
INDUSTRY OVERVIEW

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OVERVIEW OF IMMUNO-ONCOLOGY THERAPY MARKET

Global Immuno-oncology Therapy Market

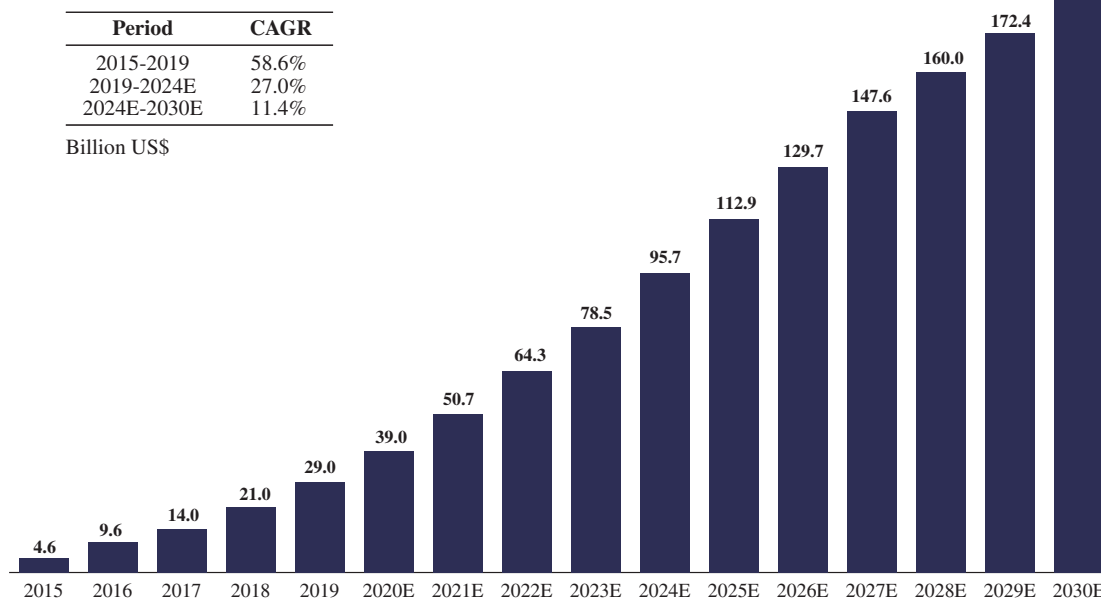
The field of cancer treatment has developed significantly in the past century, progressing from surgery to immunotherapy. Main treatment methods today include surgery, radiotherapy, chemotherapy, targeted molecular therapy, and immunotherapy. Targeted molecular therapy and immunotherapy have revolutionized cancer treatment and are expected to further propel the growth of global oncology treatment markets.

Over the last few years, immuno-oncology therapy has revolutionized cancer care. Immuno-oncology therapy is designed to stimulate the patient’s own immune system to generate or augment an antitumor immune response in order to control or eradicate cancer cells. Due to its ability to provide durable remissions while being generally well-tolerated in certain patients with advanced cancers, the discovery and development of immuno-oncology therapy marks an important milestone in cancer treatment. Major types of immuno-oncology therapy include cellular immunotherapies, checkpoint inhibitors, therapeutic cancer vaccines and cytokines.

As shown in the following diagram, the global immuno-oncology therapy market has expanded significantly in recent years, and is expected to further expand at an accelerated pace in the coming years.

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Historical and Forecasted Market Size of Global Immuno-Oncology Therapies Market, 2015-2030E



Source: Frost & Sullivan Analysis

OVERVIEW OF CELLULAR THERAPY AND CAR-T MARKET

Overview of Cellular Therapy

Cellular immunotherapy, also known as adoptive cell transfer (ACT) therapy, is a type of immunotherapy in which immune cells (mostly T-cells) are given to a patient for the treatment of cancers. The T-cells are usually taken from the patient's own blood or tumor tissues, grown in large numbers in the laboratory, and then infused into the patient to help their immune system kill tumor cells.

The primary distinction between allogeneic and autologous cell therapies is the source of the cells. Autologous therapies are manufactured by harvesting the patient's own immune cells, processing and culturing *ex vivo*, then infusing them back into the same patient. On the other hand, allogeneic therapies are manufactured from cells of healthy donors who are unrelated to the patient, which can be manufactured in large quantities and used to treat many patients. Autologous therapies have higher compatibility with the patients' immune system, whereas allogeneic therapies are more scalable for manufacturing and more versatile for treatment. Currently, all commercialized CAR-T cell therapies and most CAR-T cell therapies in development are autologous therapies. Allogeneic CAR-T cell therapy is a relatively new technology at an early stage of development.

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Major types of cellular immunotherapy include CAR-T, TCR-T, NK and TIL. The table below provides an overview of their cell source, common side effects and mechanism of action.

Type	Cell Source	Common Side Effects	Mechanism of Action
CAR-T	<ul style="list-style-type: none"> Peripheral Blood Mononuclear Cells (PBMC) Autologous or allogeneic cells 	Cytokine release syndrome, B-cell aplasia, Neurotoxicity	Chimeric antigen receptors (CARs) targeting tumor-associated antigens (TAA) are genetically engineered and introduced into T-cells which could bypass MHC restriction and direct specific cytotoxicity to the antigen on tumor cells. CAR-T are expanded and infused back into patients to realize tumor suppression.
TCR-T	<ul style="list-style-type: none"> Peripheral Blood Mononuclear Cells (PBMC) Autologous or allogeneic cells 	Cytokine release syndrome, neurotoxicity, temporary fever, shivering, nausea, rash dermatitis, vitiligo, uveitis, orchitis	T-cells are taken from patients and then the T-cell receptors are modified genetically through the bioengineering of the TCR α - and β -glycoprotein antigen-binding domain. Alteration of T-cell receptors allows for the development and expansion of T lymphocytes with higher specificity to tumor neoantigens presented by the human leukocyte antigen system.
NK	<ul style="list-style-type: none"> Autologous or allogeneic (for adoptive transfer) In vivo potentiation NK cell lines 	Usually controllable immune side effects, such as fever	The NK cells, which are part of human innate immune system, are harnessed to attack cancer cells through in vivo potentiation of NK cell proliferation and activity. Activation, adoptive transfer of NK cells, or genetic modification of NK cells could enhance the tumor cell killing efficacy.
TIL	<ul style="list-style-type: none"> Fresh resected tumor specimen or allogeneic cells 	Thrombocytopenia, chills, anemia, febrile neutropenia	Naturally occurring tumor-infiltrating lymphocytes (TILs) are harvested, and then the T-cells are later activated and expanded <i>ex vivo</i> and re-infused into lymphodepleted patients, where they can then seek out and destroy tumors.

Source: Frost & Sullivan Analysis

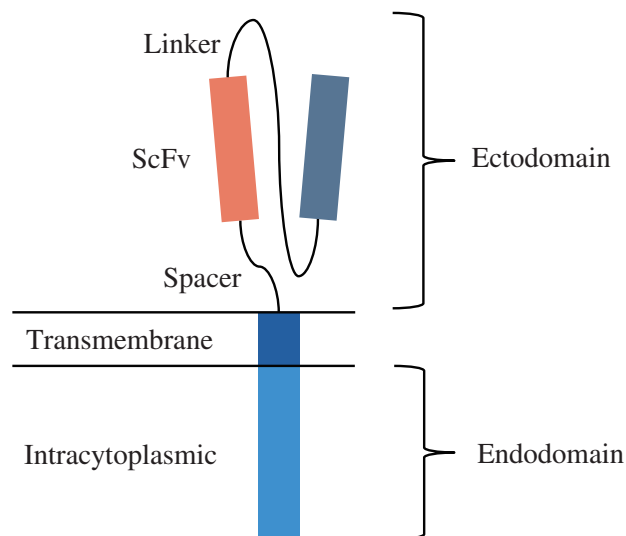
Mechanism and Structure of CAR-T

CAR-T are T-cells that have been genetically modified to produce an artificial antigen receptor, which gives T-cells the new ability to target a specific protein.

The genetically modified T-cells have receptors on their surface called chimeric antigen receptors (CARs). The CARs can combine with antigens on the tumor cell surface to trigger the intracellular signaling to activate T-cells, resulting in the elimination of tumor cells.

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The following diagram illustrates the mechanism of action of CAR-T:



Source: Frost & Sullivan Analysis

CARs' extracellular domain consists of the single chain variable fragment (scFv) from a monoclonal antibody, which recognizes a tumor-associated antigen (TAA). Various hinges and transmembrane domains are used to link the recognition domain with the intracellular signaling molecules.

Advantages Compared to Common Cancer Treatments

Cellular immunotherapy has the following advantages:

- *Specificity*: Cellular immunotherapy activates T-cells that target specific tumor antigens. Some activated T-cells differentiate into effector cells that can kill tumor cells directly or indirectly, while other activated T-cells can promote the differentiation of B cells into antibody-producing plasma cells.
- *Adaptability*: Tumor cells in patients often mutate frequently allowing it to evade targeted therapies and the immune system. However, the immune system is able to produce a limited number of T-cells and B cells aimed at mutated antigens. These immune cells can be activated and expanded in vitro then infused back into the patients to kill the mutated tumor cells. In cellular immunotherapy, tumor antigens will be released after T-cells kill the tumor cells, which can in turn activate more T-cells and B cells to kill mutated tumor cells.

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- *Persistence and long lasting efficacy:* Cellular immunotherapy can stimulate the body's immune memory and prolong the immune system's antitumor response. Some activated immune cells become memory cells which can maintain the specific ability to recognize antigens and clear lesion cells during subsequent antigen invasions. The durability of cancer immunotherapy therefore has a significant advantage in preventing tumor recurrence compared with traditional cancer therapies.

CAR-T therapies have the following specific advantages:

- *Efficacy for r/r patients:* The treatment of hematological cancers is challenging as some patients many fail to respond to treatment or are more susceptible to relapse due to drug resistance. CAR-T therapies provide an effective treatment option for patients who have failed previous lines of treatment, thereby increasing their chance of getting better survival benefits.
- *Shorter course of treatment:* Compared to conventional therapies, such as chemotherapy and rituximab based combo-therapies that typically require treatment of six to eight months and longer hospital stays for toxicity management, CAR-T therapy generally can be administered with a single infusion with typically less than two weeks of hospitalization for monitoring, leading to potentially less adverse side effects and better patient tolerance, as well as smaller psychological burden.
- *Promising for older age groups:* Unlike conventional therapies that need to be used in sub-optimal doses to treat older patients due to lower tolerance levels, CAR-T therapies have shown promising results indicating that they are well-tolerated in all age groups.

Global CAR-T Market

After the approval of the first two CAR-T products, Yescarta and Kymriah, in 2017, the global CAR-T market expanded from approximately US\$13 million in 2017 to approximately US\$734 million in 2019. It is expected to further expand to US\$4.7 billion in 2024, representing a CAGR of 45.3% from 2019, and to US\$18.1 billion in 2030 at a CAGR of 25.0% from 2024.

Currently, there is fierce competition in the area of cellular immunotherapy. Regulatory authorities now require CAR-T products to demonstrate good efficacy results in terms of high response rate as well as good safety data to obtain approval in the targeted indications. In the future, with a clearer regulatory pathway in the area, it is expected that CAR-T therapies may need to show data beyond short-term response rate, such as long-term efficacy results to demonstrate its long-lasting efficacy and their ability to achieve long-term remission.

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Regulatory Framework for CAR-T Therapies

Even though the regulatory structure and commercialization framework for CAR-T therapies in China, the US and the EU have differences, there is no apparent difference in the procedure of obtaining an IND or NDA for CAR-T products in these regions. In all cases, the product's sponsors must obtain IND approval to carry out clinical trials, collect sufficient data to prove the efficacy and safety of the product/therapy, and obtain NDA approval for marketing. In addition, post-marketing observational studies involving patients treated with CAR-T products are required by regulators in China, the US and the EU. The following table is a comparison of the regulatory framework for CAR-T therapies in China, the US and the EU.

Region	Registration Category	Clinical Data Evaluated by	Market Authorization Issued by	Approval Based Upon	Post-marketing Study
China	Biologics	CDE	NMPA	Efficacy, Safety, Severity of targeted indications	Required
U.S.	Vaccines, Blood & Biologics	CBER	FDA	Efficacy, Safety, Severity of targeted indications	Required
EU	ATMP	EMA	EC	Efficacy, Safety, Severity of targeted indications	Required

Note: ATMP = Advanced Therapy Medicinal Product; CDE = Center for Drug Evaluation; CBER = Center for Biologics Evaluation and Research; NMPA = National Medical Products Administration; FDA = Food and Drug Administration; EC = European Commission

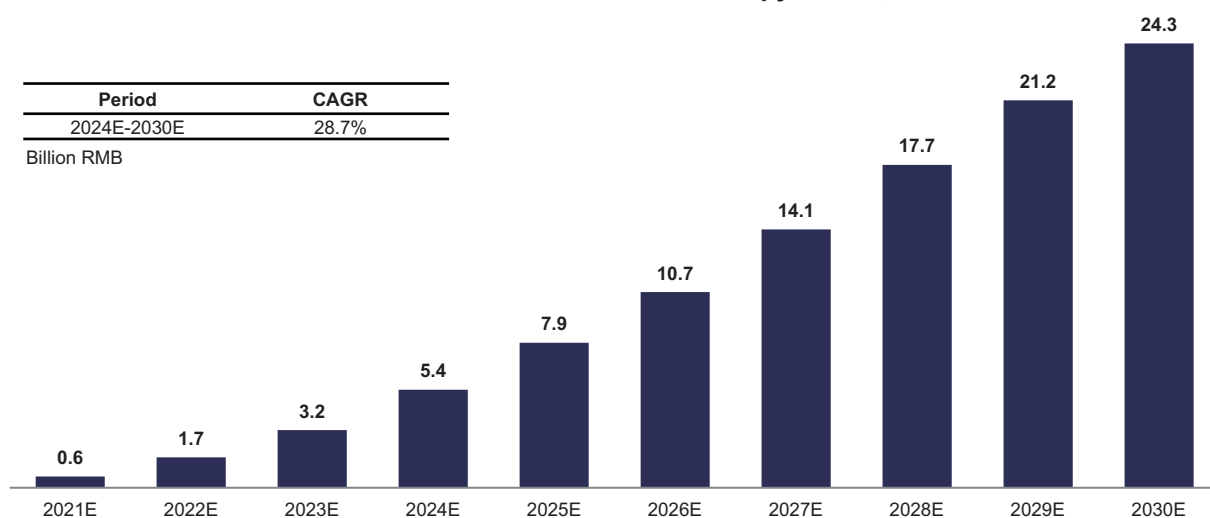
Source: Literature Review, Frost & Sullivan Analysis

China CAR-T Market

While there are currently no approved CAR-T products in China, due to the expected launch of new products, the size of the China CAR-T market is expected to be RMB0.6 billion by 2021. Driven by an increasing number of patients diagnosed with cancer, growing affordability and favorable regulatory environment, the China CAR-T market is expected to grow to RMB5.4 billion by 2024 and to RMB24.3 billion by 2030, respectively, at a CAGR of 28.7% from 2024.

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Forecasted Market Size of China CAR-T Therapy Market, 2021-2030E



Source: Frost & Sullivan Analysis

Broad Drivers Contributing to China CAR-T Market Growth

The broad drivers contributing to the growth of China's CAR-T market are as follows:

Increasing Patient Population Diagnosed with Cancer

The increasing incidence of cancer, especially of treatment naïve and early-stage patients, is driving the development of cellular immunotherapy in China. New cases of cancer patients have been increasing steadily in past years due to an increasingly aging population, dietary habits and the implementation of early screening, reaching a total of approximately 4.4 million in 2019. In 2019, in China, the cancer incidence reached approximately 3.1 thousand cancer patients per million people. Additionally, in 2019, the total cancer incidence reached approximately 4,400 thousand, among which approximately 200 thousand are hematological cancers, accounting for 4.5% of overall cancer incidence in China. Clinical trials for CAR-T product candidates are still predominantly for hematological cancers. Moreover, only one CAR-T product had initiated clinical trials in China for solid tumors, while the remaining 15 products' clinical trials had been initiated for hematological cancers, accounting for 93.8% of all CAR-T clinical trials. As of July 31, 2020, according to available information from the CDE, all CAR-T products in China involved clinical trials in Class III Grade A hospitals. However, the increasing patient population still has limited cancer treatment options. Cellular immunotherapy, which is able to address unmet clinical needs with potentially superior efficacy and less side effects, represents a significant market opportunity in China.

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Improving Affordability

Driven by rapid economic development, the average disposable income of Chinese households has increased significantly in the last five years, and is expected to further increase in the future, which will enhance the willingness and ability of patients to pay for more expensive treatments. Furthermore, due to a favorable regulatory environment, demand for commercial health insurance has also shown significant growth since 2017, and consequently, is expected to lead to an increase in healthcare expenditures and increasing acceptance of expensive and innovative treatments. From 2014 to 2018, the commercial health insurance premium per capita in China experienced rapid growth, representing a CAGR of 35.4%. In 2019, 3.6% of the total healthcare expenditures in China were paid with commercial health insurance and is expected to increase rapidly to 17.9% by 2030.

In recent years, the National Reimbursement Drug List (NRDL) has conducted three price negotiations and incorporated over 30 anti-cancer drugs in order to control drug prices and increase affordability for patients, which could signify a potential opportunity for cellular immunotherapies to be covered by the NRDL in the future.

Favorable Policy

Since 2017, China's healthcare system has pushed forward significant reforms, including the promulgation of a number of policies that encourage drug innovation, simplification of the review process of clinical trial and new drug application and expansion of medical reimbursement. For example, the implied approval system for INDs allow the applicant to start conducting clinical trials in accordance with its submitted clinical trial plan, if a negative or doubtful opinion is not received from the CDE within 60 days of the submission of the IND application. As a result of these favorable policies and guidelines, currently over ten cellular immunotherapy products have obtained implied approval and started clinical trials, which is expected to expedite the development and drive the growth of China's cellular immunotherapy market.

In addition, Chinese regulations strictly oversee and regulate the collection and utilization of human inheritance material, such as organs, tissues and cells. As such materials cannot be collected, stored and processed by foreign-controlled entities, the cellular immunotherapy products have to be manufactured in China.

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Increasing CAR-T Therapy Eligible Hospitals

Currently, most hospitals in China that have been selected as clinical trial sites for CAR-T therapy are Class III Grade A hospitals. China's hospitals are categorized as Class I, Class II and Class III. Each class has three grades: A, B and C. The class and grade are assessed based on the hospital's achievements, allocation of department resources, its medical team and management, technique level, medical devices and other factors. The highest level is Class III Grade A (三級甲等). Since Class III Grade A hospitals have strong scientific medical research capabilities, qualified personnel and adequate laboratories and equipment, they are more likely to be eligible to provide CAR-T therapy. As there is already a large number of Class III Grade A hospitals in China (approximately 1,442), it is expected that as more hospitals become qualified to provide CAR-T therapies, this will contribute to the growth of the China CAR-T market. As advised by our PRC Legal Advisor, there are no restrictions or regulations that restrict the number of clinical trials for similar drug products that can be conducted in one hospital.

Increasing Capital Investment

A large number of investors consider cellular immunotherapies to be promising for the treatment of cancer, especially their potential capacity to significantly increase overall survival rates. This has stimulated investor interest in bringing substantial capital into the field, which significantly promotes the progress of cellular immunotherapy development in China.

Overview of CD19-Targeted CAR-T

CD19 is one of the important membrane antigens involved in the activation and proliferation of B cells. It is expressed on all stages of B cells except in plasma cells. It is involved in modulating both B cell receptor-dependent (BCR dependent) and independent signaling, and thus critical for the body to mount an optimal immune response. The majority of B cell malignancies, such as NHL, ALL and CLL, express CD19 at normal to high levels in all of a patient's cancer cells.

CD19-targeted CAR-T works by preventing BCR or other related ligands from binding to CD19, and at the same time elicits the immunological activity of T-cells. The binding of CD19+ cells and CAR-T activates the T-cell receptors' signaling cascade that leads to an overall impaired humoral immune response and ultimately lysis of the targeted tumor cells.

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Competitive Landscape of CD19 Market in China

The following table shows the pipeline of CAR-T products targeting CD19 in China.

Company	Partner	Product	Target	Indications	Principal Investigator and Affiliation	Status	Date	Clinical Trial Number
JW Therapeutics	Bristol Myers Squibb (June)	CAR-T	CD19	R/R B-cell NHL	Jun Zhu (Beijing Cancer Hospital)	NDA	2020-6-30	/
Fosun Kite	Kite	CAR-T	CD19	R/R B-cell NHL	Weili Zhao (Ruijin Hospital Affiliated with Shanghai Jiaotong University Medical College)	NDA	2020-2-26	/
Novartis	None	CAR-T	CD19	R/R B-cell NHL	Jun Zhu (Beijing Cancer Hospital)	Phase III	2020-6-15	CTR20200561
Carsgen Therapeutics	None	CAR-T	CD19	R/R B-cell NHL	Jie Jin (The First Affiliated Hospital, Zhejiang University School of Medicine)	Phase II	2019-6-13	CTR20191134
Immunochina Medical	Simcere	CAR-T	CD19	R/R B-cell NHL	Yuqin Song (Beijing Cancer Hospital)	Phase I/II	2020-6-30	CTR20200754
Hrain Biotech	None	CAR-T	CD19	R/R B-cell NHL	Peng Liu (Zhongshan Hospital, Fudan University)	Phase I	2018-8-19	CTR20181354
				R/R ALL	Xianmin Song (Shanghai General Hospital)	Phase I	2019-1-4	CTR20181970
Galaxy Biomedical	None	CAR-T	CD19	R/R B-cell NHL	Ting Liu (West China Hospital, Sichuan University)	Phase I	2019-3-14	CTR20190470
Shanghai Cell Therapy	None	CAR-T	CD19	R/R B-cell NHL	Lugui Qiu (Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences)	Phase I	2019-8-23	CTR20191703
Precision Biotech	None	CAR-T	CD19	R/R B-cell ALL	Jianfeng Zhou (Tongji Hospital, Huazhong University of Science and Technology)	Phase I	2019-11-25	CTR20191243
Huadao CAR T	None	CAR-T	CD19	R/R ALL	Jianmin Yang (Changhai Hospital)	Phase I	2019-12-2	CTR20192479
				R/R B-cell NHL				CTR20192478
Juventas Biotech	CASI Pharma	CAR-T	CD19	R/R B-cell NHL	Dehui Zou (Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences)	Phase I	2020-1-13	CTR20192705
				R/R ALL	Jianxiang Wang (Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences)	Phase I	2020-1-16	CTR20192701

- Note:*
- (1) Pipeline information as of July 31, 2020; for NDA candidates, date refers to the NDA acceptance date while for clinical-stage candidates, date refers to CDE initial public date (首次公示信息日期). The partner refers to any licensing partners, either in-license or out-license, regarding the corresponding CAR-T product.
 - (2) The information of principal investigator and affiliation is summarized from CDE registration information and may change in the clinical trial operation.
 - (3) It is common market practice that a leading PI would be allocated to clinical trials for competing products. Dr. Zhu Jun, as a professional and seasoned PI, has followed and will follow pre-defined protocols and guide the clinical trial process for different products accordingly.

Source: CDE, Frost & Sullivan Analysis

Overview of BCMA-Targeted CAR-T

BCMA is a protein normally expressed in B cells, and its overexpression and activation are associated with MM through a proliferation-inducing ligand (APRIL) or B cell activating factor (BAFF) ligand binding, which promotes proliferation, survival, drug-resistance and anti-apoptosis of myeloma cells. Upon interaction between the genetically modified CARs and tumor-associated antigen (BCMA in this case) on the targeted tumor cells, cellular lysis will be initiated, thereby leading to cancer cell death.

Competitive Landscape of BCMA Market in China

There are currently no approved CAR-T products globally that target BCMA. The following table shows the clinical stage CAR-T products targeting BCMA in China and the current status of their respective clinical trials.

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Company	Partner	Product	Target	Indications	Principal Investigator and Affiliation	Clinical Trial Status	Date	Clinical Trial Number
Legend Biotech	JNJ	CAR-T	BCMA	R/R MM	Saijuan Chen (Ruijin Hospital Affiliated with Shanghai Jiaotong University Medical College)	Phase II	2018-8-13	CTR20181007
Carsgen Therapeutics	None	CAR-T	BCMA	R/R MM	Wenming Chen (Beijing Chao-yang Hospital, Capital Medical University); Chengcheng Fu (The First Affiliated Hospital of Soochow University)	Phase I	2019-6-6	CTR20190955
Hrain Biotech	None	CAR-T	BCMA	R/R MM	Weijun Fu (Shanghai Changzheng Hospital)	Phase I	2019-6-13	CTR20191141
IASO Biotherapeutics/ Innovent Biologics	None	CAR-T	BCMA	R/R MM	Chunrui Li (Tongji Hospital, Huazhong University of Science and Technology)	Phase I	2020-1-14	CTR20192510

- Note:*
- (1) Pipeline information as of July 31, 2020; for clinical-stage candidates, date refers to CDE initial public date (首次公示信息日期). The partner refers to any licensing partners, either in-license or out-license, regarding the corresponding CAR-T product.
 - (2) The information of principal investigator and affiliation is summarized from CDE registration information and may change in the clinical trial operation.
 - (3) In addition to the foregoing, there are some BCMA-targeted CAR-T products currently in the pre-clinical phase of development, including the Company's JWCAR129.

Source: CDE, Frost & Sullivan Analysis

Competitive Landscape of IIT with CAR-T in China

The following table set forth the top hospitals conducting hospital sponsored CAR-T trials. Although healthcare institutions initiate numerous CAR-T trials outside the IND pathway, it should be noted that IIT data under such circumstance is not directly eligible for the preparation and submission of an NDA. Currently, none of the ongoing CAR-T cell therapy IND-based clinical trials are initiated by healthcare institutions, and thus hospitals are not comparable competitors.

Hospital	Number of IIT Trials Registered	Number of CD19 CAR-T Related Trials	Number of BCMA CAR-T Related Trials
Chinese PLA General Hospital	13	8	1
The First Affiliated Hospital of Soochow University	9	6	3
Hebei Yanda Ludaopei Hospital.	9	8	2
Henan Cancer Hospital	8	5	2
Southwest Hospital, China.	7	1	1
The First Affiliated Hospital with Nanjing Medical University	6	1	1
Zhujiang Hospital	6	2	0
Second Affiliated Hospital, School of Medicine, Zhejiang University.	5	1	0
Institute of Hematology & Blood Diseases Hospital.	5	3	1
Shenzhen Second People's Hospital.	5	3	1

- Note:*
- (1) The top hospitals conducting hospital sponsored trials are determined by ranking the number of the IIT trials being conducted in each hospital disclosed at clinicaltrial.gov website, with the top 10 selected and presented.
 - (2) These IIT trials are purely for clinical trial purposes and not for commercial purposes.

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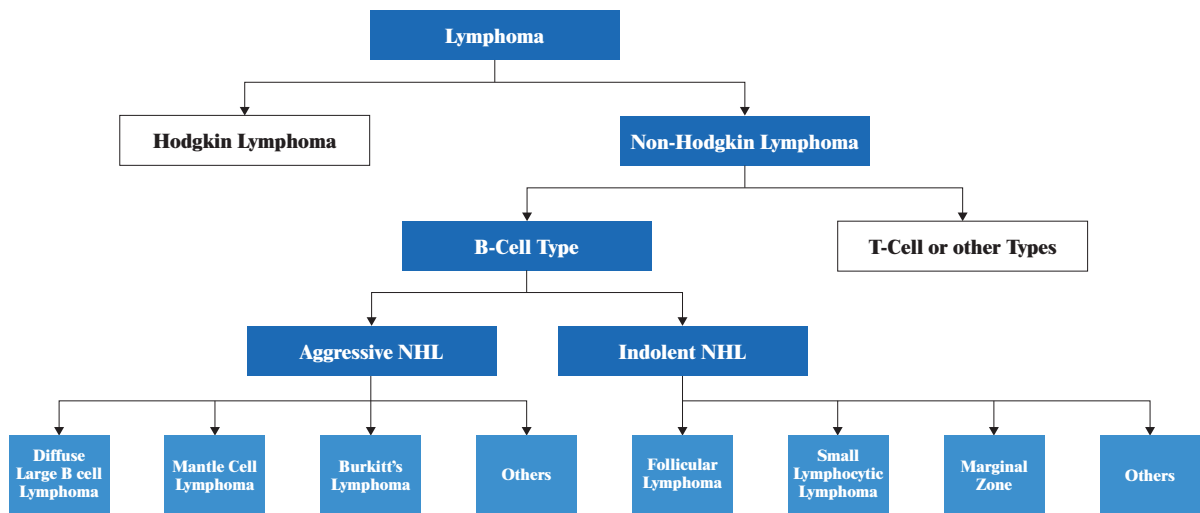
OVERVIEW OF THERAPEUTIC AREAS OF INTEREST

Lymphomas

Overview

Lymphomas are hematologic cancers involving lymphocytes of the immune system. They can be broadly categorized into non-Hodgkin's lymphomas (NHL), and Hodgkin's lymphoma (HL). NHL consists of a heterogeneous group of malignancies arising from lymphoid tissues, and accounts for around 90% of all lymphomas.

Depending on the origin of the cancer cells, NHL can be characterized as either B cell, T-cell or other types of lymphomas. B cell lymphomas account for approximately 85% of all NHL subtypes and consist of various distinct diseases involving B cells at different stages of maturation or differentiation. B cell lymphomas can also be categorized into aggressive NHL, such as Diffuse Large B Cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL), and Burkitt's Lymphoma (BL), and indolent NHL, such as Small Lymphocytic Lymphoma (SLL), Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL). The following diagram illustrates the categorization of different types of lymphomas.

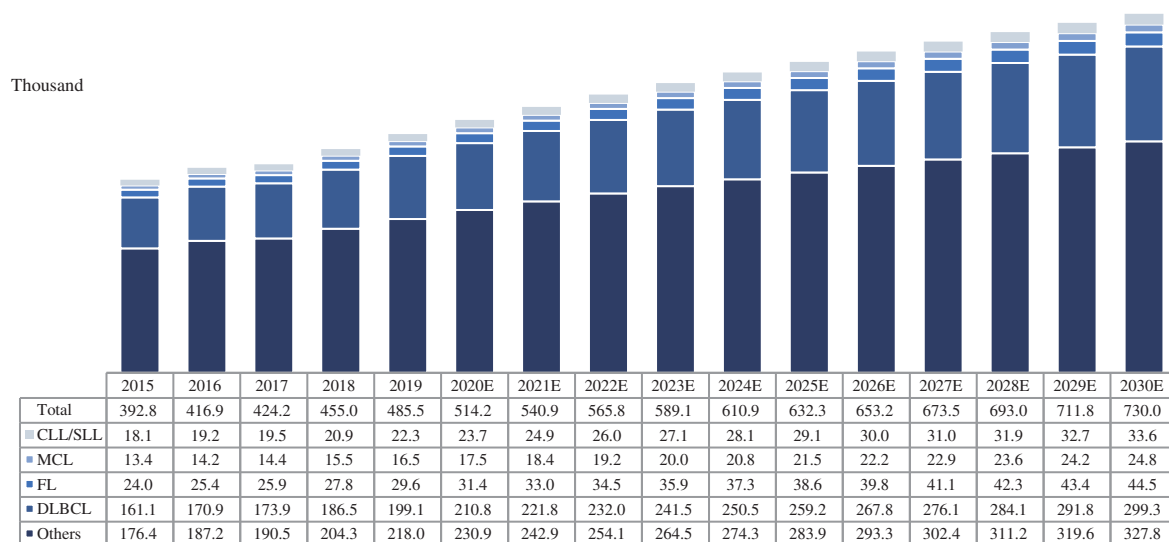


Source: *Journal of Diagnostics Concepts & Practice, Frost & Sullivan Analysis*

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In China, NHL prevalence reached 485.5 thousand in 2019 and is expected to reach approximately 610.9 thousand in 2024, representing a CAGR of 4.7% from 2019, and approximately 730.0 thousand in 2030, representing a CAGR of 3.0% from 2024. The following chart shows the historical and expected NHL prevalence in China by the subtypes:

Prevalence of China NHL Subtype, 2015-2030E



Note: CLL and SLL are the different forms of the same disease.

Source: NCCR, Frost & Sullivan Analysis

Additionally, new cases of NHL in China reached 90.3 thousand in 2019, and is expected to increase to approximately 101.8 thousand in 2024, representing a CAGR of 2.4% from 2019, and to approximately 115.9 thousand in 2030 at a CAGR of 2.2% from 2024. In 2019, the addressable market for 3L DLBCL, 3L FL and 3L MCL in China was estimated to be approximately 28.7 thousand, 5.2 thousand and 3.4 thousand patients, respectively, after taking into account the effectiveness of prior lines of treatment in China.

Treatment Paradigm, Limitations and Unmet Medical Needs

Currently, as there is no cure, the primary treatment goal for NHL is to induce and prolong remission. The primary treatment options for NHL in China vary by specific patient conditions and different subtypes of NHL, but generally comprise a monoclonal antibody (rituximab) in combination with chemotherapy. The following tables illustrate the current treatment paradigms and their corresponding features for DLBCL, FL, MCL and CLL in China.

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Treatment paradigm for DLBCL in China:

Therapy Regimen	Drug Categories	Recommended Drugs & Therapies	Features
1 st Line	Monoclonal antibody + Chemotherapy	R-CHOP, R-miniCHOP, R-CHOEP, R-DAEPOCH	<ul style="list-style-type: none"> Rituximab in combination with traditional chemotherapy is currently the major choice covering all lines of DLBCL treatment. Emerging therapies such as BTK inhibitors ibrutinib is also mentioned with a lower evidence level of recommendation to treat non-GCB subtype of R/R DLBCL patients. However, so far, ibrutinib has not been approved for DLBCL worldwide.
2 nd Line	Monoclonal antibody + Chemotherapy	R-DHAP, R-ICE, R-GDP, R-ESHAP, R-GD, R-DAEPOCH, R-GemOx, R-MINE	
	Small molecule targeted therapy	Ibrutinib (BTK inhibitor)	
3 rd Line	Monoclonal antibody + Chemotherapy	R-DHAP, R-ICE, R-GDP, R-ESHAP, R-DAEPOCH, R-GemOx, R-MINE	
	Small molecule targeted therapy	Ibrutinib (BTK inhibitor)	
	Monoclonal antibody + Small molecule targeted therapy	R2	

Abbreviations
<p>R-CHOP(rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); R-CHOEP(rituximab, cyclophosphamide, doxorubicin, vincristine ,etoposide, prednisone); R-DAEPOCH(rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin); R-miniCHOP(rituximab, lower dosage of CHOP) ; R-DHAP(rituximab, dexamethasone, cisplatin, cytarabine); R-ESHAP(rituximab, etoposide, methylprednisolone, cytarabine, cisplatin);</p>
<p>R-GemOx(rituximab, gemcitabine, oxalipatin); RICE(rituximab, ifosfamide, carboplatin, etoposide); RMINE(rituximab, mesna, ifosfamide, mitoxantrone, etoposide);R²(rituximab, lenalidomide); R-GD(rituximab, gemcitabine, dexamethasone); R2 (rituximab, revlimid) R-GDP(rituximab, gemcitabine, dexamethasone, cisplatin);</p>

Source: CSCO, Frost & Sullivan Analysis

Treatment paradigm for FL in China:

Therapy Regimen	Drug Categories	Recommended Drugs & Therapies	Features
1 st Line	Monoclonal antibody	Rituximab, Obinutuzumab	<ul style="list-style-type: none"> Rituximab in combination with traditional chemotherapy is currently the major choice covering all lines of FL treatment. Since FL is likely to transform into DLBCL when relapse occurs, so the second line FL treatment regimen could refer to the corresponding regimen of DLBCL. Emerging therapies such as some PI3K inhibitors are also mentioned in the guidelines for R/R FL treatment, but both of them has low accessibility because they are not marketed in China. Since FL is currently incurable, all treatment regimens will fail ultimately due to drug resistance and lead to relapse.
	Chemotherapy	Chlorambucil, Cyclophosphamide	
	Monoclonal antibody + Chemotherapy	R-CHOP, R-CVP, R-Bendamustine, R-Alkylating agent	
	Monoclonal antibody + Small molecule targeted therapy	R-Lenalidomide	
2 nd Line*	Monoclonal antibody	Rituximab	
	Chemotherapy	Chlorambucil, Cyclophosphamide	
	Monoclonal antibody + Chemotherapy	R-CHOP, R-CVP, R-Bendamustine, Alkylating agent - Rituximab	
	Monoclonal antibody + Small molecule targeted therapy	R-Lenalidomide	
	Small molecule targeted therapy	Idelalisib, Copanlisib (PI3K inhibitors)	

* The second line therapy of FL can also refer to the second line therapy regimen of DLBCL.

Source: CSCO, Frost & Sullivan Analysis

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Treatment paradigm for MCL in China:

Therapy Regimen	Drug Categories	Recommended Drugs & Therapies	Features
1 st Line	Monoclonal antibody	Rituximab	<ul style="list-style-type: none"> Rituximab in combination with traditional chemotherapy is currently the major choice covering all lines of MCL treatment. BTK inhibitor Ibrutinib has been approved for MCL treatment in late stage is recommended in the guidelines with a high level. Since MCL is currently incurable, all treatment regimens will fail ultimately due to drug resistance and lead to relapse.
	Monoclonal antibody + Chemotherapy	R-CHOP, R-DHAP, R-HyperCAVD, R-Bendamustine, VR-CAP, RBAC	
	Monoclonal antibody + Small molecule targeted therapy	R-Lenalidomide	
2 nd Line	Small molecule targeted therapy	Lenalidomide, Bortezomib, Ibrutinib (BTK inhibitor)	
	Monoclonal antibody + Small molecule targeted therapy	R-Lenalidomide, R-Bortezomib, R-Ibrutinib, R-Ibrutinib-Lenalidomide	
	Monoclonal antibody + Chemotherapy	R-Bendamustine	
	Monoclonal antibody + Chemotherapy + Small molecule targeted therapy	R-Bendamustine-Bortezomib	

Source: CSCO, Frost & Sullivan Analysis

Treatment paradigm for CLL in China:

Therapy Regimen	Drug Categories	Recommended Drugs & Therapies	Features
1 st Line	Chemotherapy + Monoclonal antibody	Chlorambucil-R, Bendamustine-R, Methylprednisolone-R, FCR, Fludarabine-R	<ul style="list-style-type: none"> Currently, chemotherapy in combination with monoclonal antibody, as well as small molecule targeted therapy (BTK inhibitor) are primarily recommended for CLL treatment. Even though BTK inhibitor has brought new front-line treatment options for CLL patients, some patients will ultimately develop drug resistance and lead to relapse.
	Small molecule targeted therapy	Ibrutinib (BTK inhibitor)	
	Monoclonal antibody	Rituximab	
	Chemotherapy	Bendamustine, Chlorambucil	
2 nd Line	Small molecule targeted therapy	Ibrutinib (BTK inhibitor), Lenalidomide	
	Chemotherapy + Monoclonal antibody	Methylprednisolone-R, Chlorambucil-R, Bendamustine-R, FCR, Cyclophosphamide-R	
	Small molecule targeted therapy + Monoclonal antibody	Lenalidomide-R	

Source: CSCO, Frost & Sullivan Analysis

For DLBCL, FL, MCL and CLL, current treatment options generally have limited efficacy and rarely lead to a cure in patients. While emerging targeted drugs, such as BTK inhibitors, provide wider treatment options for MCL and CLL patients and potentially for patients of other NHL subtypes in the future, typically they eventually lead to drug resistance, which is a common drawback of targeted therapies. About 50% of NHL patients will eventually experience disease progression due to drug resistance, indicating a need for new treatment options. In particular,

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around 15% of DLBCL (the most common subtype of NHL) patients are characterized as primary refractory towards first-line R-CHOP therapy. For these refractory patients, treatments options with new modalities are needed.

In addition, NHL patients suffer from long treatment cycles (typically 6-8 cycles) and extended hospital stays, which are intended to facilitate monitoring by physicians. The treatment period may last even longer if the initial treatment combination fails to work and a switch to a different treatment is required. Another limitation of current treatments is the severe systemic adverse effects that result from off-target toxicity, potentially leading to side effects such as vomiting, nausea and hair loss. All of these factors may exert a heavy economic and physiological burden on patients, creating an urgent need for new treatment methods that have a better safety and efficacy profile.

For NHL, the existing treatment options, including monoclonal antibodies and small molecule targeted drugs, provide less costly treatment options and are currently more standardized treatment recommended than CAR-T therapies. Some of these antibodies or small molecule targeted drugs have entered the NRDL, such as rituximab, lenalidomide, bortezomib and ibrutinib. In addition, there are drugs of other modalities, including monoclonal antibodies and bi-specific antibodies being developed for the treatment of NHL. These therapies, even though are still under development, may have potentially comparable efficacy and safety profile and are less costly when compared to CAR-T therapies. However, even with these emerging therapies, many patients fail to demonstrate response or are more susceptible to relapse due to drug resistance, while CAR-T therapies may potentially provide an effective treatment option for them.

Acute Lymphocytic Leukemia

Overview

Leukemia is a general name given to a group of cancers that develop in the bone marrow. Most cases of leukemia originate in developing white blood cells, but some leukemias are known to start in other blood cell types. There are several types of leukemia, which can be divided into four main categories based on disease progress (chronic or acute) and location (lymphocytic or myeloid) of the cancer. Acute lymphocytic leukemia (ALL) is characterized by a rapid increase in the number of immature blood cells, in which the DNA of the blood cells is damaged, and never matures to function as normal cells. ALL is more common in children and youth, also known as pediatric ALL (p-ALL), than in adults.

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The prevalence of ALL in China grew to 142.6 thousand in 2019, and is expected to grow to approximately 149.0 thousand in 2024 representing a CAGR of 0.9% from 2019, and to approximately 156.8 thousand in 2030 representing a CAGR of 0.8% from 2024. In China, new cases of ALL increased to 12.6 thousand in 2019, and is expected to grow to approximately 13.6 thousand in 2024 representing a CAGR of 1.5% from 2019, and to approximately 14.7 thousand in 2030 representing a CAGR of 1.4% from 2024. p-ALL accounts for approximately 85% of ALL cases in China.

Treatment Paradigm, Limitations and Unmet Medical Needs

Currently, chemotherapies are the most widely used therapies for p-ALL in different stages of the therapy. Even though some small-molecule targeted therapies such as TKI has been adopted to treat certain subtypes of p-ALL, these patients will eventually develop drug resistance. In addition, for the relapsed p-ALL patients, available treatment options are limited, demonstrating further unmet clinical needs.

Multiple Myeloma

Overview

Multiple Myeloma (MM) is a cancer of the plasma cells in the bone marrow. Plasma cells are antibody-producing white blood cells that are critical to the immune system. Myeloma begins when healthy plasma cells become cancerous and grow out of control. MM often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. Multiple myeloma can be subdivided into hyperdiploid MM (h-MM) and non-hyperdiploid MM (nh-MM) based on their aneuploidy status, both of which have different prognosis and survival outcomes. Patients with h-MM tend to have a better prognosis than those with nh-MM. Symptoms of MM include bone pain, low blood count, high blood levels of calcium and symptoms relating to the nervous system.

The prevalence of MM in China grew to 101.9 thousand in 2019, and is expected to grow to approximately 167.2 thousand in 2024 representing a CAGR of 10.4% from 2019, and to approximately 266.3 thousand in 2030 representing a CAGR of 8.1% from 2024. In China, new cases of MM increased to 20.7 thousand in 2019, and is expected to grow to approximately 23.8 thousand in 2024 representing a CAGR of 2.9% from 2019, and to approximately 27.7 thousand in 2030 representing a CAGR of 2.5% from 2024.

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Treatment Paradigm, Limitations and Unmet Medical Needs

Currently, no antibody drugs are recommended as a first-line therapy for MM treatment in China. However, small molecule targeted drugs have been used in different combinations and with chemotherapy to treat patients. The following table illustrates the current treatment paradigm for MM in China.

Therapy Regimen	Drug Categories	Recommended Drugs & Therapies	Features
1st Line	Small molecule targeted therapy	BD; Rd	<ul style="list-style-type: none"> Small molecule targeted drugs such as bortezomib and lenalidomide are adopted for MM patients both at their initial and recurrent occurrence. The CD38 targeting monoclonal antibody daratumumab has been recommended in treatment of r/r MM patients but has not been approved as a first-line therapy. CAR-T trials are considered as a prioritized option for suitable relapsed/refractory patients.
	Small molecule targeted therapy + Chemotherapy	RVd; PAD; BCD; BTd; TAD; TCD; RCD; VMP; MPT; MPR	
2nd Line	Monoclonal antibody + Small molecule targeted therapy	DRD; DVD; DID	
	Small molecule targeted therapy	IRd	
	Small molecule targeted therapy + Chemotherapy	DCEP ± B; DT-PACE ± V	
	Cellular immunotherapy	CAR-T clinical trail	

Abbreviations		
BD (bortezomib, dexamethasone); Rd (lenalidomide, dexamethasone); RVd (lenalidomide, bortezomib, dexamethasone); PAD (bortezomib, doxorubicin, dexamethasone); BCD (bortezomib, cyclophosphamide, dexamethasone); BTd (bortezomib, thalidomide, dexamethasone);	TAD (thalidomide, dexamethasone, doxorubicin); IRd (Ixazomib, lenalidomide, dexamethasone); DRD (daratumumab, lenalidomide, dexamethasone); DVD (daratumumab, bortezomib, dexamethasone); DID (daratumumab, Ixazomib, dexamethasone); DCEP ± B (dexamethasone, thalidomide, etoposide, cisplatin ± bortezomib);	DT-PACE ± V (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide ± velcade) TCD (thalidomide, cyclophosphamide, doxorubicin); RCD (lenalidomide, cyclophosphamide, doxorubicin); VMP (prednisolone acetate, melphalan, bortezomib); MPT (prednisolone acetate, melphalan, thalidomide); MPR (prednisolone acetate, melphalan, lenalidomide);

Source: Chinese guidelines for diagnosis and treatment of multiple myeloma (2020), Frost & Sullivan Analysis

Even though efforts have been made to treat MM, the current treatment paradigm of MM in China presents various challenges and limitations. First, MM remains incurable and is accompanied by various serious complications as the disease progresses, which also makes the disease difficult to manage. Second, current primary treatment options generally have limited efficacy due to drug resistance leading to high relapse rates. Current treatments also often lead to severe side effects and require long treatment cycles. Finally, the aging population in China is leading to more patient fragility, which makes conventional treatments more dangerous.

Currently in the MM treatment paradigm, small molecule targeted therapies and monoclonal antibodies have dominated the treatment options as they are more standardized and less costly option compared to CAR-T therapies. Some of these small molecule targeted drugs have entered the NRDL, such as lenalidomide, bortezomib and ixazomib. Additionally, more small molecule targeted drugs and monoclonal antibodies are undergoing clinical trials, which may have potentially comparable efficacy and safety profile to benefit more patients with hematological cancer. However, even with improved treatments, outcomes are poor for those with relapsed and refractory disease, highlighting the need for new treatments.

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Hepatocellular Carcinoma

Overview

Liver cancer is the fourth most common cancer and the second leading cause of death from cancer in China in 2019. Hepatocellular carcinoma (HCC) is the predominant type of liver cancer, accounting for approximately 90% of all liver cancer cases, and is one of the most lethal cancers.

In China, new cases of HCC reached 369.4 thousand in 2019, and is expected to grow to approximately 416.5 thousand in 2024 representing a CAGR of 2.4% from 2019, and to approximately 473.4 thousand in 2030 representing a CAGR of 2.2% from 2024. The prevalence of HCC in China increased to 551.3 thousand in 2019, and is expected to grow to approximately 810.7 thousand in 2024 representing a CAGR of 8.0% from 2019, and to approximately 1.2 million in 2030 representing a CAGR of 6.8% from 2024.

Treatment Paradigm, Limitations and Unmet Medical Needs

HCC is often associated with hepatitis B, hepatitis C, cirrhosis, and non-alcoholic steatohepatitis, or NASH. Current treatments for early-stage HCC in China are limited to resection, radiation, ablation, radioimmunotherapy, which can be used in combination with transarterial chemoembolization (TACE), immunomodulators, chemotherapy or targeted therapies to achieve a better outcome. Late stage HCC treatment options primarily include small molecule targeted therapies, checkpoint inhibitors (with or without monoclonal antibodies) and chemotherapy. All of these therapeutic options have marginal survival benefits in the majority of treated patients and efficacy is generally limited. For example, the medium progression free survival is lower than 10 months for all major treatment options in China, and the medium overall survival is only around one year. For many patients the only treatment offered is palliative. Currently, there is only one CAR-T therapy, a Glypican 3 (GPC3) targeted therapy, under development for HCC in China. Such data indicates a limitation of current HCC treatment options and an urgent need for more effective and novel therapeutic options to improve current poor outcomes.

Potential Competitive Advantages of AFP and GPC3 Targeted CAR-T Therapies in HCC

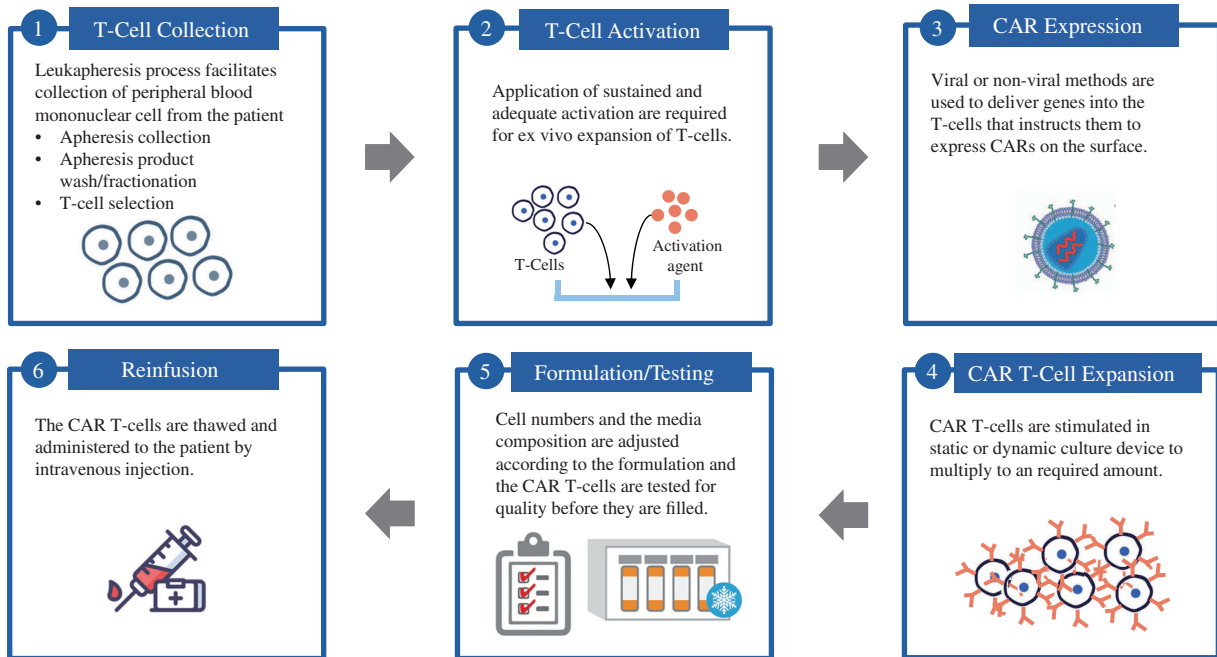
Approximately 70% of patients with HCC globally are estimated to have high serum levels of AFP, a protein which is normally present in high levels in fetal blood but drops to low levels shortly after birth. Elevated levels of AFP can signal that liver cancer is present, although they may also be due to other causes, such as liver disease or other cancers, and many patients with early-stage liver cancer have normal serum levels of AFP. AFP screening can be used to help guide treatment. Treatment efficacy is generally associated with a decline in AFP, and screening for the protein can also be used to assess whether a patient has had tumor recurrence. Another protein that is overexpressed in HCC is GPC3, which is a cell surface protein of the heparin sulfate proteoglycan family. GPC3 is expressed in an estimated 80% of HCC in China. GPC3 also has limited expression in adult tissues, including ovary, mammary gland, mesothelium, lung and kidney. This demonstrates a potential competitive advantage of AFP and GPC3 targeted CAR-T therapies in treating HCC.

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MANUFACTURING, PROCESSING AND DELIVERING TO PATIENTS

Manufacturing Processes and Techniques

The following diagram provides an overview of the manufacturing process for a CAR-T therapy for an individual patient:



Source: Frost & Sullivan Analysis

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Challenges of CAR-T Manufacturing

Due to the complexity and personalized nature of the CAR-T manufacturing process, it typically involves numerous challenges, including:

- *Difficulties in T-cell harvesting.* It is difficult to collect a sufficient quantity of blood from very ill patients. In addition, it can be difficult to collect a sufficient number of T-cells from the blood of patients who have received chemotherapy, as leukopenia is a common side effect of chemotherapy.
- *Difficulties in the transport of harvested cells.* There are potential risks of broad changes occurring in cell transcriptomes after freezing and thawing.
- *Difficulties in the activation and expansion process.* Sustained signaling can cause cell exhaustion, leading to a loss of proliferative capacity and cytotoxicity. Moreover, the process of removing the beads can cause a loss of product if T-cells fail to dissociate or are damaged by shear forces due to binding.
- *Difficulties in CAR gene transfer and editing.* Viral vectors insert transgenes randomly into the genome, causing a risk of gene silencing or insertional oncogenesis. Moreover, heterogeneous copy numbers may result in T-cell populations with highly variable cytotoxic abilities due to altered levels of surface expression.

Manufacturing Success Rate

Manufacturing success rate is defined as the percentage of conforming, on-specification CAR-T products qualified to be delivered to patients of all manufactured products. On-specification CAR-T products refer to CAR-T products that meet the pre-determined process and product requirements, which are then eligible to be released and administered to patients. Such success rate is a reflection of good CMC practices and shows a company's ability to ensure production of a safe, high quality product. The overall manufacturing success rate of Yescarta, Kymriah and Tecartus during their respective registrational clinical trials were 99%, 91%-93%, and 96%, respectively. In comparison, the manufacturing success rate of relma-cel during our DLBCL registrational clinical trial was 100%.

Pricing of Commercialized CAR-T Products

The price for the approved CAR-T therapies is US\$373,000 for both Yescarta and Kymriah to treat r/r LBCL, as well as for Tecartus to treat MCL in the U.S.. Additionally, the price for Kymriah to treat ALL is US\$475,000 in the U.S.

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REPORT COMMISSIONED BY FROST AND SULLIVAN

In connection with the Global Offering, we have engaged Frost & Sullivan to conduct a detailed analysis and to prepare an industry report on the worldwide and China oncology drug markets. Frost & Sullivan is an independent global market research and consulting company founded in 1961 and is based in the U.S. Services provided by Frost & Sullivan include market assessments, competitive benchmarking, and strategic and market planning for a variety of industries. We have included certain information from the Frost & Sullivan Report in this prospectus because we believe such information facilitates an understanding of the oncology drug market for potential investors. Frost & Sullivan prepared its report based on its in-house database, independent third-party reports and publicly available data from reputable industry organizations. Where necessary, Frost & Sullivan contacts companies operating in the industry to gather and synthesize information in relation to the market, prices and other relevant information. Frost & Sullivan believes that the basic assumptions used in preparing the Frost & Sullivan Report, including those used to make future projections, are factual, correct and not misleading. Frost & Sullivan has independently analyzed the information, but the accuracy of the conclusions of its review largely relies on the accuracy of the information collected. Frost & Sullivan research may be affected by the accuracy of these assumptions and the choice of these primary and secondary sources.

We have agreed to pay Frost & Sullivan a fee of RMB600,000 for the preparation of the Frost & Sullivan Report. The payment of such amount was not contingent upon our successful listing or on the content of the Frost & Sullivan Report. Except for the Frost & Sullivan Report, we did not commission any other industry report in connection with the Global Offering. We confirm that after taking reasonable care, there has been no adverse change in the market information since the date of the report prepared by Frost & Sullivan which may qualify, contradict or have an impact on the information set forth in this section in any material respect.

Frost & Sullivan adopted the following primary assumptions while making projections on the macroeconomic environment, the overall pharmaceutical market and various segment markets in China.

- (i) the social, economic and political environments of the PRC will remain stable during the forecast period, which will ensure a sustainable and steady development of the PRC healthcare industry;
- (ii) the PRC healthcare market will grow as expected due to rising healthcare demand and supply; and
- (iii) the PRC government will continue to support healthcare reform.