrosis	Total liver fibrosis
2017-2021	-0.8%	0.0%	1.5%	2.9%	0.6%
2021-2025E	-0.9%	0.0%	1.0%	3.8%	0.9%
2025E-2030E	-0.9%	0.2%	1.0%	3.8%	1.1%



Source: Frost & Sullivan Analysis

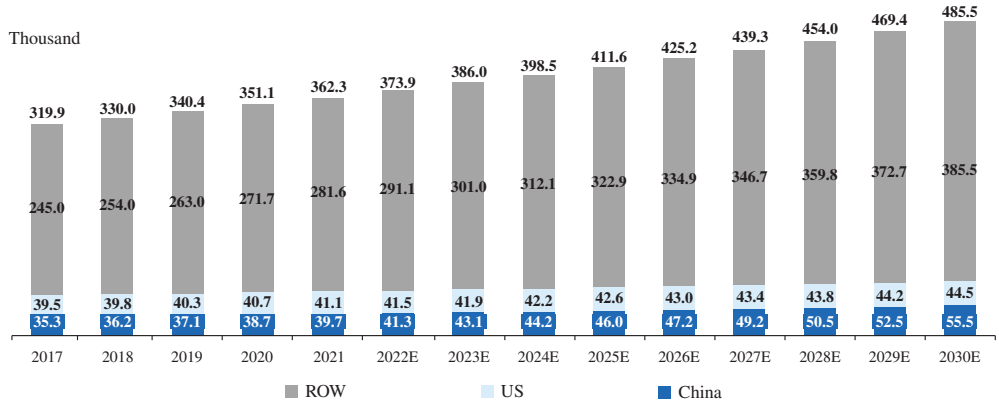
Non-Alcoholic Steatohepatitis (NASH)

NASH is an advanced form of non-alcoholic fatty liver disease (NAFLD). NAFLD is caused by build-up of fat in the liver. When this build-up causes inflammation and damage, it is known as NASH, which can lead to scarring of the liver. Scarring of the liver is a potentially life-threatening condition called cirrhosis. There are often no outward signs or symptoms associated with NASH. The most common symptoms are fatigue and pain in the upper right abdomen. NASH is most common in patients who are overweight or obese.

The following chart shows the historical prevalence breakdown of global NASH from 2017 to 2021, and the estimated prevalence from 2022 to 2030, as well as CAGRs during the periods indicated:

Prevalence Breakdown of Global NASH, 2017-2030E

CAGR	ROW	US	China	Global
2017-2021	2.9%	1.0%	3.5%	3.2%
2021-2025E	3.8%	0.9%	3.5%	3.2%
2025E-2030E	3.8%	0.9%	3.6%	3.4%



Note: ROW refers to rest of the world excluding China and US

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

Treatment Paradigm and Unmet Medical Needs

Liver Fibrosis

Currently, there are no effective specific therapies for liver fibrosis treatment, according to Frost & Sullivan. Both China and U.S. guidelines focus on prevention of the disease progression, and control liver damage and inflammation by etiological treatment.

Treatment Paradigm of Liver Fibrosis

Category	Underlying Cause	Mechanism of Action
Causal Treatment	CHB and CHC	Antiviral therapies are recommended to treat CHB and CHC. Currently, there are two classes of agents licensed for CHB treatment: standard or pegylated interferon alpha (IFN or Peg-IFN) and nucleoside/nucleotide analogues (NAs). Long-term treatment with NAs is the treatment option most often used in the majority of CHB patients. Entecavir and tenofovir, the most potent NAs with high barrier to resistance, are recommended as first-line monotherapy by all major treatment guidelines and can lead to long-lasting virological suppression, resulting in histological improvement or reversal of advanced fibrosis and reduction in disease progression and liver-related complications. According to the Chinese Medical Association Guidelines for the Prevention and Treatment of Hepatitis C, 2019, the use of sofosbuvir/velpatasvir or glecaprevir/pibrentasvir combination tablets in a pan-gene therapy regimen can effectively eliminate hepatitis C virus in most patients. In addition, sofosbuvir combined with dasabuvir and sofosbuvir/velpatasvir/vosilaprevir combination tablets are also effective in treating hepatitis C.
	NAFLD	Both the U.S. and China guidelines recommend lifestyle intervention as the most recommended therapies for NAFLD. The management of NAFLD should consist of treating liver disease as well as the associated metabolic comorbidities such as obesity, hyperlipidemia. The U.S. guideline states that thiazolidinediones, GLP-1 analogues and vitamin E can be used only on a case-by-case manner after careful evaluation.
	Alcohol Associated Liver Disease	Alcohol cessation therapy is recommended. For relapse prevention, medication also includes those to reduce the level of addiction, including naltrexone, acamprosate and gabapentin.
Anti-fibrosis Treatment	N/A	At early stage of the disease, liver fibrosis is an important process of liver damage repair and has disease defensive effect. Therefore, causal treatment and anti-inflammation therapy are recommended. With fibrosis progression to later stage and cirrhosis, anti-fibrosis treatment are recommended. Currently, there are no approved drugs specifically targeting liver fibrosis. Liver protective drug, anti-inflammatory drug, and antioxidants are currently recommended to improve the fibrosis condition in the China CMA guideline, including glucocorticoids, glycyrrhizic acid, silymarin, etc.

Source: Literature Review, Frost & Sullivan analysis

NASH

In both the U.S. and China, treatment of NASH is currently limited to lifestyle change and specific treatment of comorbidities, and no evidence-based pharmacological therapy is approved, according to Frost & Sullivan. The NASH treatment is moving towards a multi-mechanistic strategy of combination therapy, given the complexity in pathophysiology and heterogeneity nature of the disease.

U.S. Guidance of NASH:

Category	Classification	Target	Mechanism of Action
Behavior Intervention	Lifestyle Intervention	N/A	Lifestyle modification consisting of diet, exercise, and weight loss has been advocated to treat patients with NAFLD/NASH.
Drug Intervention	Thiazolidinediones/ Pioglitazone	(PPAR)-γ	Peroxisome proliferator-activated receptor gamma (PPAR)-γ, nuclear transcription factor, have broad effects on glucose and lipid metabolism, as well as vascular proliferation and inflammation.
	Vitamin E	N/A	Oxidative stress is considered a key mechanism of hepatocellular injury and disease progression in subjects with NASH. Vitamin E is an antioxidant and has been investigated as a treatment for NASH.
Surgical Intervention	Bariatric Surgery	N/A	Weight loss is effective in improving all disease features of NAFLD, including fibrosis. Bariatric surgery improves or eliminates comorbid disease in most patients and improves long-term survival of NASH.

China Guidance of NASH:

Category	Classification	Target	Mechanism of Action
Behavior Intervention	Lifestyle Intervention	N/A	In order to achieve weight loss and reduce BMI value, diet and adequate exercises has been used to treat patients with NAFLD/NASH.
Drug Intervention	Metformin + Liraglutide/ Pioglitazone	GLP-1/ (PPAR)-γ	For patients with metabolic syndrome (MetS), such as diabetes, hypertension and obesity, metformin and other precision drugs are recommended to regulate the metabolism of patients, thereby improve NAFLD indices and delay the progression of NAFLD/NASH.
	Hepatoprotective drugs	N/A	A category of drugs improve liver function, promote regeneration of damaged liver cells, and enhance liver detoxification functions.
Surgical Intervention	Bariatric surgery	N/A	For patients with severe (BMI>40 kg/m^2) or moderate obesity (35 kg/m^2≤BMI≤39.9 kg/m^2), bariatric surgery are recommended to efficiently reduce the weight of patients.

Note: MetS = Metabolic Syndrome

Source: Frost & Sullivan analysis

Competitive Landscape

Liver Fibrosis

Currently, no specific anti-liver fibrosis drug candidates have been approved worldwide. There are a number of active anti-liver fibrosis drug candidates in Phase II or later clinical stage globally. In China, there are five anti-liver fibrosis drug candidates in clinical stage as shown in the table below.

Drug	Target	Company	Indication	Status	First Posted Date
Hydronidone	TGFβ	BJContinent Pharmaceuticals Limited	Chronic hepatitis B liver fibrosis	Phase III	2021-10-14
BI456906	GCGR, GLP1R	Boehringer Ingelheim	NASH and liver fibrosis	Phase II	2021-09-01
Fluorofenidone	TGFβ	Hainan Haiyao	Liver fibrosis	Phase II	2021-10-18
TB001	GLP-1R/GCGR agonist	Turier Biotech	Liver fibrosis	Phase I	2021-12-16
GST-HG151	MAP3K5	Fujian Cosunter	NASH with liver fibrosis	Phase I	2022-03-03

Notes:

* First posted date denotes the date when the trial is first publicly announced.

Not including liver cirrhosis indication. Information as of April 30, 2023

Source: ClinicalTrials.gov, CDE, Frost & Sullivan analysis

NASH

Currently, there are no approved drug candidates for commercialization in terms of NASH treatment globally, according to Frost & Sullivan. There are a number of drug candidates under development globally for NASH. The table below summarizes all the later clinical-stage (Phase III and NDA) drugs for NASH treatment globally:

Global Pipelines for NASH Treatment

Pipeline	Target	Company	Status	First Posted Date*
Obeticholic Acid	FXR	Intercept Pharmaceuticals	NDA	2022/12/23
Resmetirom (MGL-3196)	THRβ	Madrigal Pharmaceuticals, Inc.	Phase III	2019/4/3
Semaglutide	GLP1R	Novo Nordisk	Phase III	2021/3/30
IVA337	PPAR	Inventiva Pharma	Phase III	2021/4/19
Aramchol	SCD	Galmed Pharmaceuticals	Phase III	2019/09/26
MSDC-0602K	NA	Cirius Therapeutics, Inc.	Phase III	2019/05/31

Notes: Excluding clinical trials only conducted in China. Only including pipelines in Phase III and later. Information as of April 30, 2023.

* First posted date denotes the date when the trial is first publicly announced.

Source: ClinicalTrials.gov, FDA, Frost & Sullivan analysis

There are a number of drug candidates under development in China for NASH. The table below summarizes all the later clinical-stage (Phase II or later) drugs for NASH treatment in China:

Pipelines for NASH Treatment in China[1]

Drug	Target	Company	Indication	Status	Fist Post Date*
Semaglutide	GLP1R	Novo Nordisk	NASH	III	2021/07/27
Cotadutide	GCGR,GLP1R	Astra Zeneca	NASH	II/III	2022-10-31
TVB-2640	FASN	3-V Biosciences/Ascletis	NASH	II	2020/4/30
Tropifexor	FXR	Norvatis	NASH	II	2020/12/17
PF-06865571 /+ PF-05221304	DGAT2	Pfizer	NASH	II	2021/03/15
HEC96719	FXR	HEC Pharma	NASH	II	2021/07/27
BI 456906	GLP-1	Boehringer Ingelheim	NASH and liver fibrosis	II	2021/09/01
Chiglitazar Sodium	PPAR	Chipscreen	Insulin Resistance NASH with High Triglycerides	II	2021/12/07
ASC41	THRB	Ascletis Pharma Inc.	NASH	II	2022/06/21
ZSP1601	PDE	Zhongsheng Pharma	NASH	II	2022/12/30

Notes: The table only includes pipelines in Phase II and later clinical stage, as well as approved drugs. Information as of April 30, 2023.

* First posted date denotes the date when the most advanced clinical stage of a clinical trial for an indication is first publicly announced.

Source: CDE, Frost & Sullivan analysis

HEREDITARY HEMORRHAGIC TELANGIECTASIA AND PROTEUS SYNDROME

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is a disorder in which some blood vessels do not develop properly. A person with HHT may form blood vessels without the capillaries (tiny blood vessels that pass blood from arteries to veins) that are usually present between arteries and veins.

Although there are no clear guidelines for the treatment of HHT, there are a number of treatments for the symptoms of HHT according to the "Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Distal Capillary Dilatation". Antiestrogens such as tamoxifen and raloxifene, drugs that stop blood vessel growth such as bevacizumab, and drugs that slow down the breakdown of blood clots such as tranexamic acid have all been used to control symptoms such as blood vessel growth and excessive bleeding caused by HHT.

Currently, there are no HHT drugs approved globally and no HHT drugs under clinical stage in China. The following table sets forth the competitive landscape of HHT drugs in clinical trials globally.

Global Pipelines for HHT Treatment

Pipeline	Target	Company	Status	First Posted Date*
Tranexamic acid	PLG	Baxter Healthcare	Phase III	2009/12/15
Nintedanib	PDGFR/FGFR/VEGFR	Boehringer Ingelheim	Phase II	2021/7/26
VAD044	AKT	Vaderis Therapeutics	Phase I	2022/6/6

Notes: Information as of April 30, 2023.

* First posted date denotes the date when the trial is first publicly announced.

Source: Clinical Trials, Frost & Sullivan Analysis

Proteus Syndrome

Proteus syndrome is a rare condition characterized by overgrowth of the bones, skin, and other tissues. Organs and tissues affected by the disease grow out of proportion to the rest of the body. The overgrowth is usually asymmetric, which means it affects the right and left sides of the body differently. Newborns with Proteus syndrome have few or no signs of the condition. Overgrowth becomes apparent between the ages of six and 18 months and gets more severe with age. The cause of the disorder is a mosaic variant in a gene called AKT1.

As an extremely rare disease, there are no guidelines for the treatment of Proteus syndrome. Treatment of this disease is limited to supportive care and surgical intervention. Genetic mosaicism, such as the activated AKT1 mutation, has been suggested as an important cause of Proteus syndrome.

Currently, there are no approved drugs for the treatment of Proteus syndrome globally. There are no Proteus syndrome drugs under development that reaching clinical stage in China. The following table sets forth the competitive landscape of Proteus syndrome drugs in clinical trials globally.

Global Pipelines for Proteus Syndrome Treatment

Pipeline	Target	Company	Status	First Posted Date*
MK-7075 /Miransertib	AKT1	Merck	Phase II	2021/7/28

Notes: Information as of April 30, 2023.

* First posted date denotes the date when the trial is first publicly announced.

Source: ClinicalTrials, Frost & Sullivan Analysis

REPORT COMMISSIONED BY FROST & SULLIVAN

In connection with the [**REDACTED**], we commissioned Frost & Sullivan, an Independent Third Party, to prepare a report on global and China's oncology and liver fibrosis drug markets. Except as otherwise noted, all data and forecasts in this section come from the Frost & Sullivan report. We have agreed to pay a total of US$76,500 in fees for the preparation of the Frost & Sullivan report. Frost & Sullivan is a market research and consulting company that provides market research on a variety of industries including healthcare. In preparing the report, Frost & Sullivan collected and reviewed publicly available data such as government-derived information, annual reports and industry association statistics, as well as market data collected by conducting interviews with key industry experts and leading industry participants. Frost & Sullivan has exercised due care in collecting and reviewing the information so collected.