Certain information and statistics set out in this section have been extracted from various official government publications, available sources from **[REDACTED]** *data providers and a report prepared by an independent third party source, Frost & Sullivan, which was commissioned by us. The information from official government sources has not been independently verified by our Company, the Joint Sponsors, the* **[REDACTED]**, *the* **[REDACTED]**, *the* **[REDACTED]**, *the* **[REDACTED]**, *the* **[REDACTED]**, *any of the* **[REDACTED]**, *any of our or their respective directors, officers, employees, agents or advisers or any other person or party involved in the* **[REDACTED]**, *and no representation is given as to its accuracy.*

SOURCE OF INFORMATION

We engaged Frost & Sullivan, a market research consultant, to prepare the Frost & Sullivan Report for use in this document. The information from Frost & Sullivan disclosed in this document is extracted from the Frost & Sullivan Report and is disclosed with the consent of Frost & Sullivan. In preparing the Frost & Sullivan Report, Frost & Sullivan collected and reviewed publicly available data such as government-derived information, annual reports, trade and medical journals, industry reports and other available information gathered by not-for-profit organizations as well as market data collected by conducting interviews with industry key opinion leaders.

Frost & Sullivan has exercised due care in collecting and reviewing the information so collected and independently analyzed the information, but the accuracy of the conclusions of its review largely relies on the accuracy of the information collected. We agreed to pay Frost & Sullivan a fee of RMB700,000 for the preparation and update of the Frost & Sullivan Report, which is not contingent on the **[REDACTED]** proceeding.

OVERVIEW OF IMMUNO-ONCOLOGY MARKET

Immuno-oncology has emerged as a revolutionary class of cancer treatment that aims to eradicate cancer cells through the stimulation and activation of patients' own immune systems. Major types of immuno-oncology therapy include immune checkpoint inhibitors, cell therapies, and therapeutic cancer vaccines. Immune checkpoint inhibitors, in particular, have been one of the most successful cancer therapies in the past decade, demonstrated by the unprecedented indication and market expansion of PD-1/PD-L1 inhibitors since their first approval in 2014. So far, PD-1/PD-L1 inhibitors have been approved for the treatment of a broad range of cancers worldwide, and their global sales reached US$40.2 billion in 2022.

Currently approved immuno-oncology therapies primarily focus on the stimulation of adaptive immune responses through T-cell activation. However, those T-cell based immunotherapies face certain limitations. PD-1/PD-L1 inhibitors, for example, only produce meaningful responses in 10% to 25% of patients across almost all major cancer indications when used as monotherapy. The response rates to immunotherapies targeting adaptive immune checkpoints are particularly low in "cold tumors" (tumors that lack T-cell infiltration), or in a non-T cell-inflamed immune-suppressive tumor microenvironment (TME), suggesting an urgent need for immunotherapies to improve treatment outcomes. Recent studies have revealed that the limitations of current immunotherapies could be overcome by leveraging the power of innate immunity and the synergistic effects between the innate and adaptive immunities. To date there has not been any approved innate immune checkpoint-targeted therapy worldwide, indicating a vast untapped global market.

Overview of Innate and Adaptive Immune Systems

Generally, the human immune system can be divided into the innate immune system and the adaptive immune system. The innate immune system forms the body's first line of defense, identifies foreign substances and elicits an immediate and non-specific immune response. Major innate immune cells include macrophages, natural killer (NK) cells and dendritic cells (DCs). The adaptive immune system, including T cells and B cells, functions as the second line of defense that identifies and eliminates abnormal cells with specificity. The table below sets forth a comparison between critical adaptive and innate immune cells in the TME:

	Adaptive Immunity		Innate Immunity		
Activation Process	Antigen priming required		First line of defense, short response time, no need for antigen priming		
Key Immune Cell Type	T cell	B cell	Macrophage	NK cell	DC
Tumor Tissue Distribution[(1)]	10-30%	3%-40%	20-50%	5%-10%	3%-10%
Major Immune Checkpoints	PD-1/PD-L1, CTLA-4, LAG-3, TIM-3, TIGIT	CD40/CD40L, CD19, CD22	CD47/SIRPα, CD24/Siglec-10, PSGL-1, EP4	KIR family, CD94-NKG2A, CD24/Siglec-10, TIGIT, EP4	PD-1/PD-L1, CD47/SIRPα, EP4
Major Immune Functions	• T-cell mediated killing of tumor cell via exocytosis of cytotoxic granules (perforin, granzymes) and secretion of antitumor cytokines	• Antibody production • Cytokine secretion	• Macrophage-mediated phagocytosis • Attracting T cells to the tumor microenvironment (TME) • Antigen presentation • Trogocytosis	• NK cell-mediated cytolysis via the secretion of perforin and granzymes • Activating of T cells, macrophages and DCs through release of cytokines	• Attracting T cells to the TME • Antigen presentation

Note: The tumor tissue distribution is the proportion of certain immune cells in different tumor tissues.
Source: *Frost & Sullivan*

Compared with adaptive immune cells, innate immune cells are more extensively distributed in tumor tissues. In addition to providing the first-line defense, innate immune cells play a critical role in promoting the adaptive immune responses, thereby generating a more integrated and enhanced immune response. For instance, activated macrophages and DCs secrete cytokines and chemokines, such as CXCL9 and CXCL10, which can recruit T cells to the TME, thus transforming "cold tumors" to "hot tumors" (tumors infiltrated by T cells and responsive to immunotherapy). Macrophages and DCs may further promote T-cell response through antigen presentation. Activated NK cells can enhance T-cell response by promoting T-cell differentiation and activation. Thus, the combination of therapies targeting innate immune checkpoints and therapies activating adaptive immunity has significant potential in overcoming the limitations faced by currently approved immunotherapies.

Overview and Limitations of Current Immuno-oncology Therapies

Currently approved immuno-oncology therapies primarily target T-cell immune checkpoints, such as PD-1/PD-L1, CTLA-4, and LAG-3. Although T-cell immune checkpoint inhibitors, such as PD-1/PD-L1 antibodies, are widely used in the clinic (including in the frontline treatment), their response rates remain low across almost all major cancer indications as shown in the table below.

Tumor Response Rate to PD-1/PD-L1 Inhibitor Monotherapy

	NSCLC	SCLC	CRC	GC	HNSCC	HCC	ESCC	BTC	RCC	OC	CC	UC	STS	DLBCL
PD-1	19-20%	12-19%	<10%	13-14%	13-16%	16-17%	19-20%	3-22%	22%	8-15%	14%	20-29%	5-18%	45%
PD-L1	14%	2-10%						5%		10%		13-24%		

Notes: (1) The response rates are based on the latest label from FDA and NMPA except for CRC, GC, SCLC, OC, BTC and STS, which are based on the published clinical results. (2) Only monotherapy clinical results are listed. (3) Results of adjuvant therapy are excluded. Results may vary from different cancer sub-types or clinical trials. (4) The clinical results listed are from general cancer population regardless of PD-L1 expression, except for the ORR of CC, which is restricted in PD-L1 positive population (combined positive score (CPS)≥1).

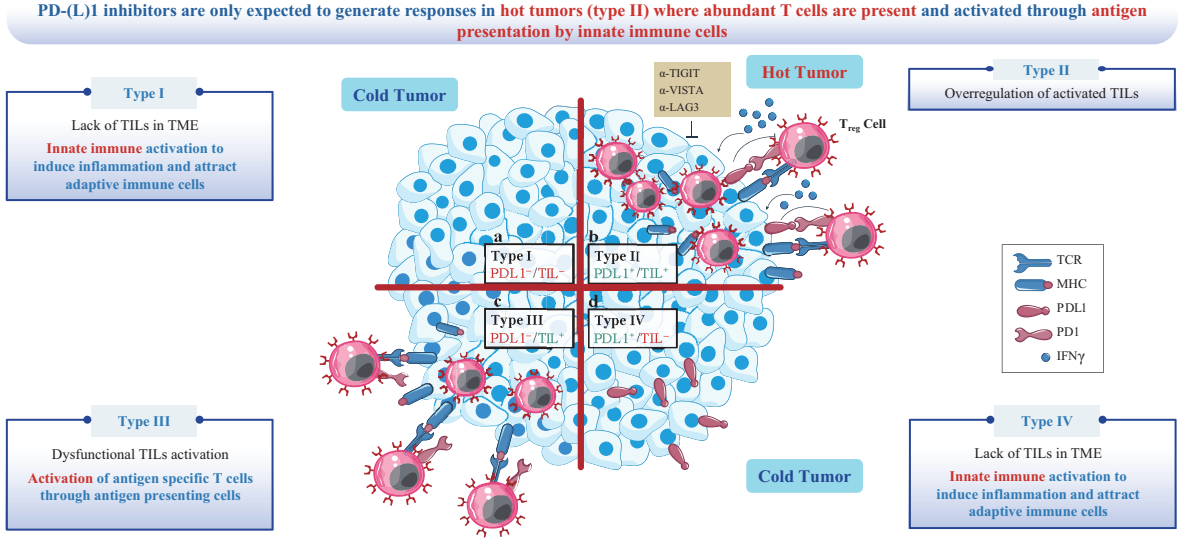
Definitions: NSCLC refers to non-small cell lung cancer; SCLC refers to small cell lung cancer; CRC refers to colorectal cancer; GC refers to gastric cancer; HNSCC refers to head and neck squamous cell carcinoma; HCC refers to hepatocellular carcinoma; ESCC refers to esophageal squamous cell carcinoma; BTC refers to biliary tract cancer; RCC refers to renal cell carcinoma; OC refers to ovarian cancer; CC refers to cervical cancer; UC refers to urothelial carcinoma; STS refers to soft-tissue sarcomas; DLBCL refers to diffuse large B-cell lymphoma.

Source: Frost & Sullivan

Other T-cell immunotherapies also face challenges in terms of safety and efficacy. Though treatment with chimeric antigen receptor (CAR)-T therapy produces remarkable and durable responses in some subsets of B-cell leukemia, lymphoma and multiple myeloma (MM), certain limitations still exist, including life-threatening cytokine release syndrome (CRS) and neurotoxicity, exceptionally high cost, and less desirable efficacy targeting solid tumors. Similarly, T-cell engagers, exemplified by CD3-based bispecific antibodies, also present worrying safety concerns, including severe CRS and "on-target, off-tumor" toxicity in healthy tissues. Up to date, intolerable toxicity of CAR-T therapy and CD3 bispecific antibodies have resulted in the termination or suspension of multiple clinical studies for numerous drug candidates worldwide, including Atara's ATA2271 (autologous mesothelin CAR-T), Amgen's AMG673 (CD3×CD33), AMG427 (CD3×FLT3) and AMG701 (CD3×BCMA), Regeneron's odronextamab (CD3×CD20), and Pfizer's elranatamab (CD3×BCMA). According to Frost & Sullivan, for the treatment of solid tumors, only one T-cell engager is currently being marketed, that is tebentafusp approved for the treatment of uveal melanoma (a rare disease), and there has been no CAR-T therapy approved for solid tumors anywhere in the world.

In recent years, research findings have highlighted the potential of innate immunity-targeted approach to overcome the limitations of T-cell based immunotherapies. Innate immune cells are widely distributed in tumor tissues, and once activated, they can directly combat cancer cells and elicit adaptive immune responses through crosstalk with T cells. For example, as detailed in "— Overview of Innate and Adaptive Immune Systems" above, macrophages can be activated by macrophage-targeted immunotherapies and further induce potent adaptive immunity. Since macrophages as a major type of antigen-presenting cell can release cytokines and chemokines to attract T cells, the activation of macrophages should enhance the abundance of T cells in the TME, turning "cold tumors" into "hot tumors." Other critical innate immune cells like NK cells and DCs can also promote T-cell immune responses through various mechanisms. The synergistic effects achieved by harnessing both innate and adaptive immunities shall maximize the effectiveness of immunotherapies and potentially achieve potent antitumor activity in "cold tumors."

The Responses of Hot Tumor and Different Types of Cold Tumors to PD-1/PD-L1 Inhibitors



Source: Frost & Sullivan, Literature Review

In addition, innate immunity-targeted molecules, if well-designed, could be safe and well tolerated in humans. Overall, novel drug candidates targeting innate immune checkpoints promise great clinical potential as immunotherapies and are expected to capture considerable market opportunities.

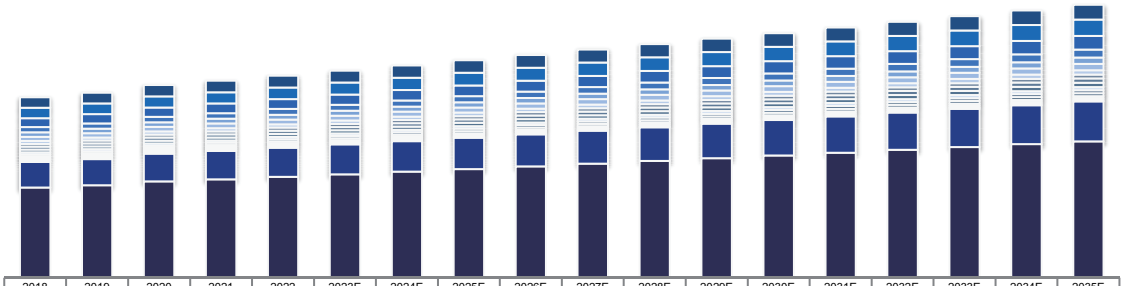
Global and China Immuno-oncology Therapy Market

Due to continued indication expansion, diverse combination strategies, and the emergence of new immunotherapeutic approaches, especially the development of immunotherapies targeting innate immune checkpoints, the addressable patient population and market size of immuno-oncology therapies are expected to rapidly increase in the near future.

Immuno-oncology therapies can bring clinical benefits to an increasing number of patients across almost all major cancer types around the world. The following tables provide the global and China's incidences of major cancer types for the periods indicated, respectively:

Global Incidence of Major Cancer Types, 2018–2035E

Thousands



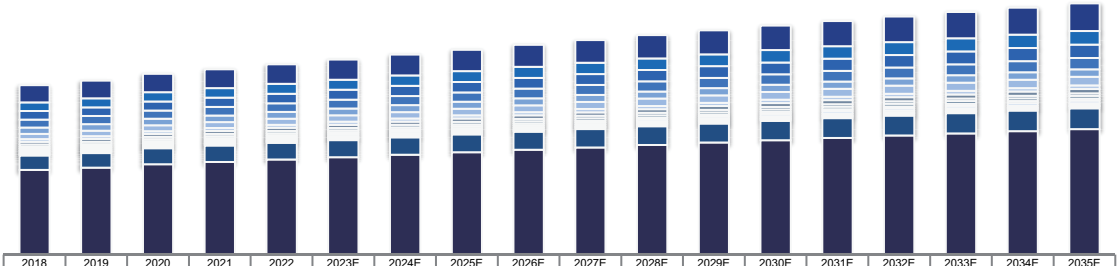
	2018	2019	2020	2021	2022	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E
Breast	2,089	2,134	2,261	2,301	2,348	2,395	2,442	2,489	2,536	2,584	2,631	2,678	2,726	2,773	2,820	2,866	2,911	2,957
Lung	2,094	2,153	2,207	2,266	2,330	2,396	2,463	2,530	2,599	2,669	2,740	2,812	2,885	2,958	3,033	3,106	3,180	3,254
Colorectum	1,801	1,849	1,881	1,928	1,981	2,035	2,090	2,146	2,203	2,261	2,321	2,381	2,441	2,503	2,566	2,628	2,691	2,754
Stomach	1,034	1,061	1,089	1,121	1,151	1,183	1,214	1,247	1,280	1,313	1,348	1,382	1,417	1,453	1,488	1,524	1,560	1,596
Head and Neck	888	909	932	952	973	995	1,017	1,039	1,061	1,083	1,106	1,128	1,150	1,173	1,195	1,217	1,239	1,260
Liver	841	862	906	930	953	976	1,000	1,024	1,049	1,074	1,099	1,124	1,150	1,175	1,201	1,227	1,253	1,279
Lymphoma	590	603	627	640	655	669	684	699	714	730	745	761	777	793	809	826	842	858
Cervical	570	580	604	616	626	637	647	658	668	678	688	698	708	718	728	738	747	756
Esophagus	572	588	604	622	638	655	672	689	707	725	743	761	779	797	815	834	852	870
Bladder	549	565	573	588	606	624	642	661	681	700	721	741	762	784	806	828	850	873
Leukaemia	437	446	475	483	493	503	513	523	533	544	555	565	576	587	599	610	621	633
Kidney	403	413	431	440	451	462	473	484	496	507	519	531	543	555	567	579	591	603
BTC	345	356	368	380	392	405	418	431	444	458	472	487	501	516	531	545	561	576
Ovary	295	302	314	320	326	333	340	346	353	360	366	373	380	387	393	400	407	413
MDS/CMML	274	280	286	292	298	304	311	317	324	331	338	345	351	359	366	373	380	387
STS	172	177	185	191	196	201	207	213	219	224	230	236	243	248	254	260	266	272
Others	5,126	5,252	5,549	5,669	5,819	5,970	6,124	6,281	6,440	6,603	6,768	6,936	7,106	7,279	7,455	7,631	7,809	7,987
Total	18,079	18,529	19,293	19,737	20,236	20,743	21,257	21,779	22,308	22,845	23,390	23,940	24,497	25,059	25,627	26,192	26,760	27,329

Definitions: BTC refers to biliary tract cancer; MDS refers to myelodysplastic syndrome; CMML refers to chronic myelomonocytic leukemia; STS refers to soft-tissue sarcomas

Source: Globocan, IARC, Frost & Sullivan analysis

China's Incidence of Major Cancer Types, 2018–2035E

Thousands



	2018	2019	2020	2021	2022	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E
Lung	868	895	924	954	984	1,015	1,047	1,078	1,110	1,142	1,174	1,206	1,238	1,269	1,301	1,331	1,361	1,390
Stomach	442	456	470	484	499	513	528	544	559	574	589	605	620	634	649	663	677	690
Colorectum	427	440	453	468	482	497	512	527	542	558	573	588	604	619	634	649	663	677
Liver	400	410	421	431	442	452	463	473	484	494	505	515	525	534	544	553	562	571
Breast	321	326	332	336	341	346	350	354	358	361	365	368	371	373	375	377	378	380
Esophagus	272	280	290	299	309	318	328	338	348	358	368	377	387	397	406	415	424	433
Head and neck	137	140	143	146	149	152	155	158	160	163	165	168	170	172	174	176	178	180
BTC	136	141	145	150	155	160	165	170	175	181	186	192	197	202	208	213	218	223
Cervical	116	117	118	119	120	121	122	123	124	124	125	125	125	126	126	126	126	126
Lymphoma	93	95	100	102	105	107	110	112	115	117	120	122	125	127	129	132	134	136
Leukaemia	83	84	85	87	88	89	91	92	94	95	96	98	99	100	101	103	104	105
Bladder	82	85	86	89	92	95	98	101	104	107	111	114	117	121	124	127	131	134
Kidney	70	72	74	75	77	79	81	83	85	86	88	90	92	94	95	97	98	100
Ovary	53	54	55	56	57	58	59	59	60	61	61	62	62	63	63	64	64	64
STS	41	43	45	46	47	49	50	52	53	55	56	58	60	61	63	64	66	67
MDS/CMML	22	22	23	23	23	24	24	25	25	26	26	26	27	27	28	28	29	29
Others	722	739	806	823	840	857	873	890	907	923	939	955	971	987	1002	1017	1031	1045
Total	4,285	4,400	4,569	4,688	4,810	4,932	5,055	5,179	5,302	5,425	5,548	5,669	5,789	5,907	6,022	6,135	6,245	6,351

Definitions: BTC refers to biliary tract cancer; MDS refers to myelodysplastic syndrome; CMML refers to chronic myelomonocytic leukemia; STS refers to soft-tissue sarcomas

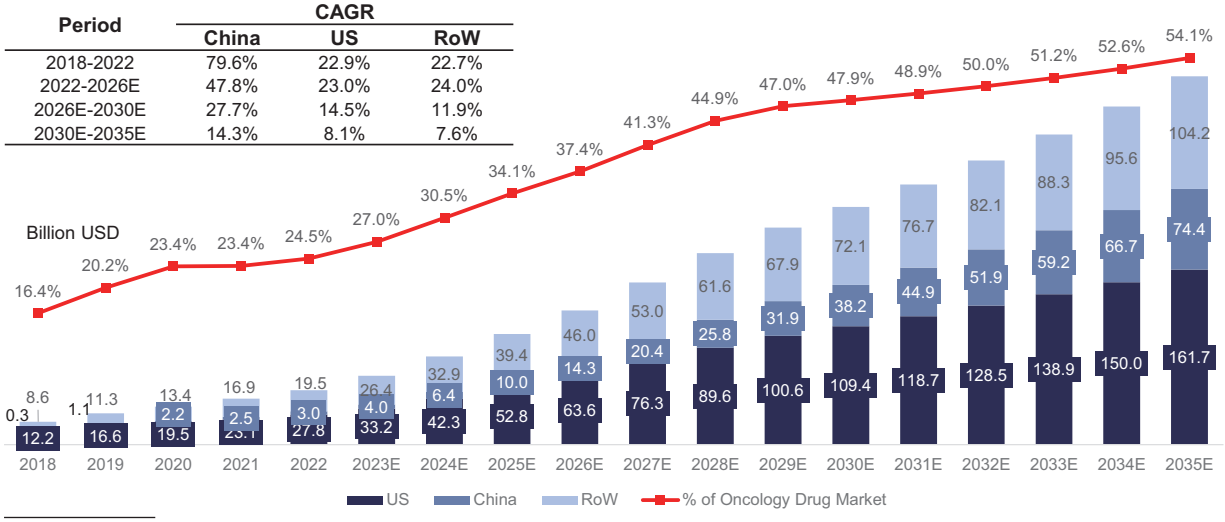
Source: NCCR, Frost & Sullivan analysis

According to Frost & Sullivan, the global market size of immuno-oncology therapy reached US$50.2 billion in 2022, and it is expected to continue to grow rapidly in the foreseeable future, driven by the increasing cancer incidence, longer patients' survival and duration of treatment, and the development of immunotherapies. In 2035, the global immuno-oncology therapy market is projected to reach US$340.4 billion, accounting for over 54% of the total global oncology market. Benefiting from continuous launches of new drugs and improved patient affordability, China's immuno-oncology therapy market grew, and is expected to further grow at a faster pace than that of the global and the U.S. market.

The following diagram sets forth the historical and projected immuno-oncology therapy market size globally, in the U.S. and China, and the global market share of immuno-oncology therapy as a percentage of the global oncology market for the periods indicated:

Immuno-Oncology Therapy Market Globally, in the U.S. and in China, 2018–2035E

Period	CAGR		
	China	US	RoW
2018-2022	79.6%	22.9%	22.7%
2022-2026E	47.8%	23.0%	24.0%
2026E-2030E	27.7%	14.5%	11.9%
2030E-2035E	14.3%	8.1%	7.6%



Note: RoW refers to all countries and regions in the world except the U.S. and China.
Source: *Frost & Sullivan*

Growth drivers and future trends of global and China's immuno-oncology therapy market

According to Frost & Sullivan, the growth drivers and future trends of immuno-oncology therapy market globally and in China include the following:

Increasing addressable patient population

The incidence of cancer has steadily increased both globally and in China, and it is expected to continuously grow due to increasing lifespan, aging of population, modern sedentary lifestyle, and obesity. The increasing incidence rate combined with improving healthcare access and affordability, and the growing demand for effective cancer treatments will fundamentally drive the continued growth of immuno-oncology therapy market. Furthermore, currently approved immuno-oncology therapies often encounter low response rates, high recurrence rates and other limitations, presenting attractive market opportunities for immunotherapies to further improve treatment outcomes.

Emerging innate immune targets

The remarkable historical growth of immuno-oncology market was largely contributed by drug development efforts around several key T cell immune checkpoints, including PD-1/PD-L1, CTLA-4 and LAG-3. In recent years, breakthroughs in scientific research have identified promising innate immune checkpoints as the immunotherapeutic targets, such as CD47/SIRPα, CD24/Siglec-10, CD94-NKG2A/KIR family, PSGL-1, EP4, and TREM2. Mounting research has revealed the potential of novel innate immune checkpoint-based therapies in treating a broad spectrum of cancer indications. Among innate immune checkpoints, CD47/SIRPα pathway as a critical macrophage checkpoint has gained significant attention in the industry. CD47, overexpressed on numerous tumor cells, binds with SIRPα to convey a "don't eat me" signal, inhibiting tumor phagocytosis by macrophages and evading macrophage-mediated immune responses. CD47/SIRPα-targeted drug candidates are thus developed to activate macrophages by blocking such inhibitory "don't eat me" signal. Recently, emerging CD47/SIRPα-targeted therapies have introduced a novel strategy to induce an "eat me" signal in addition to the inhibition of "don't eat me" signal to fully activate macrophages. CD24 and certain early-stage innate immune targets, such as NKG2A and PSGL-1, also exhibit high potential to be developed for activating innate immune cells, which can further promote adaptive immune responses to achieve potent synergistic effects between two arms of immune systems. For example, in addition to mediating phagocytosis against tumor cells, fully activated macrophages can secrete certain cytokines and chemokines to recruit T cells to tumor sites, thus turning "cold tumors" into "hot tumors". Activated NK cells can also further promote T-cell differentiation and T-cell response. As a result, the development and clinical application of immunotherapies targeting the emerging innate immune checkpoints, in addition to adaptive immune targets, will further improve clinical benefits for patients and continue to drive the growth of the immuno-oncology market.

Development of bispecific molecules and combinations to maximize therapeutic benefits

Clinical evidence suggests that synergistic combination and bispecific strategies enabling the dual activation of innate and adaptive immune systems, as well as combination of immunotherapies with other treatments, could induce enhanced tumor-killing effects and improve clinical outcomes, presenting a tremendous market potential. Currently there are eight marketed bispecific molecules for cancer treatment globally, including LUNSUMIO® (mosunetuzumab, CD20×CD3), AKESO® (Cadonilimab, PD-1×CTLA4), TECVAYLI® (Teclistamab, CD20×CD3), COLUMVI® (Glofitamab, CD20×CD3, EPKINLY® (epcoritamab, CD20×CD3), TALVEY® (talquetamab, GPRC5D×CD3), RYBREVANT® (amivantamab, EGFR×c-MET), and BLINCYTO® (blinatumomab, CD19×CD3). Meanwhile, numerous bispecific molecules are under clinical development for cancer treatment, such as bispecific molecules targeting CD3/BCMA, LAG-3/PD-(L)1, VEGF/PD-(L)1, CTLA-4/PD-(L)1, CD47/PD-(L)1, CD47/CD20, CD47/CD19, and CD47/HER2, representing the future trend of immuno-oncology therapies.

Synergistic combination modalities, especially those enabling the activation of both immune systems and those combining immunotherapies with targeted therapies, have shown a high potential to improve clinical outcome for therapeutic benefits in cancer patients. To date, multiple combination therapies of PD-1/PD-L1 inhibitors and targeted therapies have been approved for the treatment of numerous cancer indications in first- and/or later-line settings. For instance, the combination of TECENTRIQ® (atezolizumab) and AVASTIN® (bevacizumab) has been approved for the first-line treatment of NSCLC and HCC, the combination of KEYTRUDA® (pembrolizumab) with AVASTIN® (bevacizumab) has been approved for recurrent or metastatic CC, and the combination of TYVYT® (sintilimab) and BYVASDA® (bevacizumab biosimilar) has been approved for the first-line treatment of HCC. These new modalities and strategies allow immunotherapies to explore unprecedented therapeutic applications in the oncology space, thereby addressing the unfulfilled needs of a huge market.

Indication expansion and advancement of treatment line of immuno-oncology therapies

The development of immunotherapies in previously untapped indications benefits a growing patient population. PD-1/PD-L1 inhibitors, for instance, were initially approved for the treatment of melanoma in 2014 and have now been approved for use in a wide range of cancers, such as NSCLC, HNSCC, HCC, RCC, UC and Hodgkin lymphoma (HL). In addition, immuno-oncology therapies initially approved for second- or later-line treatments have been gradually advanced towards first-line treatment. For example, pembrolizumab was first approved in 2015 for the treatment of metastatic NSCLC patients with ≥1% tumor cells expressing PD-L1 who relapsed or progressed after chemotherapy, and its combination with chemotherapy was later approved in 2018 for the first-line treatment of metastatic NSCLC regardless of PD-L1 expression levels. Clinical use of immunotherapy in the frontline treatment can significantly increase its addressable patient population and treatment duration, thus further driving the immunotherapy market size.

PROMISING IMMUNOTHERAPIES TARGETING INNATE IMMUNE CHECKPOINTS

Immunotherapies targeting innate immune checkpoints have demonstrated the potential to have broad-spectrum clinical applications and address the limitations of currently approved immunotherapies that target adaptive immunity. By activating innate immune responses and orchestrating the synergistic effects between innate and adaptive immune systems, immunotherapies targeting innate immune checkpoints can induce and drive potent and long-lasting wholistic immune responses against hematologic and solid tumors. To date, a few key innate immune checkpoints have been studied, including CD47/SIRPα, CD24/Siglec-10, CD94-NKG2A/KIR family, PSGL-1, EP4, and TREM2, so far there has not been any approved innate immune checkpoint-targeted therapy worldwide, indicating a vast untapped global market.

Overview of CD47/SIRPα-targeted Drugs

CD47, which is overexpressed on the surface of numerous tumor cells, has been identified as a critical macrophage checkpoint. Upregulating CD47 is a mechanism commonly used by tumor cells to evade macrophage-mediated immune responses. By binding with SIRPα, an inhibitory receptor expressed on macrophages, CD47 conveys a "don't eat me" signal to inhibit tumor phagocytosis by macrophages. CD47/SIRPα-targeted drugs are designed to activate macrophages by blocking the inhibitory "don't eat me" signal. Activated macrophages can further elicit T-cell immune responses through the crosstalk between innate and adaptive immune systems. Macrophages, as a major type of innate immune cells, are widely distributed in a broad range of tumor types, accounting for 20% to 50% of cells in respective tumor tissues, including NSCLC, SCLC, breast cancer (BC), GC, CRC, HNSCC, HCC, ESCC, BTC, OC, lymphoma, acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and MM. Thus, macrophage-activating strategy could be an effective approach to further improve treatment outcomes in a broad range of cancers.

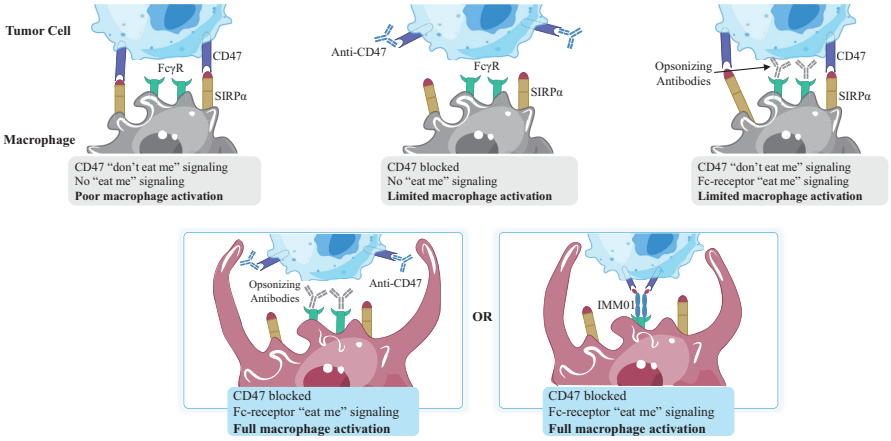
Given its critical role in modulating macrophage activity, CD47-SIRPα pathway has attracted growing attention from the biopharmaceutical industry and has been pursued by many multinational corporations as the next revolutionary immune checkpoint after PD-1/PD-L1.

Mechanism of macrophage activation

Although antibodies targeting CD47 or SIRPα can block the CD47-SIRPα axis and thus inhibit the "don't eat me" signal, the blockade alone is not sufficient to fully activate macrophages. Activation of macrophages also requires the simultaneous delivery of an "eat me" signal through Fc-FcγR (especially FcγRIIA) engagement or co-stimulatory pathways, such as the STING pathway. To achieve potent antitumor activity, CD47-targeted agents must be able to exert dual mechanisms: blocking the "don't eat me" signal and simultaneously delivering an activating "eat me" signal to fully activate macrophages. As most CD47 antibodies with IgG2 or IgG4 cannot

activate Fc effector function on their own, an additional "eat me" signal is further required for combination therapies to achieve efficacy. The following diagrams illustrate how the dual mechanisms work:

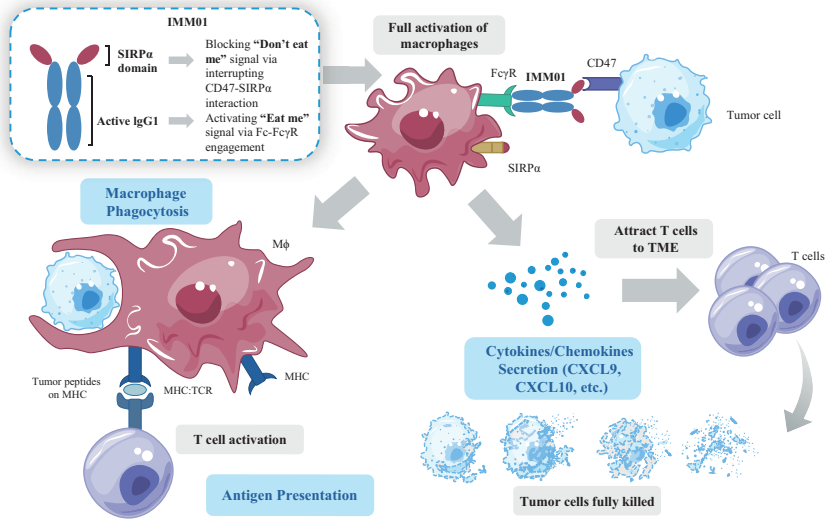
Dual Mechanisms of Macrophage Activation



Source: Frost & Sullivan, Literature Review

Upon full activation, macrophages can mediate phagocytosis against tumor cells, and assist in promoting tumor-specific adaptive immune responses by remodeling immunosuppressive TME and increasing T cell-mediated cytolysis. Activated macrophages can release a slew of cytokines and chemokines, such as CXCL9 and CXCL10, to recruit T cells into the TME, effectively inflaming "cold tumors" into "hot tumors." Additionally, macrophages can present tumor-associated antigens to T cells, thereby activating a T cell-mediated response against tumor cells. The diagram below illustrates how fully activated macrophages combat cancer cells:

Integrated Antitumor Immune Responses Induced by Macrophage Activation



Definition: MHC refers to major histocompatibility complex.
Source: Frost & Sullivan, Literature Review

Validation of CD47-SIRPα pathway by clinical evidence and global transactions

There are 59 CD47/SIRPα-targeted drug candidates currently under clinical development in China and globally, including 6 CD47-targeted fusion proteins, 19 CD47-targeted monoclonal antibodies, 24 CD47-targeted bispecific molecules, and 10 SIRPα-targeted monoclonal antibodies. Therapeutic potential of CD47-targeted agents has been validated by accumulating clinical data in recent years. Multiple agents have shown positive safety and efficacy results in ongoing clinical trials either as monotherapy or in combination with other cancer agents for the treatment of both hematologic and solid tumors, such as non-Hodgkin lymphoma (NHL), MDS, AML, SCLC, HNSCC, OC and GC. The chart below summarizes published clinical trial results of five drug candidates in the global pipeline:

Drug Name	Molecule	Indications	Clinical Phase	Patient Number	Results				Regimen
					ORR	CR	PR	SD	
Forty Seven (Gilead)'s Hu5F9-G4 (Magrolimab)	Monoclonal Antibody (IgG4)	R/R Non-Hodgkin's Lymphoma (NHL)	I/II (US, Row)	22	50%	36%	14%	14%	Hu5F9-G4 1-30mg/kg weekly +Rituximab 375mg/m^2
		R/R Diffuse Large B-cell Lymphoma (DLBCL)		33	52%	39%	12%	6%	
		R/R Follicular Lymphoma (FL)		7	71%	43%	28%	0%	
		Untreated Higher-risk Myelodysplastic Syndrome (MDS)	Ib (US, Row)	95	75%	33%	42%	/	Hu5F9-G4 1-30 mg/kg QW/Q2W +AZA 75mg/m^2 days 1-7
		Untreated Acute Myeloid Leukemia (TP53-mutant AML)		22	73%	59%	14%	/	
		R/R Ovarian Cancer (OC)	Ib (US)	18	/	/	/	56%	Hu5F9-G4 45mg/kg weekly+PD-L1 inhibitor Avelumab 800mg Q2W
		Untreated Acute Myeloid Leukemia (AML)	Ib/II (US)	41	80%	71%	10%	/	Hu5F9-G4 1-30 mg/kg QW/Q2W +AZA 75mg/m^2 days 1 -7+VEN 400mg days 1-28
ALX Oncology's ALX148 (Evorpacept)	Fusion Protein (IgG1 inert)	R/R Non-Hodgkin Lymphoma (NHL)	I (US, Row)	22	41%	18%	23%	27%	ALX148 10mg/kg QW + Rituximab
				10	70%	30%	40%	10%	ALX148 15mg/kg QW + Rituximab
		Untreated Head and Neck Squamous Cell Carcinoma (HNSCC)	I (US, Row)	13	39%	8%	31%	46%	ALX148 10 or 15 mg/kg QW+ Pembrolizumab + 5FU+ Cisplatin or Carboplatin as 1st line therapy, or in combination with trastuzumab (T) + ramucirumab (R) + paclitaxel (P) as ≥2nd line treatment
		Previously Treated Gastric/Gastroesophageal Cancer (GC)		18	72%	6%	67%	17%	
Trillium (Pfizer)'s TTI-621	Fusion Protein (IgG1)	R/R Diffuse Large B-cell Lymphoma	I (US, Row)	7	29%	14%	14%	/	TTI-621 dosing from 0.2 to 2.0 mg/kg weekly
		R/R Cutaneous T-cell Lymphoma		62	19%	3%	16%	/	
		R/R Peripheral T-cell Lymphoma		22	18%	9%	9%	/	
Trillium (Pfizer)'s TTI-622	Fusion Protein (IgG4)	R/R Lymphomas	I (US)	27	33%	7%	26%	/	TTI-622 weekly intravenous doses between 0.8 and 18 mg/kg
I-Mab (AbbVie)'s TJC4 (Lemzoparlimab)	Monoclonal Antibody (IgG4)	R/R Non-Hodgkin Lymphoma	I (China, US)	7	71%	57%	14%	29%	Lemzoparlimab 20 or 30 mg/kg weekly +Rituximab 375 mg/m^2 QW
		Untreated IPSS-R intermediate or high-risk MDS	II	53	86%	31%	55%	/	Lemzoparlimab 30 mg/kg weekly + AZA at 75 mg/m^2

Notes: (1) ORR refers to objective response rate (objective response was defined as a complete or partial response), CR refers to complete responses, PR refers to partial responses, SD refers to stable disease, R/R refers to relapsed/refractory. (2) Clinical data are extracted from company website and published literature. (3) QW refers to once a week; Q2W refers to once every two weeks. (4) The phase mentioned above refers to the clinical phase corresponding to the disclosed clinical trial results, rather than the latest clinical phase. (5) There were no head-to-head comparison clinical trials conducted between these drugs. The results of clinical trials of a drug cannot be directly compared to that of another drug and may not be representative of the overall data. (6) In the clinical trials for magrolimab in combination with azacitidine in frontline TP53m AML and HR MDS, anemia (29% and 52%, respectively) and thrombocytopenia (32% and 55%, respectively) were observed. In the clinical trials for TTI-621 as monotherapy for the treatment of R/R lymphoma, anemia (12%) and thrombocytopenia (30%) were also observed. As discussed in "— Scientific barriers to CD47/SIRPα-targeted drug development" below, since CD47 is ubiquitously expressed on human RBCs and platelets, a CD47/SIRPα blocking agent may bind to normal blood cells and cause blood toxicity. However, by modifying the structure, SIRPα-Fc fusion protein can avoid binding to normal blood cells to certain extent. The decrease in platelets observed in SIRPα-Fc fusion protein trials conducted by Trillium and ImmuneOnco was also transient and it would not be expected to pose any particular class risk for SIRPα-Fc fusion proteins.

Source: *Frost & Sullivan, Literature Review, Official Websites of Relevant Companies*

Having seen the compelling clinical value of CD47-targeted agents, a number of leading pharmaceutical players entered the CD47 area by striking multibillion-dollar deals, further validating the potential of this class of therapeutics. The following table lists significant global deals surrounding CD47-targeted agents:

Licensing

OSE & Boehringer Ingelheim
2018.4
Boehringer Ingelheim has licensed in a pre-clinical SIRPα inhibitor (BI765063) from OSE Immuno-therapeutics, with a total consideration of €1.13 billion in upfront and milestone payments, plus future royalties on worldwide net sales, for the exclusive global rights to develop, register and commercialize BI765063.

Alector & Innovent
2020.3
Innovent has licensed in a pre-clinical SIRPα inhibitor AL008 (IBI397) from Alector for the development and commercialization rights in China.

I-MAB & AbbVie
2020.9
AbbVie has licensed in a CD47 antibody (lemzoparlimab) in clinical stage from I-MAB with up to $1.94 billion payment for the ex-China global rights. AbbVie will also pay tiered royalties from low-to-mid teen percentages on global net sales outside of greater China.

MacroGenics & Zai Lab
2021.6
Zai Lab has licensed in four pre-clinical CD47- or CD3-based bispecific molecules from MacroGenics for regional Asian and global rights with initial consideration of $55 million and up to $1.4 billion potential payments.

M&A

Forty Seven (Gilead)
2020.3
Gilead acquired Forty Seven, together with its CD47 targeted antibody program, for $4.9 billion.

Trillium Therapeutics (Pfizer)
2021.8
Pfizer acquired Trillium, an immuno-oncology company with two lead (SIRPa-Fc)-CD47 targeted molecules, TTI-622 and TTI-621, for $2.26 bn.

Note: For the Licensing column, companies listed in the front are licensors, and companies listed behind are licensees. For the M&A column, companies listed in the front are acquirees, and companies listed in the parentheses are acquirers.
Source: *Frost & Sullivan, Official Websites of Relevant Companies*

Scientific barriers to CD47/SIRPα-targeted drug development

While being a clinically-validated cancer immunotherapy target with a significant market potential, CD47 still faces great challenges in drug design and development. As of the Latest Practicable Date, the clinical trials of multiple CD47 antibodies have been suspended or partially suspended due to safety issues, such as Bristol-Myers (Celgene)'s CC-90002, Surface Oncology's SRF231. In early 2022, the FDA placed a partial clinical suspension on studies to evaluate Gilead's magrolimab in MDS, AML, MM and diffuse large B-cell lymphoma (DLBCL) due to an imbalance in investigator-reported suspected unexpected serious adverse reaction (SUSAR) between study arms observed in trials, all of which have been subsequently lifted as the FDA determined that, following a comprehensive review of the safety data from each trial, the clinical sponsor had satisfactorily addressed the deficiencies. Barriers to the development of effective and safe CD47-targeted drugs are as follows:

- Blood toxicity: Safety issues have been the primary concerns around CD47. Other than tumor cells, CD47 is also ubiquitously expressed on human red blood cells (RBCs) and platelets. Thus, a CD47/SIRPα blocking agent may also bind to normal blood cells and cause severe blood toxicity, such as anemia, thrombocytopenia and hemagglutination

(clumping of RBCs). In fact, a number of clinical-stage CD47 antibodies show severe strong RBC binding, leading to severe adverse effects, and cases resulting in trial suspensions or termination.

- Antigenic sink: Due to ubiquitous expression of CD47 on normal cells, CD47-targeted agents, especially CD47 antibodies, may be quickly exhausted after administration, resulting in limited drug exposure in tumor tissues. "Antigenic sink" issues require a higher dose to reach the minimum effective concentration threshold. Higher doses would in turn cause more severe blood toxicity, especially when used in combination therapies.

- Fc isotype selection: Due to the inevitable binding of CD47 antibodies to RBCs, most of those antibodies resort to a less potent IgG4 Fc region, trading their therapeutic efficacy for safety and thus requiring a much higher dose. In contrast, IgG1 Fc is able to elicit strong ADCP activity by macrophages through much more efficient engagement with activating Fcγ receptors.

- T-cell apoptosis: CD47 is also expressed on T cells. Upon binding with a particular CD47 epitope on T cells, certain CD47-targeted antibodies may induce T-cell apoptosis, resulting in compromised efficacy, drug resistance and severe side effects.

These challenges pose high scientific entry barriers for the development of CD47-targeted therapies. Due to these hurdles, several companies have started to develop SIRPα-targeted therapeutics, most of which are still in early stages. However, since anti-SIRPα antibodies usually adopt IgG4 Fc, they cannot fully activate macrophages and thus are unlikely to elicit potent immune responses against tumor cells.

Global and China CD47/SIRPα-targeted drugs market size

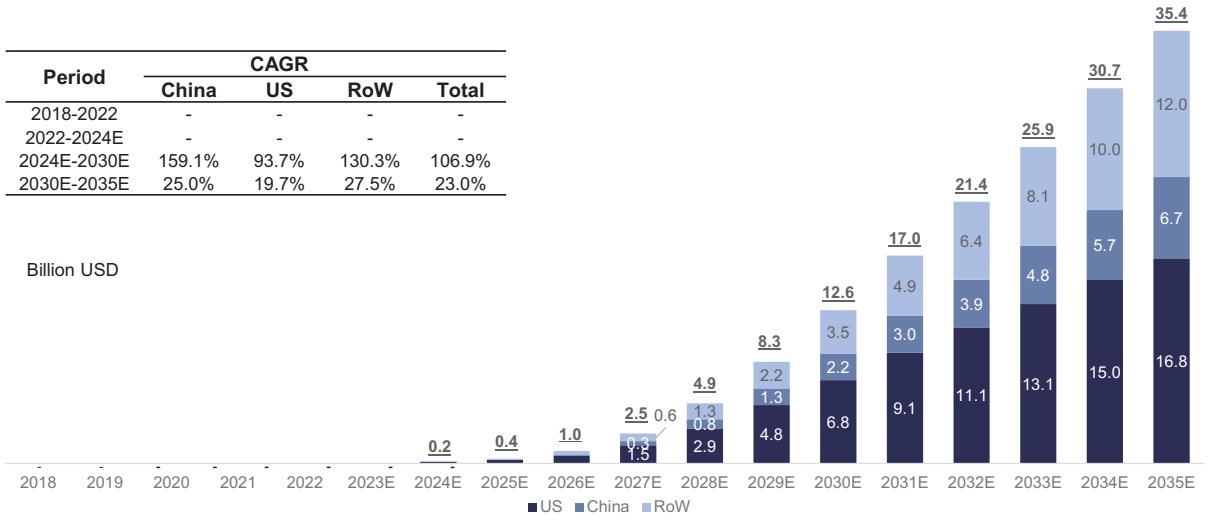
According to Frost & Sullivan, the global market of CD47/SIRPα-targeted therapies is projected to expand rapidly after the expected launch of the first drug of this class in 2024. This market is projected to increase from US$0.2 billion in 2024 to US$12.6 billion in 2030, representing a CAGR of 106.9% between 2024 to 2030, and further increase to US$35.4 billion in 2035 at a CAGR of 23.0% between 2030 and 2035. CD47/SIRPα-targeted therapy market in the U.S. is expected to reach US$6.8 billion in 2030 at a CAGR of 93.7% from 2024 to 2030, and further to US$16.8 billion in 2035 at a CAGR of 19.7% from 2030 to 2035.

China's CD47/SIRPα-targeted therapy market is expected to grow at a higher speed compared to the global market. The China market is expected to grow from US$0.01 billion in 2024 to US$2.2 billion in 2030, representing a CAGR of 159.1% between 2024 to 2030. It is estimated to further reach US$6.7 billion in 2035 at a CAGR of 25.0% between 2030 to 2035.

In the global and China's CD47/SIRPα-targeted therapy market, CD47-targeted therapies are expected to contribute a substantially higher proportion than SIRPα-targeted therapies, as most SIRPα-targeted therapies are still in relatively early stages. The diagram below sets forth the market size of CD47/SIRPα-targeted therapies in China, the U.S. and the rest of the world for the periods indicated:

Global CD47/SIRPα-Targeted Therapies Market, 2018–2035E

Period	CAGR			
	China	US	RoW	Total
2018-2022	-	-	-	-
2022-2024E	-	-	-	-
2024E-2030E	159.1%	93.7%	130.3%	106.9%
2030E-2035E	25.0%	19.7%	27.5%	23.0%



Notes: (1) Market size for CD47-targeted and SIRPα-targeted drugs, including monoclonal antibody, bispecific antibody, antibody conjugate drug (ADC), fusion protein. (2) RoW refers to all countries and regions in the world except the U.S. and China.

Source: *Frost & Sullivan*

Global and China CD47/SIRPα-targeted drugs competitive landscape

As of the Latest Practicable Date, there were no commercialized CD47/SIRPα-targeted drugs globally. Given the therapeutic and market potential of CD47/SIRPα-targeted agents, many drug candidates are currently under clinical development, including fusion proteins, monoclonal antibodies and bispecific molecules. Among the numerous drug developers, ImmuneOnco and Trillium are the only two companies to have observed complete response (CR) in monotherapy clinical trials with a well-tolerated safety profile. There are five anti-SIRPα monoclonal antibodies under clinical development globally, all of which are still in early stages.

CD47-targeted fusion proteins and monoclonal antibodies

The following chart illustrates comparisons of major clinical-stage CD47-targeted fusion proteins and monoclonal antibodies worldwide:

Drug Name	Company	Molecule	Fc isotype	RBC binding	1st in human	Monotherapy CR	Indication(1)	Latest Stage(2)
Hu5F9 (Magrolimab)	Forty Seven (Gilead)	mAb	IgG4	Yes	2014.8	No	AML, MDS, MM, NHL, HNSCC, TNBC, OC, CRC	Ph III (combo) (Partial Suspension by the Company)
TTI-621	Trillium Therapeutics (Pfizer)	SIRPαFc	IgG1	No	2016.1	Yes	AML, MDS, MM, Lymphoma, Leiomyosarcoma, Solid Tumor	Ph II (mono & combo) (Partial Suspension by the Company)
TTI-622		SIRPαFc	IgG4	No	2018.5	Yes	AML, MM, Lymphoma, OC	Ph II (combo)
CC-90002	Celgene (BMS)	mAb	IgG4	Yes	2015.2	No	AML, MDS, MM, NHL, Solid tumor	Ph I (combo) (Partial Suspension by the Company)
SRF231	Surface Oncology	mAb	IgG4	Yes	2018.4	No	Advanced Solid Cancers, Hematologic Cancers	Ph I (mono) (Suspension by the Company)
ALX-148 (Evorpacept)	ALX Oncology	SIRPαFc	IgG1 Fc(Inert)	Yes	2017.1	No	AML, MDS, NHL, Solid Tumor	Ph II/III (combo)
SHR1603	HengRui 恒瑞	mAb	IgG4	Yes	2018.10	No	Advanced Malignancies, Lymphoma	Ph I (mono) (Suspension by the Company)
AO-176	Arch Oncology	mAb	IgG2	Minimal	2019.2	No	MM, GC, NSCLC, HNSCC, OC, Prostate Cancer, Endometrial Carcinoma	Ph I/II (combo) (Suspension by the Company)
IBI188 (Letaplimab)	Innovent 信达生物	mAb	IgG4	Yes	2018.11	No	AML, MDS, Lymphoma, Solid Tumor	Ph Ib/III (combo) (Partial Suspension by the Company)
TJC4 (Lemzoparlimab)	I-Mab 天境生物 /AbbVie	mAb	IgG4	Minimal	2019.5	No	AML, MDS, MM, CD20 Positive Lymphoma, Advanced Solid Tumor	Ph III (combo) (Partial Suspension by the Company)
IMM01	ImmuneOnco 宜明昂科	SIRPαFc	IgG1	No	2019.9	Yes	MDS, AML, CMML, HL, NHL, Solid Tumor	Ph II (combo)[12]
AK117	Akesobio 康方生物	mAb	IgG4	Minimal	2020.4	No	AML, MDS, Lymphoma, TNBC, HNSCC, NSCLC, SCLC, OC, CRC, HCC	Ph II (combo)

Notes: (1) Denotes the indications targeted by either combination therapy or monotherapy of each drug candidate. Most drug candidates listed in this table are developed primarily through combination strategies rather than as a monotherapy. (2) Denotes the latest clinical development stage of each drug candidate considering its monotherapy and combination trials as a whole. (3) Clinical data are extracted from official websites of relevant companies, reported clinical trials and published literature. (4) Despite a comparison is made here, the key results are not from head-to-head studies. (5) 1st in human refers to the first posted date of the first clinical trial. (6) The stage listed here is the latest clinical trial of the drug. (7) Partial suspension means not all clinical trials of this drug are suspended, such as monotherapy of CC-90002, which has been suspended but its combination therapy with rituximab has been completed. (8) For the drugs associated with two companies, the company in parenthesis is the acquirer. (9) The FDA has lifted all of the partial clinical hold placed on several trials evaluating magrolimab, as it determined that, following comprehensive review of the safety data from each trial, that the clinical sponsor had satisfactorily addressed the deficiencies. (10) As to the monotherapy CR column, "No" means that no CR was achieved in a completed or suspended clinical trial. (11) The dark-gray parts of the diagram indicate that trials are terminated. (12) The most advanced clinical trial of IMM01 is an ongoing Phase II trial evaluating the combination therapy of IMM01 and azacitidine. We had terminated the Phase II clinical trial of IMM01 monotherapy as of the Latest Practicable Date.

Source: *Frost & Sullivan, Official Websites of Relevant Companies*

As indicated in the table above, all of those CD47 antibodies exhibit RBC binding activity, and as such they resorted to IgG4 or IgG2 Fc with less potent receptor engagement activity. In contrast, CD47-targeted fusion proteins, including TTI-621 developed by Trillium and IMM01 developed by ImmuneOnco, do not bind with RBCs *in vitro*, enabling the use of an IgG1 Fc region with a better ability to engage Fc receptors to elicit stronger effector functions compared with other isotypes. Among all CD47-targeted drug candidates, only IMM01 developed by ImmuneOnco, and TTI-621 and TTI-622 developed by Trillium have achieved CR in clinical study as monotherapy. Given TTI-622 adopts an IgG4 Fc with weaker Fc function, its monotherapy CR rate was lower than TTI-621 at a higher dose for peripheral T cell lymphoma (PTCL) and DLBCL. Since ALX-148 contains an inert IgG1 Fc that exhibits no Fc function, no CR was observed in its monotherapy clinical trials. The following chart demonstrates a comparison and considerations of the four subtypes in molecule design:

IgG Subtypes

	IgG1	IgG2	IgG3	IgG4
Plasma Level	60-70%	20-30%	5-8%	1-4%
Half-life Period /days	**21**	21	9	21
Antigen	Proteantigen	Carbohydrate antigen	Proteantigen	Chronic antigenic stimulus and inflammation
FcγR Affinity	**Strong**	Weak	Strong	Weak
ADCC Activity	**Strong**	Weak	Strong	Weak
ADCP Activity	**Strong**	Weak	Strong	Weak
CDC Activity	**Strong**	Weak	Strong	No
Representative Drug	Daratumumab	Denosumab	-	Pembrolizumab

Source: Frost & Sullivan

As of the Latest Practicable Date, there were two clinical-stage CD47-targeted fusion proteins in China and four in the U.S. and the rest of the world. According to Frost & Sullivan, our IMM01 is the first SIRPα fusion protein that has entered in clinical stage in China. The table below summarizes the global pipeline of CD47-targeted fusion proteins:

Global Pipeline of CD47-targeted Fusion Proteins

Drug Name/Code	Company	Fc Isotype	RBC Binding	Monotherapy CR	Indications	Clinical Stage	First Posted Date	Proposed Line of Treatment	Region
ALX148 (Evorpacept)	ALX Oncology	IgG1 (inert)	Yes	No	AML, MDS, NHL, Solid Tumor	Phase II/III	2021/08/12	1L or above	US, RoW
TTI-621	Trillium Therapeutics (Pfizer)	IgG1	No	Yes	AML, MDS, MM, Lymphoma, Leiomyosarcoma, Solid Tumor	Phase II (Partial Suspend by the Company)	2021/08/09	2L or above	US
TTI-622		IgG4	No	Yes	AML, MM, Lymphoma, OC	Phase II	2022/08/19	1L or above	US
IMM01	ImmuneOnco 宜明昂科	IgG1	No	Yes	MDS, AML, CMML, HL, NHL, Solid Tumor	Phase II	2021/09/23	1L or above	China
SG404	SumgenBio 尚健生物	/	/	/	Advanced Malignancy	Phase I	2020/12/10	2L or above	China
HCB101	FBD Biologics 汉康生技	IgG4	/	/	Advanced Solid Tumor, NHL	Phase I	2023/06/07	2L or above	US

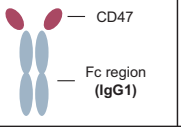
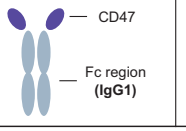
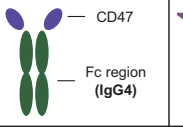
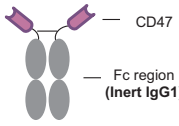
Notes: (1) Company's information is from the Company and industry information is as of August 12, 2023. (2) First posted date refers to the date on which the study record was first available on Chinadrugtrials.org.cn or Clinicaltrials.gov. (3) RoW refers to regions out of China and the U.S. (4) The clinical stage refers to the latest clinical trials as well as the first posted date. (5) The clinical stage refers to the latest clinical trials. (6) As to the monotherapy CR column, "No" means that no CR was achieved in a completed or suspended clinical trial. "/" represents there has been no disclosed information about the results of the clinical trials so far.

Definitions: *AML refers to acute myeloid leukemia; MDS refers to myelodysplastic syndrome; HL refers to Hodgkin lymphoma; NHL refers to non-Hodgkin lymphoma; MM refers to multiple myeloma; GC refers to gastric cancer; HNSCC refers to head and neck squamous cell carcinoma; CMML refers to chronic myelomonocytic leukemia.*

Source: *Frost & Sullivan, CDE, ClinicalTrials, Literature Review, Official Websites of Relevant Companies*

The following chart demonstrates a comparison among major CD47-targeted fusion proteins:

Comparison of Major CD47-Targeted Fusion Proteins

	ImmuneOnco	Trillium		ALX Oncology
	IMM01	TTI-621	TTI-622	ALX148
Structure				
CD47 binding domain	Engineered SIRPα D1	Natural SIRPα D1		Engineered SIRPα D1
CD47 binding affinity	Moderate	Moderate		Very high
RBC binding	No *in vitro* binding	No *in vitro* binding		Strong RBC binding
Fc isotype	IgG1	IgG1	IgG4	IgG1 (inert)
Fc function (ADCP, ADCC)	Strong	Strong	Weak	No
Safety	Well tolerated	Well tolerated		Well tolerated
Single agent activity	Yes	Yes	Yes	Very limited
"Eat me" signal activation	Yes	Yes	Weak	No
Combination potential with IgG4 antibody	Strong	Strong	Moderate	Weak

Notes: (1) RBC refers to red blood cell; (2) ADCP refers to antibody-dependent cellular phagocytosis; ADCC refers to antibody-dependent cell-mediated cytotoxicity; (3) AITL refers to angioimmunoblastic T-cell lymphoma; CTCL refers to cutaneous T-cell lymphoma; PTCL refers to peripheral T-cell lymphoma; DLBCL refers to diffuse large B-cell lymphoma.

Source: *Company Website, Literature Review, Frost & Sullivan analysis*

As of the Latest Practicable Date, there were 19 CD47-targeted monoclonal antibodies under clinical development globally. All of the ongoing CD47 antibodies with known structure adopt the IgG4 Fc isotype. The table below sets forth details of the global pipeline of CD47-targeted monoclonal antibodies:

Global Pipeline of CD47-targeted Monoclonal Antibodies

Drug Name/Code	Company	Fc Isotype	RBC Binding	Monotherapy CR	Indications	Clinical Stage	First Posted Date	Proposed Line of Treatment	Region
Hu5F9 (Magrolimab)	Forty Seven (Gilead)	IgG4	Yes	No	AML, MDS, MM, NHL, HNSCC, TNBC, OC, CRC	Phase III (Partial Suspend by the Company)	2020/03/18	1L or later	US, RoW
IBI188 (Letaplimab)	Innovent 信达生物	IgG4	Yes	No	AML, MDS, Lymphoma, Solid Tumor	Phase Ib/III (Partial Suspend by the Company)	2020/07/23	1L or later	China, US
AK117	Akesobio 康方生物	IgG4	Minimal	No	AML, MDS, Lymphoma, TNBC, HNSCC, NSCLC, SCLC, OC, CRC, HCC	Phase II	2022/01/30	1L or later	China, RoW
AO-176	Arch Oncology	IgG2	Minimal	No	MM, GC, NSCLC, HNSCC, OC, Prostate Cancer, Endometrial Carcinoma	Phase I/II (Suspend by the Company)	2019/02/08	2L or later	US
TJC4 (Lemzoparlimab)	I-Mab 天境生物 /AbbVie	IgG4	Minimal	No	AML, MDS, MM, CD20 Positive Lymphoma, Advanced Solid Tumor	Phase III (Partial Suspend by the Company)	2021/03/29	1L or later	China, US
Gentulizumab	GenSci 金赛药业	/	/	/	AML, MDS, Advanced Solid Tumor or Lymphoma	Phase I	2021/01/12	2L or later	China
CC-90002	Celgene (BMS)	IgG4	Yes	No	AML, MDS, MM, NHL, Solid tumor	Phase I (Partial Suspend by the Company)	2015/02/20	2L or later	US
SRF231 (Urabrelimab)	Surface Oncology	IgG4	Yes	No	Advanced Solid Cancers, Hematologic Cancers	Phase I (Suspend by the Company)	2018/04/30	2L or later	US, RoW
SHR1603	HengRui 恒瑞	IgG4	Yes	No	Advanced Malignancies, Lymphoma	Phase I (Suspend by the Company)	2018/10/26	2L or later	China
ZL-1201	Zai Lab 再鼎医药	IgG4	Yes	/	Advanced Solid Tumor or Hematologic Malignancies	Phase I	2020/02/06	2L or later	China, US
IMC-002/3D-197	ImmuneOncia/ 3D Medicines 思路迪	IgG4	No	/	Lymphoma, Solid Tumor	Phase I	2020/03/12	2L or later	China, US, RoW
MIL95/CM312	MabWorks/KeyMed 天广实生物/康诺亚生物	/	Minimal	/	Advanced Solid Tumor or Lymphoma	Phase I	2020/11/27	2L or later	China
TQB2928	Chia Tai Tianqing 正大天晴	/	/	/	Advanced Solid Tumors and Hematological Malignancies	Phase I	2021/04/22	2L or later	China
sB24M	Swiss Biopharma Med	/	/	/	PV; PG; PPG; Pyoderma	Phase I	2021/05/20	3L or later	RoW
STI-6643	Sorrento Therapeutics	IgG4	Minimal	/	Advanced Solid Tumor	Phase I	2021/05/25	2L or later	US
LD002	LanDun 蓝盾药业	/	/	/	Advanced Solid Tumor, NL	Phase I	2022/03/09	2L or later	China
F527	XinShiDai 新时代药业	/	/	/	Lymphoma	Phase I	2022/04/14	2L or later	China
HMPL-A83	HutchMed 和黄医药	IgG4	Minimal	/	AML, MDS, Lymphoma, Solid Tumor	Phase I	2022/05/26	2L or later	China
FP002	Fapon Biopharma 菲鹏制药	IgG4	Minimal	/	Advanced Malignant Tumor	Phase I	2023/06/20	2L or above	China

Notes: (1) Industry information is as of August 12, 2023. (2) First posted date refers to the date on which the study record was first available on Chinadrugtrials.org.cn or Clinicaltrials.gov. (3) RoW refers to regions out of China and the U.S. (4) The clinical stage refers to the latest clinical trials as well as the first posted date. (5) As to the monotherapy CR column, "No" means that no CR was achieved in a completed or suspended clinical trial. "/" means that no published clinical data is available so far. (6) According to public information, Zai Lab has decided to de-prioritize its internal development of ZL-1201 solely for strategic reasons and will explore out-licensing opportunities. According to Frost & Sullivan, such decision would not have any material impact on the competitive landscape of CD47/SIRPα-targeted drugs. Compared to ZL-1201, IMM01 does not bind with RBCs *in vitro*, thus enabling the adoption of an IgG1 Fc fragment capable of inducing full macrophage activation. (7) The clinical trials of drug candidates marked as dark-gray have been suspended.

Definitions: AML refers to Acute Myeloid Leukemia; MDS refers to Myelodysplastic Syndrome; NHL refers to Non-Hodgkin Lymphoma; MM refers to multiple myeloma; HNSCC refers to Head and Neck Squamous Cell Carcinoma; TNBC refers to triple negative breast cancer; OC refers to Ovarian cancer; PV refers to Pyoderma Vegetans; PG refers to Pyoderma Gangrenosum; PPG refers to Parastomal Pyoderma Gangrenosum; CRC refers to Colorectal Cancer.

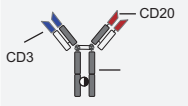
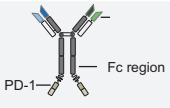
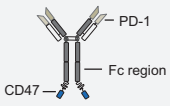
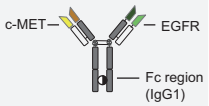
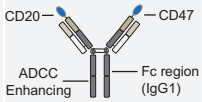
Source: Frost & Sullivan, CDE, ClinicalTrials, Literature Review, Official Websites of Relevant Companies

CD47-targeted bispecific molecules

Bispecific molecules are designed to recognize and specifically bind to two epitopes or targets simultaneously. There has been a rapid development in the bispecific molecule field since the debut of bispecific molecules as a new therapeutic approach. As of the Latest Practicable Date, there were eight marketed bispecific molecules for cancer treatment globally.

Besides potential cost benefit and ease of use compared to the combination of two monoclonal antibodies, bispecific molecules with immuno-oncology targets could achieve improved clinical benefits depending on the biological synergy between the targeted pathways and structure design. Over the past decades, various formats of bispecific molecules have been explored. Those formats differ in several aspects, including structure, presence/absence of an Fc-domain, Fc isotype, symmetry, molecule size, antigen-binding sites, and resulting mechanism of action. The following table sets forth a comparison among three major formats of bispecific molecules, namely T cell engagers, and checkpoint/signaling blockers with or without Fc effector function:

Major Bispecific Molecule Formats

	T Cell Engager		Dual Checkpoint/Signaling Blockade without Fc Effectors		Dual Checkpoint/Signaling Blockade with Fc Effects	
Structure	 **Blincyto (Amgen)**	 **Mosunetuzumab (Roche)**	 **AK112 (Akesobio)**	 **HX009 (Hans Bio)**	 **Rybrevant (Janssen)**	 **IMM0306 (ImmuneOnco)**
Function	• Bring T cells into close contact with tumor cells, and elicit immediate T-cell immune responses against tumor cells		• Through targeting and blocking of immune checkpoints or tumor signaling pathways, it reactivates suppressed immune cell functions		• Apart from the blocking of immune checkpoints or tumor signal pathways, it also activates innate immune cells through IgG1 Fc, inducing ADCC, ADCP, and potentially ADCT • Innate immune cells could further recruit and active T cells, eliciting long-lasting immune response	
Characteristics	• Induce direct tumor killing through T cell activation and the secretion of perforin and granzymes • Severe CRS triggered by immediate T cell response and massive induction of cytokines such as IL-6, interferons, tumor necrosis factors etc.		• Efficacy achieved through dual signaling blockade • Loss of Fc effector function, as the Fc end has been blocked and IgG • Manageable safety profile compared to T cell engagers		• Efficacy achieved through dual signaling blockade, as well as full Fc effector function delivered through IgG1 Fc • Able to bring innate immune cells into close contact with tumor cells, and induce strong ADCC, ADCP, potentially ADCT effects • Manageable safety profile compared to T cell engagers	
Example	**Blincyto®** • ORR: 42%, CRS: 15% (ALL) **AMG 701** • ORR: 83%, CRS: 65% (MM) **Mosunetuzumab** • ORR: 80%, CRS: 44.4% (FL)		**AK112** • ORR: 46.0% (NSCLC, 1L) • ORR: 60.0% (NSCLC, 1L, TPS≥1%) • ORR: 76.9% (NSCLC, 1L, TPS≥50%) **HX009** • ORR: 15%, PR: 15% (Advanced malignancies)		**Rybrevant®** • ORR: 40%, CR: 3.7%, PR: 36% (NSCLC with EGFR exon 20 insertion mutations)	

Note: The clinical results listed in the example line refer to the treatment outcome of monotherapy for R/R diseases, except for AK112, which is designed for the first-line treatment of NSCLC.

Definitions: ADCC refers to antibody-dependent cell-mediated cytotoxicity; ADCP refers to antibody-dependent cellular phagocytosis; CDC refers to complement dependent cytotoxicity; ALL refers to acute lymphoblastic leukemia; MM refers to multiple myeloma; NSCLC refers to non-small cell lung cancer; Example refers to representative approved drugs or underdevelopment drugs.

Source: Frost & Sullivan, Literature Review, Official Websites of Relevant Companies

As exhibited in the table above, the molecular structure design is critical to the success of bispecific molecules. The CD3-based bispecific T-cell engagers can bring T cells into close contact with tumor cells and elicit T-cell immune responses, inducing potent tumor killing effects. However, this type of bispecific molecules may trigger severe CRS through massive induction of cytokines such as IL-6. For example, CRS was seen in 65% of patients in its reported clinical study of Amgen's AMG701 (CD3×BCMA) in MM. Due to safety issues, numerous clinical trials for the T cell engagers have been suspended or terminated.

In terms of dual checkpoint/signaling blockers, the selection of different Fc types could have a significant impact on the activity of the molecules. Two bispecific molecules addressing the same targets, EGFR and c-Met, are excellent examples. Johnson & Johnson's amivantamab uses an IgG1 Fc and has obtained an accelerated approval from the FDA based on the clinical benefits primarily attributed to Fc-mediated antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular trogocytosis (ADCT), while the clinical development of Eli Lilly's LY3164530 with an IgG4 Fc was suspended due to limited patient benefits and severe toxicity.

CD47-targeted bispecific molecules are trickier and require much careful and delicate structural design. Several critical aspects need to be taken into consideration, including RBC-binding activity, IgG subclass and target selection. Due to the two-signal requirements for macrophage activation, potent IgG1 Fc effector function has to be retained, but it can only be applicable in those that do not bind to RBCs, as exemplified by IMM2902 developed by ImmuneOnco. In comparison, those bispecific molecules with Fc region blocked will result in the loss of the Fc effector function, thus hampering their efficacy.

As of the Latest Practicable Date, there were 24 CD47-targeted bispecific molecules under clinical development worldwide, including 13 with clinical trials in China. Among these molecules, IMM0306 is the first CD47×CD20 bispecific molecule to have entered into the clinical stage worldwide, which does not bind to red blood cells *in vitro* and contains an IgG1 Fc region. In addition, IMM2902 is the only one CD47×HER2 bispecific molecule that has entered into the clinical stage globally. The table below sets forth details of the global pipeline of CD47-targeted bispecific molecules:

Global Pipeline of CD47-targeted Bispecific Molecules

Target	Drug Name/Code	Company	Fc isotype	Fc effector	Indications	Clinical Stage	First Posted Date	Proposed Line of Treatment	Region
CD47, PD-1/L1	HX009	Hans Bio 翰思生物	IgG4	No	Lymphoma, HNSCC, BTC, Esophageal Cancers, Sarcoma, Malignant Mesothelioma	Phase II	2021/05/14	2L or above	China, RoW
	6MW3211	Maiwei Bio 迈威生物	/	/	AML, MDS, Refractory or Relapsed Lymphoma, RCC, Lung Cancer	Phase II	2022/06/13	1L or above	China
	IBC0966	Sunho Bio 盛禾生物	/	/	Advanced Malignancies	Phase I/II	2021/07/08	2L or above	China
	IBI322	Innovent 信达生物	IgG4	Minimal	AML, MDS, Lymphoma, Advanced Solid Tumor	Phase Ia/Ib	2020/03/30	2L or above	China, US
	SG12473	SumgenBio 尚健生物	/	No	HL, NSCLC, CRC, HNSCC, Endometrial Carcinoma	Phase Ia/Ib	2021/05/13	2L or above	China
	PF-07257876	Pfizer	IgG1	Yes	NSCLC, HNSCC, OC	Phase I	2021/05/11	2L or above	US
	BAT7104	Bio-Thera 百奥泰	/	/	Advanced Malignancies	Phase I	2022/02/22	2L or above	China, Row
	SH009	SanHome 圣和药业	/	/	Advanced Malignancies	Phase I	2022/07/01	2L or above	China
	IMM2520	ImmuneOnco 宜明昂科	IgG1	Yes	Solid Tumor	Phase I	2023/02/07	2L or above	China, US
CD47, CD20	IMM0306	ImmuneOnco 宜明昂科	IgG1	Yes	Refractory or Relapsed CD20-positive B-NHL	Phase I/II	2020/03/23	3L or above	China, US
	JMT601	JMT-Bio (Conjupro Biotherapeutics) 津曼特(石药集团)	IgG1	Yes	Refractory or Relapsed CD20-Positive B-NHL	Phase I/II	2021/04/21	3L or above	China, US
	CC-96673	Celgene (BMS)	/	/	NHL	Phase I	2021/04/27	2L or above	US, Row
CD47, CD38	ISB 1442	Ichnos Sciences SA	IgG1/IgG3	Yes	MM	Phase I/II	2022/06/22	4L or above	US, Row
	SG2501	SumgenBio 尚健生物	/	/	MM, Lymphoma	Phase I	2022/03/24	2L or above	US
CD47, HER2	IMM2902	ImmuneOnco 宜明昂科	IgG1	Yes	HER2-positive and HER2 Low-expression Advanced Solid Tumor	Phase I/II	2021/09/22	2L or above	China, US
	D3L-001	D3 Bio (Wuxi) 德昇濟醫藥(無錫)	/	/	HER-2 Positive Advanced Solid Tumors	Phase I	2023/07/24	/	/
CD47, CD19	TG-1801/ NI-1701	TG Therapeutics /Novimmune SA	IgG1	Yes	B-Cell Lymphoma, Chronic Lymphocytic Leukemia	Phase I	2019/01/15	2L or above	US, RoW
CD47, CD40L	SL-172154	Shattuck Labs	IgG4	No	AML, MDS, OC, Fallopian Tube Cancer, PPC, cSCC; HNSCC	Phase I (Partial Suspend by the Company)	2020/05/28	2L or above	US
CD47, 4-1BB	DSP107	Kahr Medical	IgG4	No	AML, MDS, CMML, Advanced Solid Tumor	Phase I/II	2020/06/22	2L or above	US
CD47、MSLN	NI-1801	Novimmune SA	IgG1	Yes	OC, TNBC, NSCLC	Phase I	2022/06/03	2L or above	Row
CD47, CLDN-18.2	PT886	Phanes Therapeutics	/	/	GC, Pancreas Adenocarcinoma	Phase I	2022/08/01	2L or above	/
	BC007	Dragon Boat	/	/	Advanced Solid Tumor with CLDN18.2 Expression	Phase I	2022/10/31	2L or above	China
	SG1906	SumgenBio 尚健生物	IgG1	/	Advanced Solid Tumor with CLDN18.2 Expression	Phase I	2023/03/13	2L or above	China
CD47, DLL3	PT217	Phanes Therapeutics	/	/	SCLC, LCNEC, NEPC, GEP-NET	Phase I	2022/12/15	2L or above	/
CD47, CD24	IMM4701	ImmuneOnco 宜明昂科	IgG1	Yes	Solid Tumor	CMC	CMC	/	China, US

Notes: (1) Company's information is from the Company and industry information is as of August 12, 2023. (2) First posted date refers to the date on which the study record was first available on Chinadrugtrials.org.cn or Clinicaltrials.gov. (3) RoW refers to regions out of China and the U.S. (4) The clinical stage refers to the latest clinical trials as well as the first posted date.

Definitions: B-NHL refers to B-cell Non-Hodgkin Lymphoma; HNSCC refers to Head and Neck Squamous Cell Carcinoma; NSCLC refers to Non-small Cell Lung Cancer; PPC refers to Primary Peritoneal Cancer; cSCC refers to cutaneous squamous cell cancer; OC refers to Ovarian cancer; TNBC refers to Triple Negative Breast Cancer; LCNEC refers to Large Cell Neuroendocrine Cancer; NEPC refers to Neuroendocrine Prostate Cancer; GEP-NET refers to Gastroenteropancreatic Neuroendocrine Tumors.

Source: Frost & Sullivan, CDE, ClinicalTrials, Literature Review, Official Websites of Relevant Companies

SIRPα-targeted monoclonal antibodies

SIRPα-targeted drug candidates are designed to bind with SIRPα expressed on immune cells and block CD47/SIRPα interaction, however they are not expected to further activate the "eat me" signal regardless of the IgG isotype used. As of the Latest Practicable Date, there were 10 SIRPα-targeted monoclonal antibodies under clinical development globally, all of them are in phase I/II stage. There is no clinical-stage SIRPα-targeted bispecific molecule worldwide. The table below sets forth details of the global pipeline of SIRPα-targeted monoclonal antibodies:

Global Pipeline of SIRPα-targeted Monoclonal Antibodies

Drug Name/Code	Company	Molecule	Fc Isotype	Monotherapy CR	Indications	Clinical Stage	First Posted Date	Region
LM-101	LaNova Medicines 礼新医药	mAb	/	/	Advanced Malignant Tumors	Phase I/II	2023/01/06	China
CC-95251	Celgene (BMS)	mAb	IgG1	No	AML, MDS, Advanced Solid Tumor, Advanced Hematologic Cancer	Phase I	2018/12/21	US, RoW
BI 765063/OSE-172	Boehringer Ingelheim/OSE	mAb	IgG4	No	Advanced Solid Tumor, Melanoma	Phase I	2019/06/18	RoW
FSI-189/GS-0189	Forty Seven (Gilead)	mAb	/	/	NHL	Phase I (Suspend by Company)	2020/08/06	US
IBI397	Innovent 信达生物	mAb	/	/	Advanced Solid Tumor	Phase Ia/Ib	2022/02/09	China
BR105	BioRay/Hisun 博锐生物/海正生物	mAb	/	/	Advanced Solid Tumor	Phase I	2022/03/14	China
ELA026	Electra Therapeutics Inc.	mAb	IgG1	/	Hemophagocytic Lymphohistiocytosis	Phase I	2022/06/13	US, Row
BYON4228	Byondis B.V.	mAb	IgG1	/	Lymphoma	Phase I	2023/02/21	/
DS-1103a	Daiichi Sankyo, Inc./AstraZeneca	mAb	IgG4	/	Advanced Solid Tumor	Phase I	2023/03/13	US
ADU-1805	Sairopa B.V	mAb	IgG2	/	Advanced Solid Tumor	Phase I	2023/05/12	US, Row

Notes: (1) Industry information is as of August 12, 2023. (2) First posted date refers to the date on which the study record was first available on Chinadrugtrials.org.cn or Clinicaltrials.gov. (3) RoW refers to regions other than China and US. (4) Clinical stage refers to the stage of the most advanced clinical trials of a drug; the first posted date refers to the start date of the first clinical trial of a drug according to public information. (5) The clinical stage refers to the latest clinical trials. (6) As to the monotherapy CR column, "No" means that no CR was achieved in a completed or suspended clinical trial. "/" represents there has been no disclosed information about the results of the clinical trials so far. (7) The clinical trials of drug candidates marked as dark-gray have been suspended.

Definitions: AML refers to Acute Myeloid Leukemia; MDS refers to Myelodysplastic Syndrome; NHL refers to Non-Hodgkin Lymphoma.

Source: CDE, ClinicalTrials, Company Website, Literature Review, Frost & Sullivan Analysis

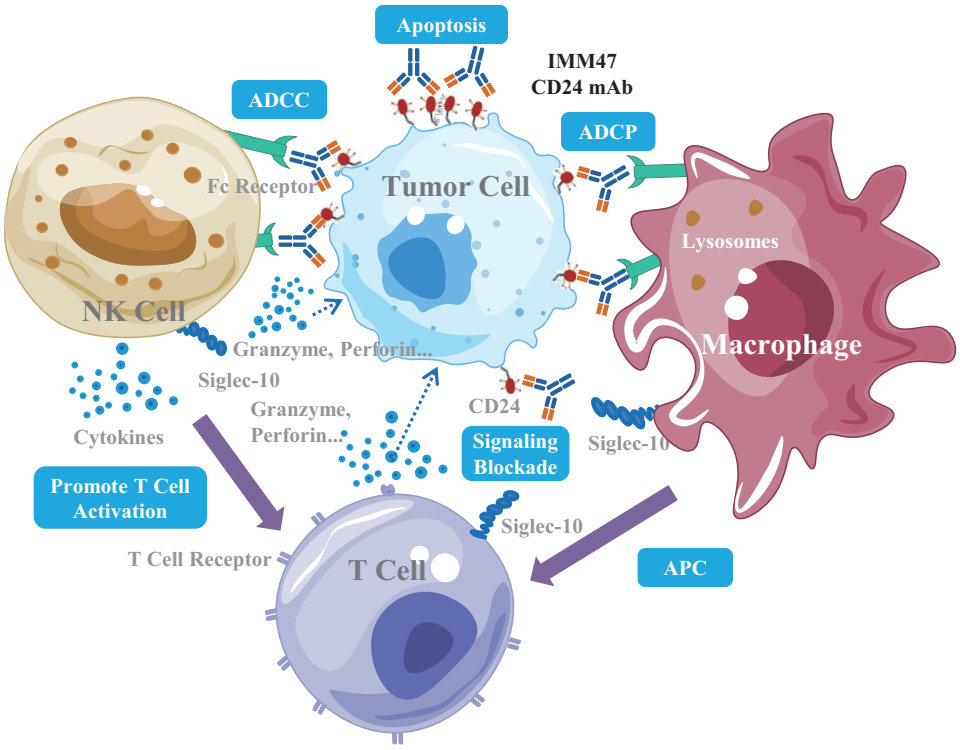
Overview of CD24-targeted Drugs

CD24, another critical innate immune checkpoint, is a highly glycosylated protein with a small protein core that is linked to the plasma membrane via a glycosyl-phosphatidylinositol anchor. It is widely expressed on numerous types of tumor cells, including BC, NSCLC, CRC, HCC, RCC and OC, and has been recognized as an important marker for poor prognosis of those cancers. It is closely related to the occurrence, development, invasion, and migration of tumor cells. CD24 interacts with its ligand, Siglec-10, an inhibitory receptor extensively expressed on the surface of various immune cells including macrophages, NK cells, T cells and B cells. The binding of CD24 and Siglec-10 activates a slew of immune cell inhibitory signal cascades and subsequently blocks the toll-like receptor-mediated inflammation to negatively regulate macrophage, NK cells, T cells and B cells, thus causing immunosuppression. Targeting both innate and adaptive immunity, CD24-targeted drugs present a significant potential in treating a wide range of cancer indications.

Mechanism of blocking the CD24/Siglec-10 signaling pathway

By blocking the CD24/Siglec-10 signaling pathway, a CD24 antibody can suppress the CD24/Siglec-10 inhibitory signals sent to macrophages, NK cells and T cells. Moreover, a well-designed CD24 antibody with potent Fc function is able to fully activate macrophage and NK cell-immune responses through ADCP and ADCC, and induce apoptosis. It may also activate and promote T-cell response likely through tumor antigen presentation by activated macrophages to T cells and direct blockade of CD24/Siglec-10 inhibitory signals. Given the all-around immune responses stimulated by blocking the CD24/Siglec-10 signaling pathway, CD24-targeted bispecific molecules and combination of CD24-targeted therapies and other immunotherapies, such as therapies targeting PD-1/PD-L1, show tremendous synergistic potential. The following diagram illustrates the mechanism of blocking the CD24/Siglec-10 pathway:

Mechanism of Blocking CD24/Siglec-10 Pathway



Source: Frost & Sullivan, Literature Review

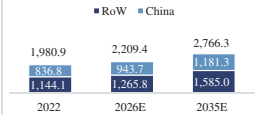
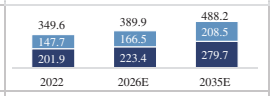
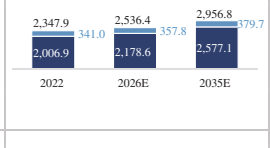
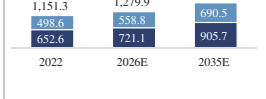
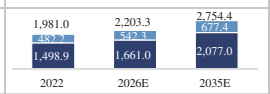
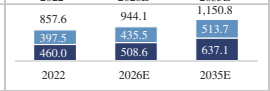
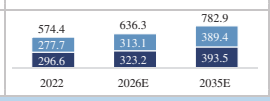
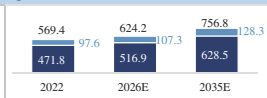
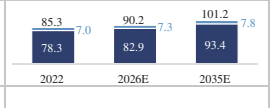
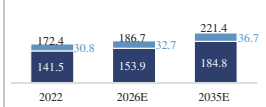
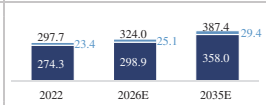
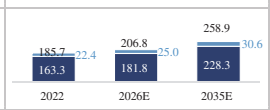
Global and China CD24-targeted drugs competitive landscape

According to Frost & Sullivan, there is no approved drug targeting CD24 globally. No CD24-targeted drug candidate has entered into clinical stage worldwide, except for one drug candidate recently receiving IND approval from the FDA for its Phase I clinical trial. Recently, Pheast Therapeutics, led by Dr. Amira Barkal and Dr. Irving Weissman, the world's pioneer in CD47, revealed their move into the development of cancer therapies targeting CD24, which is expected to stir a new wave of enthusiasm for this novel immuno-oncology target across the global biopharmaceutical industry. However, given the relatively weak immunogenicity of CD24 due to its small protein core, the screening and development of monoclonal antibodies against CD24 has been highly challenging. Globally, there is only one CD24-targeted monoclonal antibody that has recently received IND approval from the FDA for Phase I clinical trial, with very few reported CD24-targeted monoclonal antibodies under preclinical development for cancer treatment, including ImmuneOnco's IMM47. In addition, ImmuneOnco is the only company reported to have been developing CD24-targeted bispecific molecules around the world based on publicly available information, according to Frost & Sullivan.

According to Frost & Sullivan, there are two drug candidates targeting Siglec-10 (EXO-CD24/CovenD24 and CD24-Fc/MK-7110)under clinical development for the treatment of COVID-19 globally. Those drug candidates are designed to bind with Siglec-10 to inhibit cytokine secretion and reduce COVID-19 induced immune over-reaction, exhibiting completely different mechanisms from the CD24-targeted therapies, which cannot be applied for cancer treatment.

SELECTED INDICATIONS ANALYSIS

Summary of the Prevalence of Disease Subtypes, Disease Pathways and Treatment Algorithm for the Selected Indications

Disease	Incidence of Disease (thousand people)	Disease Subtypes	Treatment Algorithm			Drug Candidates	Intended Position of the Company's Product Candidates	
			First Line	Second Line	Third Line		Overseas Markets	China Market
Solid Tumors								
NSCLC		EGFR/ALK/ROS 1 WT	Chemo; VEGFi + Chemo; PD -(L)1 (only for PD -L1 expression) ;PD -(L)-1 + Chemo;	PD-(L)1; Chemo	PD-(L)1; Chemo	IMM01 IMM2520 IMM2902 IMM27M IMM2518	1L; 2L	1L; 2L
		EGFR/ALK/ROS 1 mutation	TKI	TKI	TKI		2L; 3L	2L; 3L
SCLC		/	Chemo + PD -(L)1; Chemo;	Chemo + PD -(L)1; Chemo	/	IMM01 IMM2520	1L; 2L	1L; 2L
BC		HER2 positive	HER2 -targeted mAb + chemo; TKIs + chemo	TKIs ± Chemo; HER2 -targeted ADCs; HER2 -targeted mAb + Chemo	TKIs ± Chemo; HER2 -targeted ADCs	IMM2902 IMM01 IMM47	1L; 2L; 3L	1L; 2L; 3L
		HER2 -low expression	Chemo; Chemo + TKIs	Chemo; Chemo + TKIs	Chemo; Chemo + TKIs			
		TNBC	Chemo ± PD-(L)1	Chemo	Trop -2 targeted ADCs			
GC		HER2 positive	HER2 -targeted mAb + Chemo	HER2 -targeted ADCs; Chemo ± VEGFR -2 targeted mAb;	PD -1; Chemo; HER2 -targeted ADCs; VEGFR -2 targeted therapies	IMM2902 IMM2520 IMM01	1L; 2L; 3L	1L; 2L; 3L
		HER2 negative & low expression	Chemo ± PD -1; PD -(L)1 (only for dMMR/MSI-H)	Chemo ± VEGFR -2 targeted mAb; PD -(L)1 (only for dMMR/MSI-H)	VEGFR -2 targeted therapies; Chemo			
CRC		/	PD -(L)1 (only for MSI-H/dMMR); Chemo ± targeted therapies	PD -(L)1 (only for MSI-H/dMMR); Chemo ± targeted therapies	/	IMM2520	1L; 2L	1L; 2L
HNSCC		/	PD -1+Chemo; PD -1(only for CPS>=1); Chemo ± targeted therapies	PD -1; Chemo	/	IMM01 IMM2520	1L; 2L	1L; 2L
HCC		/	Small molecule targeted drugs; Targeted therapies(anti -VEGF) ± PD -(L)1	Small molecule targeted drugs; PD -1	/	IMM2520 IMM2510 IMM2518	1L; 2L	1L; 2L
ESCC		/	PD -(L)1 + Chemo; Chemo	PD -(L)1; Chemo	/	IMM2520	1L; 2L	1L; 2L
Hematologic Malignancies								
NHL		B-cell NHL	CD20 targeted therapies + Chemo;	CD20 targeted therapies + Chemo; BTKi; CD20xCD3 bsAb	CD20 targeted therapies + Chemo; BTKis; CD20xCD3 bsAb	IMM0306	1L; 2L; 3L	1L; 2L; 3L
		NK-cell/T-cell NHL	Chemo; Radio	HDACi; PD -(L)1; PD -(L)1 + HDACi	HDACi; PD -(L)1; PD -(L)1 + HDACi	IMM01	2L	2L
cHL		/	Chemo; Radio	PD -(L)1 ± Chemo	PD -(L)1 ± Chemo	IMM01	3L	3L
AML		Fit AML	Intensive Chemo; Chemo + Targeted therapies (FLT3i, CD33i)	Chemo; Targeted therapies (CD33i)	/	IMM01	2L	2L
		Unfit AML	Low intensive chemo; Targeted therapies (BCL -2i) + chemo	/	/		1L	1L
MDS/CMML		HR-MDS/CMML	HMAs, Chemo. HSCT	HMAs + targeted therapies (BCL -2i, IDH1/2i); Chemo + HMAs	HMAs + targeted therapies (BCL -2i, IDH1/2i); Chemo + HMAs	IMM01	1L	1L
		LR-MDS/CMML	Immunomodulators; HMAs	/	/	/	/	/
MM		/	Target therapies ±Immunomodulator ± Chemo , ASCT	Target therapies ±Immunomodulator ± Chemo , ASCT	Target therapies ±Immunomodulator ± Chemo , ASCT	IMM01	≥4L	≥4L

Notes: (1) TKI refers to tyrosine kinase inhibitors; Chemo refers to chemotherapy; Radio refers to radiotherapy; WT refers to wild type; HMAs refers to hypomethylating agents; HSCT refers to hematopoietic stem cell transplant; 1L, 2L, 3L and 4L refer to the first line, the second line, the third line and the fourth line respectively; ADC refers to antibody drug conjugate; mAb refers to monoclonal antibody; dMMR/MSI-H refers to deficient DNA mismatch repair/microsatellite instability-high; CPS refers to combined positive score; bsAb refers to bispecific antibody; BTKi refers to bruton tyrosine kinase inhibitor; HDACi refers to histone deacetylase inhibitor; FLT3i refers to FLT3 inhibitor; CD33i refers to CD33 inhibitor; BCL-2i refers to BCL-2 inhibitor; IDH1/2i refers to IDH1/2 inhibitor; TNBC refers to triple negative breast cancer; NHL refers to Non-Hodgkin lymphoma; AML refers to acute myeloid leukemia; HR-MDS/CMML refers to higher risk myelodysplastic syndrome/chronic myelomonocytic leukemia. (2) The drug candidates listed below are being evaluated or have potential to target respective indications.

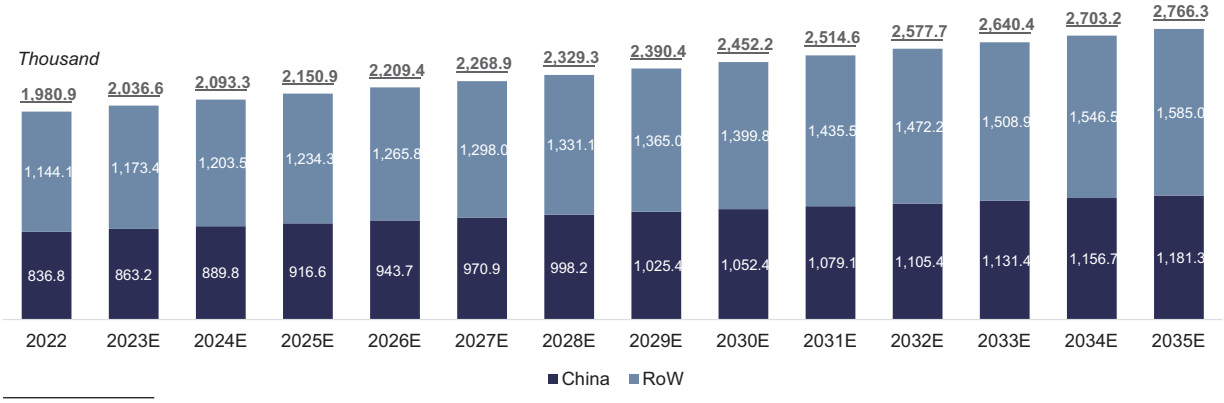
Source: *National Cancer Registry (NCCR), International Agency for Research on Cancer (IARC), Frost & Sullivan*

Solid Tumors

Non-Small-Cell Lung Cancer

Lung cancer is one of the leading causes of cancer-related mortality in China and worldwide. NSCLC is the most prevalent lung cancer and accounts for 85% of all lung cancer cases. The chart below demonstrates historical and projected incidences of NSCLC in China and around the world for the periods indicated:

China and Global Incidence of NSCLC, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.

Source: *NCCR, Frost & Sullivan*

A majority of patients with NSCLC present with advanced or metastatic disease at the time of diagnosis. For those patients diagnosed with late-stage NSCLC, chemotherapy or radiotherapy combined with targeted therapy is commonly used as the standard of care. Since some targeted therapies only work in cancer cells with specific genetic mutations and certain immuno-oncology therapies such as PD-1/PD-L1 inhibitors show limited efficacy, notable unmet medical needs persist across this large patient population.

EGFR/ALK/ROS1 wild-type NSCLC accounts for almost 65% of all NSCLC cases. For EGFR/ALK/ROS1 wild-type NSCLC, platinum-based chemotherapy had long been recommended as the standard treatment for a majority of this group. With the emergence of immuno-oncology therapies and anti-angiogenic therapies, PD-1/PD-L1 inhibitors (such as pembrolizumab) and angiogenesis inhibitors (such as bevacizumab) also become available treatment options for those patients. However, PD-1/PD-L1 inhibitor monotherapy has only shown convincing benefits in patients with ≥1% tumor cells expressing PD-L1, which subgroup accounts for less than one quarter (24.4%) of the entire NSCLC population. Even within this subgroup, the response rate of PD-1/PD-L1 inhibitor monotherapy is merely 27% in the first-line setting. The relatively low response rate is possibly due to insufficient immune activation in "cold tumors." Given the limited

efficacy of current immunotherapies, there remains an urgent need for the development of more effective novel immunotherapies, and synergistic combinations of immunotherapies and angiogenesis inhibitors or targeted therapies (such as HER2-targeted therapies) for NSCLC.

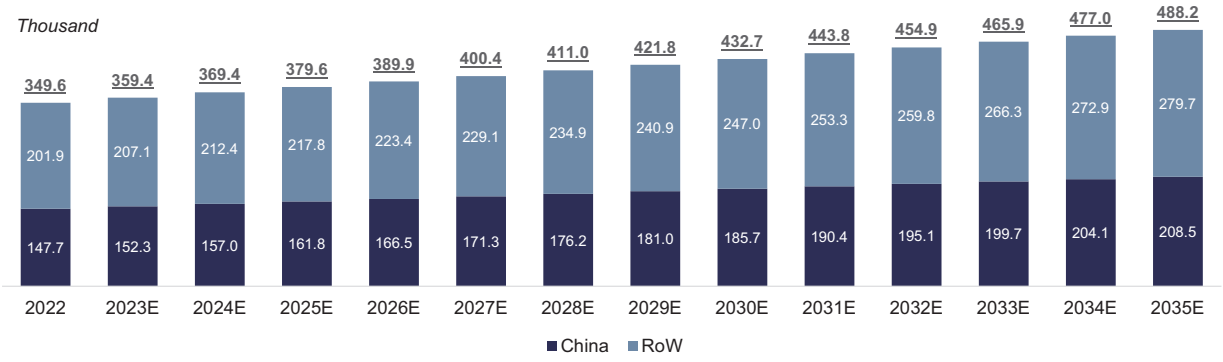
While targeted therapies, such as EGFR tyrosine kinase inhibitors (TKIs), show good efficacy in treating NSCLC harboring EGFR mutations, all the patients treated with EGFR TKIs will eventually develop acquired drug resistance, and patients with relapsed or refractory disease are left with limited effective treatment options. Similarly, while there are also TKIs specifically targeting ALK and ROS1 mutations of NSCLC, their long-term efficacy is limited due to inevitable drug resistance. Moreover, PD-1/PD-L1 inhibitors only demonstrate modest efficacy targeting this group of patients. Thus, the development of novel immunotherapies, including bispecific molecules and combination therapies, may be a promising strategy to address clinical needs of those patients.

Research has revealed that the activation of innate immunity can promote T cell responses in "cold tumors" or non-T cell-inflamed immune-suppressive TME by recruiting T cells to the TME and presenting tumor-specific antigens. Such synergistic effects between innate and adaptive immunities provide a compelling scientific rationale for dual-targeting of critical innate and adaptive immune checkpoints. Moreover, since the overexpression of innate immunity-related ligands, such as CD47 and CD24, is correlated with poor prognosis of NSCLC, therapies harnessing both immune systems and their potential combination with angiogenesis inhibitors or targeted therapies are expected to improve the treatment outcome and bring significant clinical benefits for NSCLC patients with limited response to PD-1/PD-L1 inhibitors.

Small Cell Lung Cancer

SCLC accounts for 15% of all lung cancer cases and is most commonly diagnosed in patients with histories of heavy smoking. In general, SCLC grows aggressively and is highly metastatic, resulting in a high mortality rate. The chart below illustrates historical and projected incidences of SCLC in China and around the world for the periods indicated:

China and Global Incidence of SCLC, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

Due to the asymptomatic nature and rapid progression of the disease, most SCLC patients are diagnosed at the late stage with distant metastases, or so-called the extensive stage. Given the high level of heterogeneity of SCLC, developing targeted drugs for this disease has been challenging because of the lack of common and actionable oncogenic drivers. After several decades, chemotherapy remains the front-line standard of care regimen for extensive-stage SCLC. Unfortunately, although patients with extensive-stage SCLC are generally responsive to initial chemotherapy regimens, most of them will eventually relapse due to drug resistance.

In recent years, the combination of PD-1/PD-L1 inhibitors (including atezolizumab, durvalumab and serplulimab) and chemotherapy has also been recommended for the treatment of extensive-stage SCLC in first and/or later-line settings. However, treatment benefits offered by this combination therapy are not satisfactory. Clinical trial results of atezolizumab and durvalumab, which are approved PD-1/PD-L1 inhibitors, showed only around two-month improvement in median overall survival (mOS) compared with chemotherapy alone (12.3-13.0 months vs. 10.3 months).

Additionally, most patients demonstrate either primary or rapid acquired resistance to current regimens, and very few drugs are approved as effective for second-line treatment of SCLC. Without effective treatment options, the prognosis of patients with SCLC is dismal with an mOS of 4 to 5 months.

Limitations of current regimens highlight the clear need to improve effectiveness and expand the scope of current therapeutic strategies. Considering the lack of widely expressed oncogenic drivers and corresponding targeted therapies for SCLC, the development of immuno-therapy presents a promising direction to improve the treatment results in SCLC. Macrophage infiltration and expression of CD47 and CD24 are found to be high in SCLC, and the upregulation of CD47 or CD24 has been a major mechanism exploited by tumor cells to evade immune attack. The clinical benefits of targeting CD47/SIRPα pathway for the treatment of SCLC have also been validated. Since the activation of macrophages can enhance T-cell response through the crosstalk of innate and adaptive immunities, combination therapies and bispecific molecules targeting both CD47 or CD24 and PD-1/PD-L1 may produce encouraging efficacy and achieve better outcomes in the majority of SCLC patients who are not responsive to PD-1/PD-L1 inhibitors. Such novel therapies may also have the potential to advance towards the first-line treatment for SCLC.

Breast Cancer

BC is cancer that forms in the cells of the breasts. BC is the most prevalent type of cancer in women and became the most common cancer globally as of 2022. The chart below illustrates historical and projected incidences of BC in China and around the world for the periods indicated:

China and Global Incidence of BC, 2022–2035E

Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

Human epidermal growth factor receptor 2 (HER2) is a gene that can play a critical role in the development of BC. HER2 expression level has long served as a key indicator for selecting medical treatment of BC patients. Based on their HER2 expression levels, BC patients can be categorized into three subgroups: HER2-positive (IHC3+, IHC2+ and ISH+), HER2-low expressing (IHC1+, IHC2+ and ISH-) and HER2-negative (IHC0).

Approximately 50% of all BC cases exhibit a low-level expression of HER2. In contrast to HER2-positive tumors, tumors with HER2-low expression generally do not respond to HER2-targeted antibodies, such as HERCEPTIN® (trastuzumab), and thus the clinical significance of low-level HER2 expression had been underappreciated for several decades. Until recently, there had only been one treatment approved specifically for HER2-low expressing BC, *i.e.*, ENHERTU® (trastuzuab deruxtecan), a novel HER2-targeted antibody-drug conjugate (ADCs) agent. Trastuzumab deruxtecan was approved by the FDA for HER2-positive BC in 2019 and HER2-low expressing BC in 2022. Clinical results showed that trastuzumab deruxtecan resulted in an encouraging ORR of 52.3% in HER2-low expressing group. At the same time, severe adverse events, such as interstitial lung disease and even fatal events, were reported to be associated with trastuzumab deruxtecan, raising certain safety concerns. Given the substantial proportion of patients with HER2-low expressing BC, targeting this group with highly specific and effective therapies presents a promising prospect and large market opportunities.

As to HER2-positive BC, HER2-targeted antibodies, such as trastuzumab and PERJETA® (pertuzumab), in combination with chemotherapy and TKIs, such as pyrotinib and TUKYSA® (tucatinib), are recommended as the standard of care for first-line and second-line treatments. However, most patients eventually develop resistance to current regimes, as exemplified by the only 7.2 months of median time to progression (TTP) for BC patients treated with trastuzumab. Although HER2-targeted ADCs (e.g., trastuzumab deruxtecan) were approved for relapsed disease, they have been reported to cause severe adverse events. For example, trastuzumab deruxtecan was reported to result in interstitial lung disease with an occurrence rate of 9% and a high fatality rate of 4.3%. Therefore, there remain unfilled needs for safer and more effective treatment targeting HER2-positive BC that relapsed after frontline regimens.

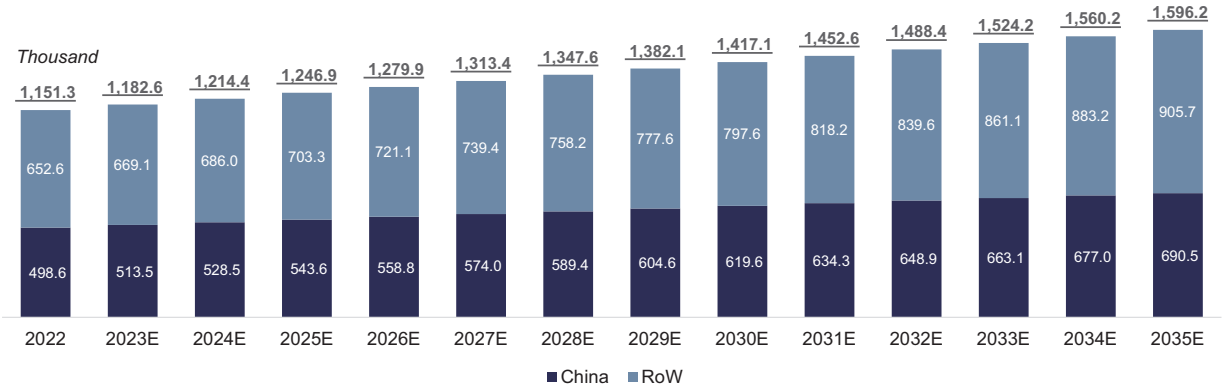
For advanced triple negative BC (TNBC), in addition to chemotherapy, PD-1/PD-L1 inhibitors (such as pembrolizumab) combined with chemotherapy and novel Trop2-directed ADCs, such as TRODELVY® (sacituzumab govitecan), are also recommended as the standard treatment. However, the combination of pembrolizumab and chemotherapy can only benefit a small subgroup of TNBC patients (less than 19%) with high PD-L1 expression (combined positive score (CPS)≥ 10), and it has exhibited limited efficacy with a median progression-free survival (mPFS) of 9.7 months. Additionally, sacituzumab govitecan showed limited improvement of progression-free survival in HR+/HER2- BC compared to chemotherapy and is reported to cause severe adverse events (such as 52% of Grade 3 and 4 neutropenia), suggesting highly unmet medical needs.

To address the significant unmet needs of BC patients, the quest to develop novel precision medicine strategies continues. Notably, since CD47 and CD24 are commonly overexpressed in BC and are important biomarkers for poor prognosis, immuno-oncology therapies targeting innate immunity, and their combination with PD-1/PD-L1 inhibitors or HER2-targeted therapies emerge as attractive solutions with the potential to improve the clinical outcomes for different subtypes of BC.

Gastric cancer

GC is a common cancer that begins in the stomach. GC was the second most common type of cancer in China in 2022. The chart below illustrates historical and projected incidences of GC in China and around the world for the periods indicated:

China and Global Incidence of GC, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

Since the awareness of early screening and detection of GC remains low in China, most cases are not diagnosed until it progresses into advanced stage and becomes metastatic disease, resulting in a high mortality rate of GC patients. Clinically, HER2 has been established as one of the most critical predictive biomarkers for the treatment of metastatic GC. Based on the HER2 expression level, GC cases are mainly categorized as HER2-positive (IHC3+, IHC2+ and ISH+) and HER2-negative (IHC0) in the treatment guideline. While the expression level of "IHC1+, IHC2+ and ISH-" is not clearly defined in the guideline, it is commonly referred to as "HER2-low expression" in academic research and clinical practices, and this new concept has emerged and proved to predict the responses to certain novel HER2-targeted therapies.

More than 25% of all GC cases have low-level HER2 expression. Despite the large population, this group has not been identified as a distinct clinical entity from HER2-negative tumors since specific and effective treatment options for this group are lacking. For HER2-low expressing and HER2-negative GC, chemotherapy alone or in combination with immuno-oncology therapy (e.g., PD-1 inhibitor) is the standard frontline treatment, and chemotherapy is a major option for second-line treatment. Since the survival improvement of PD-1/PD-L1 inhibitors combined with chemotherapy in this group is modest (mPFS of 7.7 months) and PD-1/PD-L1 inhibitors as monotherapy can only be used for a small subset of this group (e.g., deficient DNA mismatch repair (dMMR)/microsatellite instability-high (MSI-H) patient who account for 10% to 20% GC patients), there are still urgent needs to develop more efficacious combination therapies of immunotherapies and targeted therapies or angiogenesis inhibitors for the treatment of HER2-low expressing and HER2-negative GC.

For HER2-positive GC, HER2-targeted antibodies (e.g., trastuzumab) in combination with chemotherapy is recommended as the standard treatment in the first-line setting. It is inevitable that most patients eventually relapse or become refractory to the treatment of trastuzumab. For relapsed GC patients, traditionally chemotherapy is the major option for their treatment. Recently, novel HER2-targeted ADCs (e.g., trastuzumab deruxtecan) and VEGFR-2 targeted antibodies (e.g. CYRAMZA®, ramucirumab) in combination with chemotherapy have also been approved to be used in second-line treatment of HER2-positive GC. When the disease further progressed, chemotherapy, targeted therapies (e.g. AITAN®, apatinib), PD-1 antibodies (e.g. OPDIVO®, nivolumab), and HER2-targeted ADCs (e.g. AIDIXI®, disitamab vedotin) can be used for third-line treatment. While novel HER2-targeted ADCs show meaningful responses in HER2-positive GC

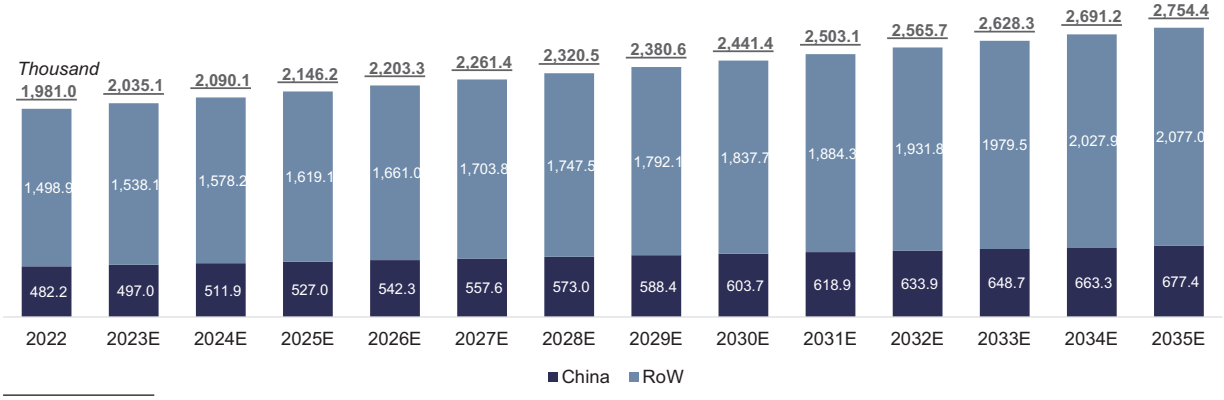
patients who have previously received trastuzumab therapy, those ADCs are typically associated with severe side effects, such as interstitial lung disease and even deaths. Moreover, the improvement in OS and PFS by ADCs is limited. For instance, in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma who have progressed after at least two prior treatment regimens, ENHERTU® only showed limited survival benefits compared to chemotherapy (mOS: 12.5 months vs. 8.4 months; mPFS: 5.6 months vs. 3.5 months).

The addition of immuno-oncology therapies to HER2-targeted agents or angiogenesis inhibitors through combination or bispecific strategies may offer new hope to patients with HER2-low expressing and HER2-negative GC, as well as GC patients who had progressed after the first-line treatment. Macrophages are pervasively present in gastrointestinal (GI) tumors, including GC, CRC and ESCC. CD47 and CD24, key macrophage checkpoints, have been recognized as important biomarkers for poor prognosis in GC. Thus, novel agents targeting CD47 and CD24 are rational combination partners for HER2-targeted agents or PD-1/PD-L1 inhibitors for the treatment of HER2-low expressing and HER2-negative GC given their ability to induce strong innate immune responses and boost integrated immune reaction.

Colorectal Cancer

CRC includes all types of cancers that begin in the colon and rectum. The chart below illustrates historical and projected incidences of CRC in China and around the world for the periods indicated:

China and Global Incidence of CRC, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

Early-detection rate of CRC in China is markedly low for a number of reasons, and 89% of CRC cases are diagnosed at a late stage. For late-stage CRC, chemotherapy or chemotherapy combined with targeted therapies, such as bevacizumab and ERBITUX® (cetuximab), are recommended for standard first- and later-line treatments. Additionally, for a small fraction of patients with MSI-H/dMMR phenotype, PD-1/PD-L1 inhibitors (e.g., pembrolizumab) are recommended for use in the first- and second-line settings.

However, since the efficacy of currently available treatments is modest, the five-year survival rate of patients with late-stage CRC is merely about 10%. Particularly, the disease lacks effective medications to slow or stop its course after treatment failure has occurred with initial standard treatment owing to toxicity or progression. In the absence of alternative therapies, the initial treatment drugs are often reused in patients who have progressed with this regimen in routine clinical practice, although response to and survival benefits of second-line chemotherapy (combined with targeted therapy) are usually very limited. In addition, a substantial majority of CRC patients do not respond to PD-1/PD-L1 inhibitors, possibly due to "cold tumors" or non-T

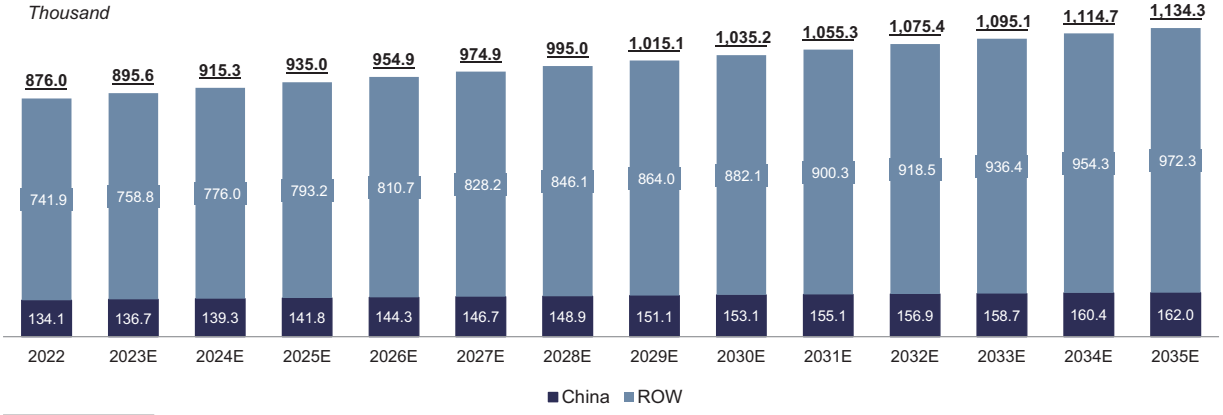
cell-inflamed immune-suppressive TME. PD-1 inhibitors are currently only approved for CRC patients with MSI-H/dMMR, accounting for less than 5% of late-stage CRC patients, while in general CRC patients, PD-1 inhibitor monotherapy merely produced weak responses with ORR below 10%.

In spite of decades-long efforts, developing targeted therapies for improved treatment of late-stage CRC still faces significant challenges since many of the key oncogenic drivers are not amenable to targeted therapy. Meanwhile, immuno-oncology therapy has demonstrated promising efficacies and good tolerance in GI-related cancers in recent years and can possibly also bring new options to CRC patients. Although PD-1/PD-L1 inhibitors are not efficient enough by themselves, the combination of PD-1/PD-L1 inhibitors with innate immuno-therapy may offer enhanced responses in metastatic CRC based on preclinical and clinical data. Macrophages are pervasively present in GI cancers, including CRC, GC and ESCC. CD47 and CD24, key macrophage checkpoints widely expressed on colorectal cancer cells, are found to be important biomarkers for poor prognosis. Therefore, targeting CD47 or CD24 can activate macrophages in tumor tissues to directly kill cancer cells and further enhance T cell responses by transforming the "cold tumors" into "hot tumors." The addition of macrophage-targeted therapies to PD-1/PD-L1 inhibitors is thus expected to enhance the responses of PD-1/PD-L1 inhibitors in a broader CRC patient population and achieve improved treatment outcomes.

Head and Neck Squamous Cell Carcinomas

HNSCC develop from the mucous membranes of the mouth, nose, and throat and are the most common cancer that arises in the head and neck region. The chart below illustrates historical and projected incidences of HNSCC in China and around the world for the periods indicated:

China and Global Incidence of HNSCC, 2022–2035E



Notes: (1) The incidence of HNSCC in the chart includes, among others, oral cancer, oropharyngeal cancer, laryngeal cancer, hypopharyngeal cancer, nasopharyngeal cancer; (2) RoW refers to all countries and regions in the world except China.

Source: *NCCR, Frost & Sullivan*

For patients with metastatic HNSCC, recommended first-line treatment options include chemotherapy, targeted therapy (e.g., cetuximab), PD-1 inhibitors, and chemotherapy combined with targeted therapy or PD-1 inhibitors. In second-line treatment, PD-1 inhibitor monotherapy (e.g., pembrolizumab and nivolumab) and chemotherapy are recommended. Despite the use of these treatment options, survival rates for metastatic HNSCC are still considerably low, indicating a need for more effective therapeutics.

Although immuno-oncology therapy presents a promising approach to treat HNSCC, currently available immuno-oncology therapies produce poor responses in a majority of HNSCC patients. In the first-line setting, the application of PD-1/PD-L1 inhibitors as monotherapy is limited to 23% of HNSCC patients who have PD-L1 expression (CPS≥1). In this selected population with PD-L1

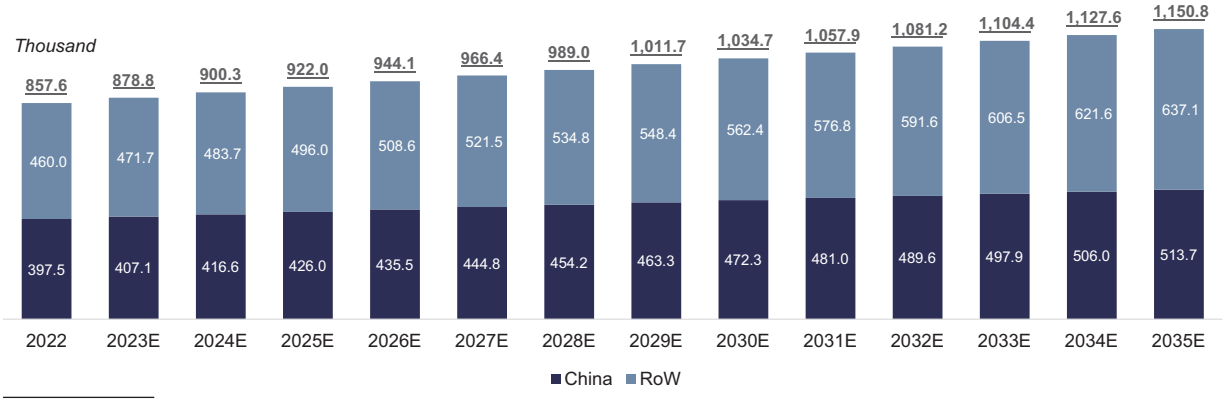
expression, the response rates to PD-1 treatment are still relatively low. According to publicly reported data, the ORR was only 19% with PD-1/PD-L1 inhibitors as single agent. When used in first-line treatment for broad HNSCC patients, PD-1/PD-L1 inhibitors combined with chemotherapy showed limited survival benefits compared to cetuximab combined with chemotherapy (mOS: 13.0 months vs. 10.7 months). For patients who have progressed on first-line treatment, the ORR of PD-1/PD-L1 inhibitors was even lower, only reaching 13.3% to 16%.

Novel combination strategies showed great promise to improve the responses to PD-1 treatment and achieve better efficacy in HNSCC. CD47, as a critical macrophage checkpoint, plays a broad role in cancer immune evasion. With wide distribution of macrophages in HNSCC, a CD47-targeted therapy with potent IgG1 Fc effector function can further promote T-cell infiltration by fully activating macrophages and facilitating their crosstalk with T cells, thus improving the responsiveness to PD-1/PD-L1 inhibitors and inducing phagocytosis of tumor cells by activated macrophages. In contrast, those CD47-targeted therapies without Fc effector function could only generate limited therapeutic benefits. For example, ALX Oncology's ALX-148 (a CD47-targeted SIRPα-Fc fusion protein with an inert IgG1 Fc) in combination with pembrolizumab and chemotherapy only showed a 3% improvement in the ORR compared to the combination of pembrolizumab and chemotherapy (39% vs. 36%) for the first-line treatment of HNSCC in its reported clinical trial. Given the synergistic effects of CD47-targeted therapy and PD-1/PD-L1 inhibitors, the combination of these two agents can potentially produce potent and integrated immune responses in HNSCC patients who do not respond to PD-1/PD-L1 inhibitors and provide a new option for metastatic disease without effective treatments.

Hepatocellular Carcinoma

HCC accounts for 85% of all liver cancer cases. It occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection, and it is a leading cause of death in people with cirrhosis. The chart below illustrates historical and projected incidences of HCC in China and around the world for the periods indicated:

China and Global Incidence of HCC, 2022–2035E



Note: RoW refers to the rest of the world except China.
Source: *NCCR, Frost & Sullivan*

Therapeutic options for HCC are generally determined based on disease staging. For late-stage HCC, systemic therapies are primarily recommended for first- and second-line treatments, two major classes of which are small molecule targeted drugs, such as NEXAVAR® (sorafenib), LENVIMA® (lenvatinib) and immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors). The corresponding combination therapies of targeted drugs or immune checkpoint inhibitors are also commonly used in first- and second-line treatments.

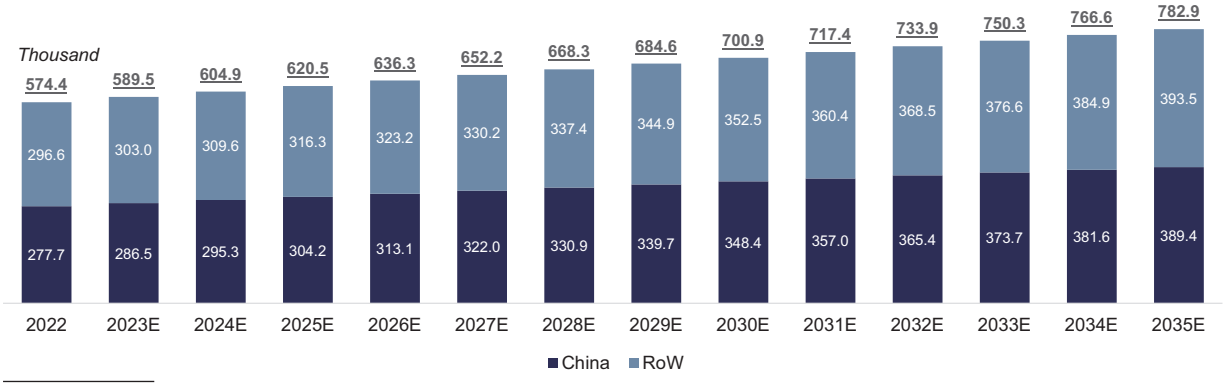
Due to the limited clinical outcomes associated with small molecule targeted drugs, PD-1/PD-L1 inhibitors have been introduced in the first- and second-line settings to improve treatment outcomes for HCC patients in recent years. However, current immuno-oncology therapy regimens still fail to yield material progression-free and overall survival benefits. For example, although the combination of a PD-1/PD-L1 inhibitor and anti-VEGF therapy, such as atezolizumab or sintilimab plus bevacizumab, has demonstrated certain efficacy (an overall mPFS of around 4 months), there is still room for improvement, indicating a need for more effective combination or bispecific strategies. When it comes to second-line treatment, treatment options become fewer and are usually less effective. For relapsed disease, both PD-1 inhibitors, such as pembrolizumab and BAIZE'AN® (tislelizumab), and small-molecule targeted therapy, such as STIVARGA® (regorafenib), only produced ORRs under 17% in monotherapy clinical trials.

The unsatisfactory efficacies of current regimens suggest the dire need for the development of more effective therapeutic strategies. As CD47 and CD24, key macrophage checkpoints, have both been found closely correlated with poor prognosis of HCC, and macrophages are widely distributed in HCC tissues, CD47/CD24-targeted immuno-oncology therapy is expected to work synergistically with PD-1/PD-L1 inhibitors to generate robust immune responses and bring differentiated clinical benefits for HCC patients. Therapies harnessing both the innate and adaptive immune systems and the combinations of immuno-oncology therapies and angiogenesis inhibitors have the potential to address the notable unmet medical needs in HCC.

Esophageal Squamous Cell Carcinoma

ESCC is the predominant histological subtype of esophageal cancer (EC), accounting for approximately 90% of EC cases. The chart below shows historical and projected incidences of ESCC in China and around the world for the periods indicated:

China and Global Incidence of ESCC, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

The treatment options for ESCC are still inadequate with a poor prognosis due to the limited knowledge of pathology and genetic drivers for ESCC resulting from its high mutational load. For advanced ESCC, PD-1/PD-L1 inhibitors, such as AIRUIKA® (camrelizumab) and pembrolizumab, in combination with chemotherapy or as monotherapy have been primarily indicated in both the first-line and second-line settings.

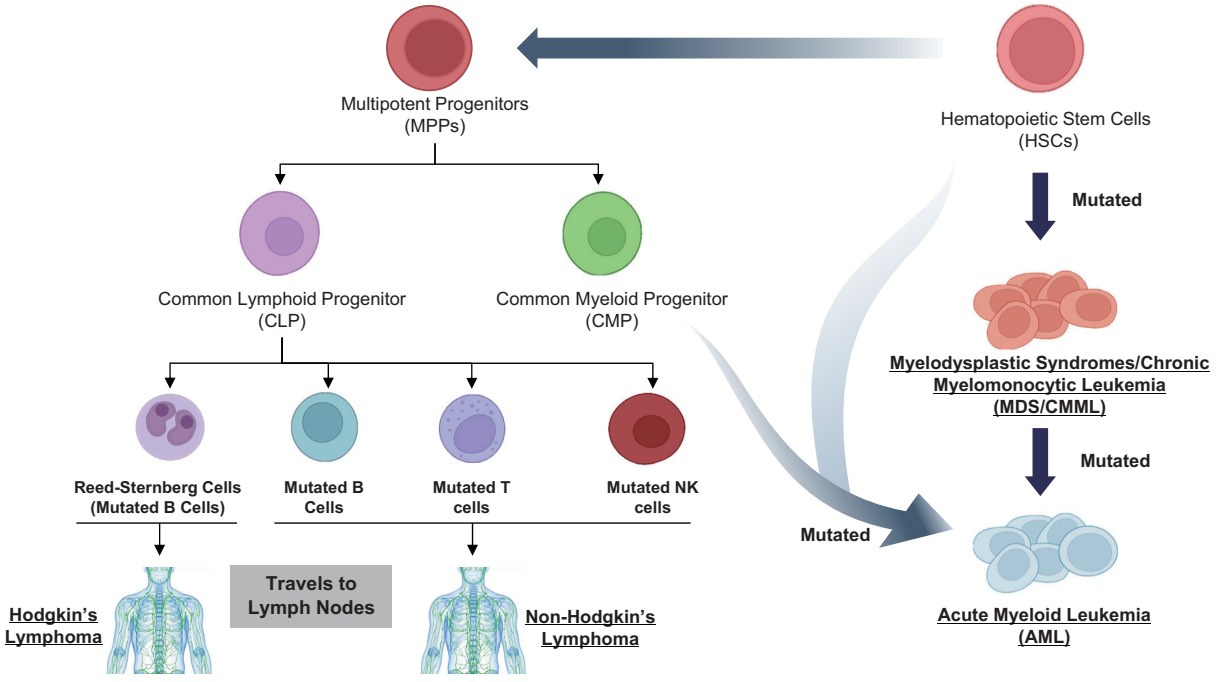
However, the PD-1/PD-L1 inhibitor-based combination therapies can only provide limited benefits for patients with advanced ESCC. For example, the combination of pembrolizumab and chemotherapy merely increased the mPFS to 6.3 months from 5.8 months of chemotherapy alone. Further, the mOS of patients treated with this combination therapy was only 12.4 months, compared to 9.8 months when chemotherapy used alone.

The paucity of specific driver gene and corresponding targeted drugs urges the development of strategies to improve the response rates of PD-1/PD-L1 inhibitors in treating ESCC. By fully eliciting potent innate and adaptive immune responses, CD47/CD24-targeted therapies combined with PD-1 inhibitors have shown immense promise in overcoming the limitations of current available treatment options. Furthermore, the wide and abundant distribution of macrophage in ESCC tumor tissues, as well as the high correlation of CD47/CD24 overexpression with poor prognosis, implies huge market potential for CD47/CD24-targeted therapies.

Hematologic Malignancies

Hematologic malignancies, also known as blood cancers, include NHL, HL, MDS/CMML and AML that stem from the abnormal differentiation of hematopoietic stem cells (HSCs) in the bone marrow.

Overview and Classification of Hematologic Malignancies



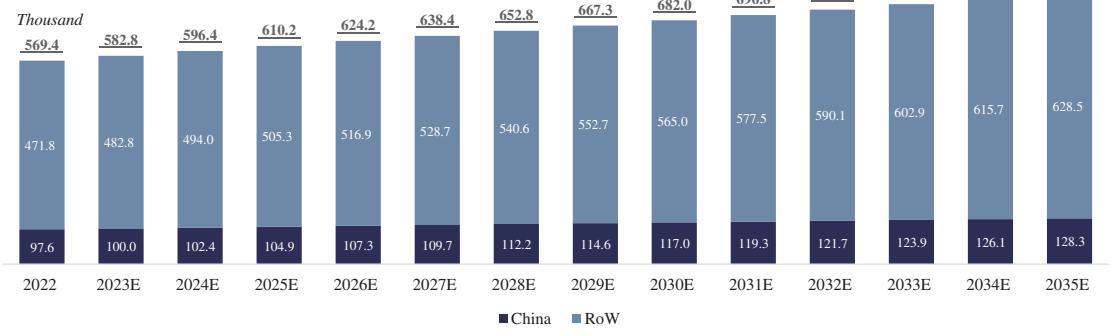
Source: Literature Review, Frost & Sullivan analysis

Non-Hodgkin Lymphoma

NHL, accounting for over 80% of lymphomas, is an umbrella term for a group of independent diseases with diverse heterogeneity developed from the lymphatic system, which can be divided into B-cell NHL and NK-cell/T-cell NHL. B-cell NHL accounts for approximately 85% of NHL cases and includes, among others, DLBCL, mantle cell lymphoma (MCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). NK-cell/T-cell NHL includes NK/T cell lymphoma (NKTCL) and PTCL. The duration of medical treatment for NHL is relatively long considering its five-year OS rate of roughly 69% to 72%. Approximately 50% of NHL patients will eventually progress to R/R NHL due to drug resistance, leaving few effective treatment options. The chart below shows historical and projected incidences of NHL in China and around the world for the periods indicated:

China and Global Incidence of NHL, 2022–2035E

Period	CAGR		
	China	RoW	Total
2022 -2026E	2.4%	2.3%	2.3%
2026E -2030E	2.2%	2.2%	2.2%
2030E -2035E	1.9%	2.2%	2.1%



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

For B-cell NHL, CD20 antibody (such as rituximab) combined with chemotherapy is the main treatment option covering the first and following lines. This combination is also primarily recommended for treating R/R B-cell NHL but only has limited efficacy. In addition, emerging targeted drugs, such as BTK inhibitors (e.g., IMBRUVICA® (ibrutinib), BRUKINSA® (zanubrutinib) and orelabrutinib) are also recommended for certain types of B-cell NHL, including CLL, DLBCL and MCL, although the disease will eventually progress due to drug resistance. Although mosunetuzumab (a novel CD20×CD3 bispecific molecule) has been approved for the treatment of R/R FL in the EU and the U.S., this drug is associated with severe safety concerns, including 44.4% of CRS reported in its clinical trials. The second-line or later-line treatment options for certain R/R lymphoma indications, such as FL, are still limited due to the lack of effective treatment with balanced safety and efficacy.

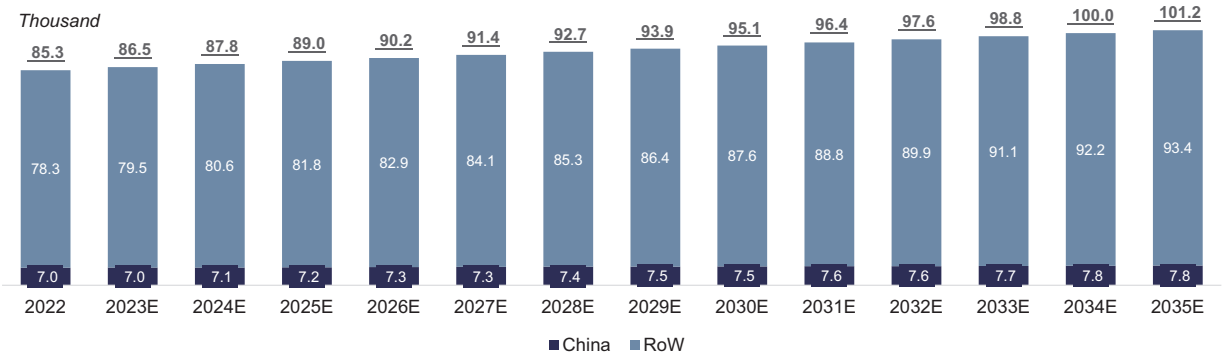
For NK-cell/T-cell NHL, chemotherapy and radiotherapy are primarily recommended. As current treatment options are insufficient, although not officially approved by the FDA or the NMPA, PD-1/PD-L1 inhibitors alone or in combination with histone deacetylase inhibitor (HDACi, such as chidamide) are commonly used for R/R NKTCL due to their efficacy, indicating certain unmet needs in availability. Although HDACi is recommended for treating certain subtypes of R/R PTCL, its median duration of response (DOR) stays relatively low at 9.9 months. Thus far, the practically available treatment options for R/R PTCL remain largely limited to chemotherapy, indicating a substantial unmet medical need.

As tumor-infiltrating macrophages constitute the major component for the TME of NHL and high expression of CD47 (often correlated with poor prognosis in multiple NHL subtypes) has been identified on NHL cells, bispecific strategies targeting macrophage checkpoints, such as CD47, in addition to CD20 show immense potential to achieve enhanced tumor killing effects compared to CD20 antibodies as the mainstay treatment of NHL.

Classical Hodgkin Lymphoma

Classical Hodgkin Lymphoma (cHL) is a malignancy of the immune system, accounting for over 90% of HL. The malignant cHL cells not only limit the presentation of tumor antigens, but also hamper the antitumor immune responses by secreting immune-suppressive cytokines. The chart below shows historical and projected incidences of HL in China and around the world for the periods indicated:

China and Global Incidence of HL, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

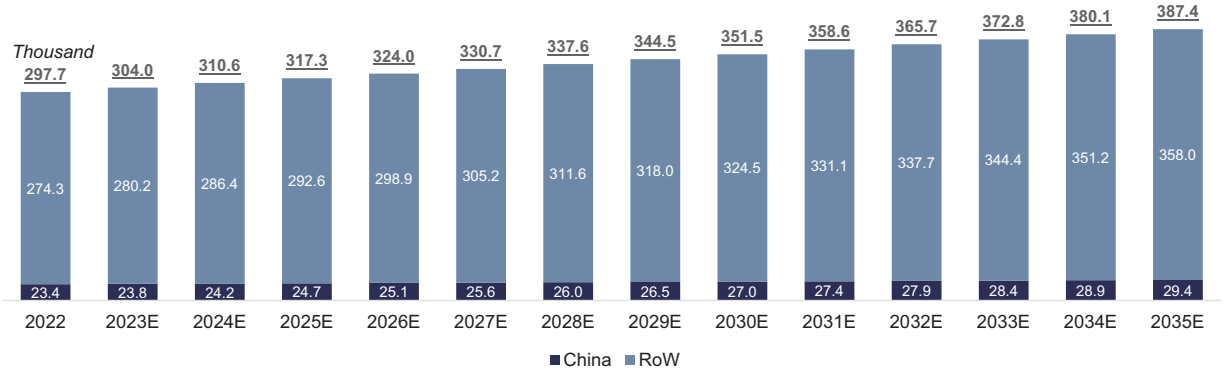
Chemotherapy and radiotherapy are mainly recommended for the first-line treatment of cHL. For R/R cHL, PD-1/PD-L1 inhibitors (e.g., sintilimab, tislelizumab, camrelizumab, nivolumab, and pembrolizumab) alone or in combination with chemotherapy are mainly recommended. Despite the fact that PD-1/PD-L1 inhibitors have shown good efficacy in R/R cHL, as demonstrated by an ORR of 66% achieved by pembrolizumab monotherapy, patients who had relapsed or progressed after PD-1/PD-L1 inhibitors are left with very limited treatment options, presenting unmet medical needs to be addressed.

As CD47 is commonly overexpressed in cHL, novel CD47-targeted drugs or its combination with PD-1/PD-L1 inhibitors could offer new prospects for those R/R cHL patients previously treated with PD-1/PD-L1 inhibitors, thus addressing a significant unmet medical need.

Myelodysplastic Syndrome/Chronic Myelomonocytic Leukemia

MDS is a type of myeloid neoplastic disease with gradual expansion of malignant hematopoietic clones leading to normal hematopoietic failure. CMML is a clinically heterogeneous disorder with poor prognosis, which was once classified as a type of MDS according to the French-American-British classification. The chart below shows historical and projected incidences of MDS/CMML in China and around the world for the periods indicated:

China and Global Incidence of MDS/CMML, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

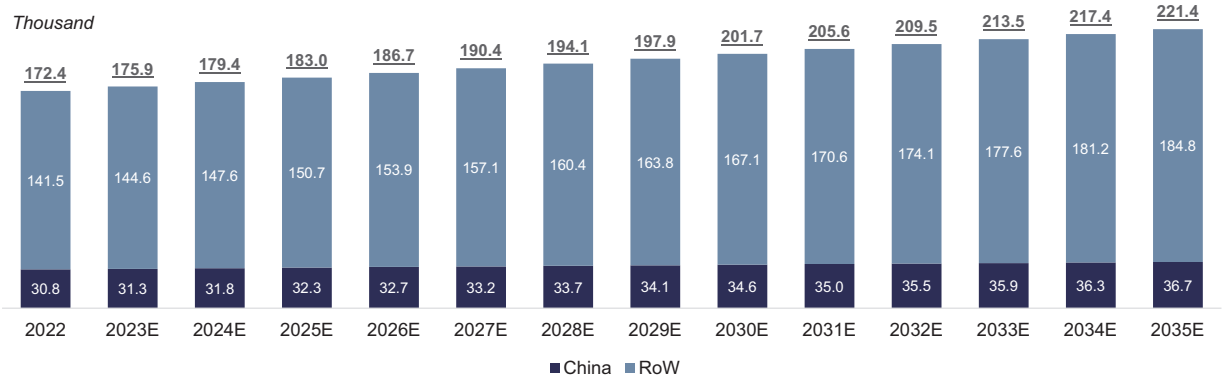
Currently, patients with MDS/CMML are treated based on risk assessment on an individual basis. Immunomodulators and hypomethylating agents can be deployed for patients with lower-risk MDS/CMML due to different clinical presentation. In contrast, MDS/CMML patients with relatively higher risk have a poor prognosis and are prone to AML transformation, thus requiring high-intensity treatment, such as hypomethylating agents (e.g., azacitidine and decitabine), chemotherapy and hematopoietic stem cell transplantation (HSCT). However, the clinical application of HSCT in MDS patients is limited due to multiple factors, such as its high relapse rate, difficulty in finding an ideal match, and significant cost. Most patients will relapse and progress to higher-risk (HR) MDS/CMML as the existing medical treatments are not curative. Initial responses of patients with HR MDS/CMML to the standard of care (e.g. hypomethylating agents) in the first-line treatment are limited to 40% to 50% and often short-lived, leaving unmet needs for more effective treatment options in the first-line setting.

Since MDS/CMML cells can evade immune attack through the upregulation of inhibitory ligands, such as CD47 which is an important biomarker for poor prognosis, strategies targeting CD47 could offer promising solutions for the treatment of HR MDS/CMML. Gilead's magrolimab in combination with azacitidine has achieved an ORR of 75% in its U.S. trial for the first-line treatment of MDS with intermediate to very high risk. However, safety issues remain a major concern of CD47 antibodies due to their severe blood toxicity observed in clinical trials. Thus, the combination of CD47-targeted therapies with potent efficacy and balanced safety profile and azacitidine will be a promising therapeutic option in addressing the unmet needs of MDS/CMML patients in China and worldwide.

Acute Myeloid Leukemia

AML is a disorder characterized by uncontrolled proliferation of undifferentiated myeloid precursor cells, which leads to the accumulation of immature myeloid cells and myeloblasts in the bone marrow and peripheral blood. The chart below shows historical and projected incidences of AML in China and around the world for the periods indicated:

China and Global Incidence of AML, 2022–2035E



Note: RoW refers to all countries and regions in the world except China.
Source: *NCCR, Frost & Sullivan*

Treatment outcomes for AML vary across patients in different age groups due to age-related physical conditions. Elderly patients generally experience shorter survival and face higher risk of treatment-related toxicity. Thus, the management of AML is dependent on the tolerability of individual patients for intensive antileukemic therapy.

Intensive chemotherapy is commonly recommended for AML patients with good physical conditions. When these AML patients have identifiable biomarkers, such as FLT3 gene mutation and CD33 protein expression, targeted drugs including FLT3 inhibitors (e.g., midostaurin) and CD33 inhibitors, such as MYLOTARG® (gemtuzumab ozogamicin), can be used to improve the treatment outcome. However, only a certain subgroup of patients can benefit from these targeted drugs. For instance, approximately 30% of AML patients with FLT3 mutation can be treated by FLT3 inhibitor, such as XOSPATA® (gilteritinib). Thus, solutions with improved efficacy and response rates are urgently needed to fill in the current first-line treatment paradigm for AML patients with good physical conditions.

For frail/unfit AML patients with poor physical conditions, low-intensity chemotherapy alone or combined with BCL-2 targeted inhibitor, such as VENCLEXTA® (venetoclax), is approved for the first-line treatment. However, the mOS of this combination therapy was only 14.7 months. Thus, there are considerable unmet needs for developing more efficacious therapies to treat AML patients.

Since CD47 is highly expressed in AML and is a biomarker for poor prognosis, strategies targeting innate immunity has strong potential to fulfill those unmet needs. The synergistic effects of CD47-targeted therapies and azacitidine have been validated in global clinical trials. For instance, Gilead's magrolimab has achieved great efficacy in the first-line treatment of AML with an ORR of 49% when used in combination with azacitidine. However, CD47 antibodies are generally associated with safety issues, including severe blood toxicity, as exemplified by the partial suspension of certain clinical trials for magrolimab as discussed above. Thus, those CD47-targeted drug candidates with better safety profiles could be an effective therapeutic option for treating AML.