JHBP (CY) Holdings Limited (6998 HK)

A biopharmaceutical company focusing on oncology and autoimmune therapies

BUY (Initiation)

Target Price	**HK$26.49**
Up/Downside	**+38.00%**
Current Price	**HK$19.20**

- **Strong pipelines focusing on oncology and autoimmune diseases.** JHBP (CY) Holdings Limited (Genor) has been strategically focusing on major therapeutic areas with substantial unmet medical needs in oncology, autoimmune and other chronic diseases. The Company's key drug candidates include GB491 (lerociclib), a differentiated oral CDK4/6 inhibitor; GB221, a novel HER2 monoclonal antibody (mAb) drug candidate; geptanolimab (GB226), a novel PD-1 mAb drug candidate; GB492, a stimulator of interferon genes (STING) agonist expected to exert synergistic effects in combination with GB226; GB242, an infliximab (Remicade) biosimilar; and GB223, a highly promising receptor activator of nuclear factor-kB Ligand (RANKL) mAb drug candidate.
- **Integrated R&D platform.** Genor has successfully built up the necessary capabilities of a fully-integrated biologic platform company. These capabilities are currently housed in four main functional platforms: research, clinical development, CMC, and business development. The Company has been developing drug candidates targeting pathways with blockbuster potentials, encompassing top three oncology targets and five out of the ten bestselling drugs globally.
- **Drug sales to start from 2021E.** Genor's most advanced drugs include GB226, GB221 and GB242. GB226 is expected to be approved by NMPA in 2021E, and GB221 and GB242 are expected to be approved by NMPA in 2022E. We also forecast GB223 to receive NMPA's approval in 2023E. GB491 and GB492 were expected to launch in China by 2024E. We forecast drug sales to start from 2021E and expect risk-adjusted revenue of RMB643mn/ RMB882mn/ RMB1,895mn in FY2022E/23E/24E. We expect Genor to continue incur net losses of RMB699mn/RMB580mn/RMB405mn in FY20E/21E/22E and expect net profit to break even in 2024E.
- **Initiate at BUY.** As a pre-revenue biotechnology company, Genor relies on future cash flow of drug sales. We derive price target of HK$26.49 based on a 10-year DCF model (WACC: 11.1%, terminal growth rate 2.0%).
- **Catalysts:** NMPA approval of GB226 (PD-1) in 2021E. NDA submission of GB221 (HER2) and GB242 (TNF-α) in 2021E.
- **Risks:** Failure in obtaining regulatory approval for drug candidates; Competition from peers; Failure in protecting intellectual property rights.

Earnings Summary

(YE 31 Dec)	FY18A	FY19A	FY20E	FY21E	FY22E
Revenue (RMB mn)	7	13	0	23	643
Attributable net profit (loss) (RMB mn)	(288)	(522)	(699)	(580)	(405)
R&D expenses	(271)	(439)	(500)	(500)	(600)
EPS (RMB)	N/A	N/A	(1.42)	(1.18)	(0.83)
Consensus EPS (RMB)	N/A	N/A	(1.60)	(2.04)	(2.56)
ROE (%)	(35)	(232)	(34)	(40)	(39)
ROA (%)	(29)	(71)	(28)	(31)	(31)
Net gearing (%)	Net cash	Net cash	Net cash	Net cash	Net cash
Current ratio (x)	6.9	1.0	7.1	5.0	7.9

Source: Company data, CMBIS estimates

China Healthcare Sector

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Mkt. Cap. (HK$ mn)	9,428
Avg. 3mths t/o (HK$ mn)	N/A
52W High/Low (HK$)	32.20/18.00
Total Issued Shares (mn)	491

Source: Bloomberg

Shareholding Structure

HHJH & HM Healthcare	26.07%
Kanghe Medical & Kangjia medical	11.77%
Walga	7.65%
Aranda Investments & TG river	6.35%
Shanghai Changnuo	5.09%
Free float	49.42%

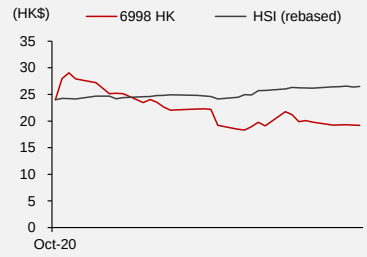
Source: HKEx, Bloomberg

Share performance

	Absolute	Relative
1-mth	-18.5%	-23.7%
3-mth	N/A	N/A
6-mth	N/A	N/A

Source: Bloomberg

12-mth price performance



Source: Bloomberg

Auditor: PWC
Web-site: www.genorbio.com

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Investment Thesis

Since its inception in 2007, JHBP (CY) Holdings Limited (Genor) has been strategically focused on major therapeutic areas with substantial unmet medical needs in oncology, autoimmune and other chronic diseases.

Rich and novel pipelines

The Company's key drug candidates include GB491 (lerociclib), a differentiated oral CDK4/6 inhibitor; GB221, a novel HER2 monoclonal antibody (mAb) drug candidate; geptanolimab (GB226), a novel PD-1 mAb drug candidate; GB492, a stimulator of interferon genes (STING) agonist expected to exert synergistic effects in combination with GB226; GB242, an infliximab (Remicade) biosimilar; and GB223, a highly promising RANKL mAb drug candidate. The Company also has a strong line-up of cutting-edge bi-specific antibody drug candidates currently in pre-clinical stage, fuelled by its differentiated bi-specific mAb antibody platform with Computer-Aided Antibody Design (CAAD) capabilities. In recent years, with research centers built in both Shanghai, China and San Francisco, US, the Company has also been expanding its R&D footprint globally to build and enrich its novel drug pipeline.

Integrated R&D platform

Genor has successfully built up the necessary capabilities of a fully-integrated biologic platform company. These capabilities are currently housed in four main functional platforms: research, clinical development, CMC, and business development. The R&D process of the Company's fully-integrated platform starts with target identification, selection, and validation. Led by its highly experienced scientific committee and scientific advisory board, the Company focuses on identifying molecules with proven or highly potential efficacy as well as meaningful market opportunities. Thereafter, the Company's discovery and research force is capable of leading the discovery and pre-clinical development of new drug candidates in five modalities, including small molecule drugs, innovative mAbs, bi-specific antibodies and ADCs as well as biosimilars.

Drug sales to start from 2021E

Genor's most advanced drugs include GB226, GB221 and GB242. GB226 is expected to be approved by NMPA in 2021E, and GB221 and GB242 are expected to be approved by NMPA in 2022E. We also forecast GB223 to receive NMPA's approval in 2023E. GB491 and GB492 were expected to launch in China by 2024E.

We forecast drug sales to start from 2021E and expect risk-adjusted revenue of RMB643mn/ RMB882mn/ RMB1,895mn in FY2022E/23E/24E. We expect Genor to continue incur net losses of RMB699mn/RMB580mn/RMB405mn in FY20E/21E/22E and expect net profit to breakeven in 2024E.

Initiate at BUY

As a pre-revenue biotechnology company, Genor relies on future cash flow of drug sales. We derive price target of HK$26.49 based on a 10-year DCF model (WACC: 11.1%, terminal growth rate 2.0%).

Investment risks

1) Failure in obtaining regulatory approval for drug candidates;

2) Competition from peers with more competing and successful drugs;

3) Failure in protecting intellectual property rights.

Company Overview

Genor being a biopharmaceutical company focusing on innovative therapies

JHBP (CY) Holdings Limited (Genor) is a biopharmaceutical company focusing on developing and commercializing oncology and autoimmune drugs. The Company's mission is to become a biopharmaceutical engine in discovery, research, development, manufacturing, and commercialization of innovative therapeutics initially for patients in China and gradually for patients globally. The Company has been developing drug candidates targeting pathways with blockbuster potentials, encompassing top three oncology targets and five out of the ten bestselling drugs globally.

Since its inception in 2007, the Company has been strategically focusing on major therapeutic areas with substantial unmet medical needs in oncology, autoimmune and other chronic diseases. For example, the Company has developed a systematic and comprehensive development plan for breast cancer-focused therapies, which includes a cyclin-dependent kinase 4/6 (CDK4/6)-targeting drug candidate and an advanced set of human epidermal growth factor receptor 2 (HER2)-targeting drug candidates, and also for a programmed cell death protein (PD-1)-targeting drug candidate targeting multiple oncology indications. In recent years, with research centers built in both Shanghai, China and San Francisco, US, the Company has also been expanding its research and development footprint globally to build and enrich its novel drug pipeline.

The Company has established a pipeline of 15 targeted drug candidates with large commercialization potentials in China that cover both proven and novel biological pathways. The Company currently has 17 clinical trials ongoing in Asia, with two new drug applications (NDAs) expected to be filed with the National Medical Products Administration (NMPA), four investigational new drug applications (INDs) to be filed with the NMPA and the US Food & Drug Administration (FDA) in the next 12 to 18 months, and one NDA recently accepted for review by the NMPA.

The Company's business is backed by its fully-integrated, end-to-end biopharmaceutical platform covering all the key drug development functionalities, including discovery, research, clinical development, CMC (Chemistry, Manufacture and Controls), and business development. Further, the Company has commercialization-ready manufacturing capabilities with quality excellence and enhanced cost efficiencies, boasting state-of-the-art concentrated fed-batch and perfusion technologies that allow it to generate higher titer and yield than the conventional technologies, reaching the high-end of the industry range.

Figure 1: Major milestones of Genor

Date	Milestone
December 2007	Genor Biopharma, the Company's key operating subsidiary, was incorporated in Shanghai, China.
October 2011	Shanghai Genor was incorporated in Shanghai, China.
July 2013	The Company obtained IND approval for GB221 in China.
July 2014	Yuxi Genor was incorporated in Yuxi, Yunnan, China.
January 2015	The Company obtained IND approval for GB242 in China.
March 2015	The Company in-licensed GB226 from Crown Bioscience (Taicang).
April 2016	The Company completed the construction of manufacturing facilities in Yuxi, Yunnan, China.

November 2016	The Company obtained IND approval for GB226 in China.
April 2017	The Company was incorporated in the Cayman Islands.
December 2017	The Company obtained IND approval for GB223 in China.
December 2018	The Company entered into the share subscription agreement regarding the December 2018 Equity Financing, and HHJH became one of its Pre-IPO Investors.
September 2019	The Company acquired 85% of the issued share capital in ABT.
October 2019	The Company entered into the share subscription agreement regarding the October 2019 Equity Financing.
May 2020	The Company entered into the share subscription agreement regarding the May 2020 Equity Financing.
June 2020	The Company in-licensed GB491 from G1 Therapeutics and GB492 from Immune Sensor Therapeutics.

Source: Company data, CMBIS

The Company's key drug candidates include GB491 (lerociclib), a differentiated oral CDK4/6 inhibitor; GB221, a novel HER2 monoclonal antibody (mAb) drug candidate; geptanolimab (GB226), a novel PD-1 mAb drug candidate; GB492, a stimulator of interferon genes (STING) agonist expected to exert synergistic effects in combination with GB226; GB242, an infliximab (Remicade) biosimilar; and GB223, a highly promising receptor activator of nuclear factor-kB Ligand (RANKL) mAb drug candidate. The Company also has a strong line-up of cutting-edge bi-specific antibody drug candidates currently in pre-clinical stage, fuelled by its differentiated bi-specific mAb antibody platform with Computer-Aided Antibody Design (CAAD) capabilities.

With an NDA filed in July 2020, the Company expects to launch its first product, namely, GB226, by the second half of 2021. The Company filed NDA of GB242 in Nov 2020 and also plans to file NDA for GB221 in the second half of 2020.

Figure 2: Key pipeline drugs of Genor

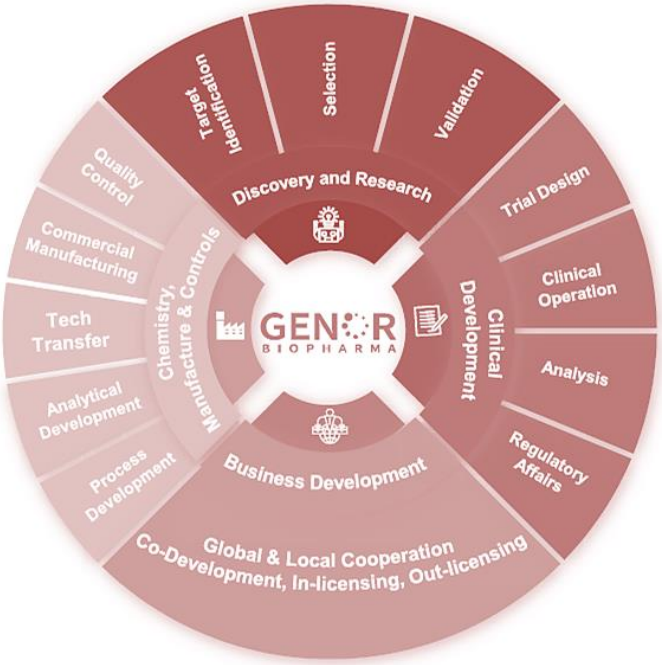
Product	Target/MoA (reference drug)	Indication**	Classification	Commercial Rights	Pre – Clinical	IND	Phase 1	Phase 2	Phase 3	NDA Filing(1)
GB491^	CDK4/6+SERD (combo w/ fulvestrant)	HR+, HER2-BC	Novel (In-license)	APAC ex-JP(2)			By G1 Therapeutics in the U.S.			
	CDK4/6+EGFR (combo w/ osimertinib)	EGFR-Mutant NSCLC					By G1 Therapeutics in the U.S.			
GB221*^	HER2	HER2+ 1L/2L+ mBC	Novel (In-house)	Worldwide						2H20
GB226*^	PD-1	2L+ r/r PTCL	Novel (In-license)	China						NDA under priority review
		2L+ r/r PMBCL							Pivotal	
		2L+ Cervical Cancer								
		ASPS								
	PD-1+VEGFR (combo w/ lenvatinib)	HCC								
	PD-1+VEGFR (combo w/ fruquintinib)	2L/3L+ EGFR+ NSCLC								
		2L+ mCRC								
GB492^	PD-1 (combo w/ GB226*^)+STING	Solid Tumours	Novel (In-license)	APAC ex-JP(3)		By ImmuneSensor in the U.S.				
GB242*^	TNF-α (infliximab)	Moderate to Severe RA	Biosimilar (In-house)	Worldwide						2H20
GB223^	RANKL	GCTB, PMO	Novel (Co-develop)	Worldwide						
GB241	CD20 (rituximab)	1L DLBCL	Biosimilar (In-house)	Co-development						
GB222	VEGF (bevacizumab)	2L+ GBM, 1L/2L nsNSCLC, 1L/2L mCRC	Biosimilar (In-house)	Worldwide						
GB224	IL-6	Moderate to Severe RA	Novel (In-license)	China						
GB235	HER2	HER2+ 1L/2L+ mBC	Novel (In-house)	Worldwide		IND approved				
GB251	HER2 ADC	HER2+ 1L/2L+ mBC	Novel (Co-develop)	Worldwide		IND approved				
GB232	TNF-α	Moderate to Severe RA	Novel (In-house)	Worldwide		IND-enabling				
GB261	CD3×CD20	NHL	Novel (In-house)	Worldwide		IND-enabling				
GB262	PD-L1×CD55	Solid Tumours	Novel (In-house)	Worldwide						
GB263	EGFR×c-Met	NSCLC	Novel (In-house)	Worldwide						

Source: Company data, CMBIS
Abbreviations: r/r=relapsed or refractory; PTCL=peripheral T cell lymphoma; PMBCL=primary mediastinal B-cell lymphoma; ASPS=alveolar soft part sarcoma; HCC=hepatocellular carcinoma; mCRC=metastatic colorectal cancer; NSCLC=non-small cell lung cancer; mBC=metastatic breast cancer; eBC=early breast cancer; BC=breast cancer; RA=rheumatoid arthritis; DLBCL=diffuse large B-cell lymphoma; GCTB=giant-cell tumor of bone; PMO=postmenopausal osteoporosis; GBM=glioblastoma multiforme; nsNSCLC=non-squamous non-small cell lung cancer; NHL=non-Hodgkin lymphoma; 1L=the first line of treatment; 2L+=the second line and later lines of treatment; 3L+=the third line and later lines of treatment; JP=Japan; US=the United States; EU=Europe.
China or PRC represents for the People's Republic of China, which for the purpose of this prospectus and for geographical reference only, excludes Hong Kong SAR, Macau SAR and Taiwan.
Greater China represents for PRC, Hong Kong SAR, Macau SAR and Taiwan.
* Denotes a Core Product.
** Progress bar denotes the most advanced ongoing clinical trial.
^ Denotes a key drug.
(1) The expected first NDA filling for key drugs.
(2) Clinical trials are sponsored by G1 Therapeutics, Inc., or G1 Therapeutics.
(3) Clinical trial is sponsored by ImmuneSensor Therapeutics, Inc., or ImmuneSensor Therapeutics.

Integrated R&D platform

Since its inception, Genor has successfully built up the necessary capabilities of a fully-integrated biologic platform company. These capabilities are currently housed in four main functional platforms: research, clinical development, CMC, and business development.

Figure 3: Genor's full development process



Source: Company data, CMBIS

The R&D process of the Company's fully-integrated platform starts with target identification, selection, and validation. Led by its highly experienced scientific committee and scientific advisory board, the Company focuses on identifying molecules with proven or highly potential efficacy as well as meaningful market opportunities. Thereafter, the Company's discovery and research force is capable of leading the discovery and pre-clinical development of new drug candidates in five modalities, including small molecule drugs, innovative mAbs, bi-specific antibodies and ADCs as well as biosimilars. The Company's research function is led by a key management team experienced with drug discovery and development. It consisted of 259 employees as of 31 May 2020. Members of the research team generally have medicine, chemistry, biotechnology, pathology, immunology, and in vivo pharmacology backgrounds.

The Company currently has 17 clinical trials ongoing in Asia, with two NDAs expected to be filed with the NMPA, four INDs to be filed with the NMPA and FDA in the next 12 to 18 months, and one NDA recently accepted for review by the NMPA.

Led by Dr. Steven Kan, this aspect of the Company's platform covers CMC functions, including process development and analytical science. The Company has established a comprehensive, product oriented platform that facilitates drugability assessment, high expression production cell line development, cell culture, purification, formulation and fill/finish process development and scale-up, analytical development, technology transfer, commercial manufacturing, and quality control.

The Company's Yuxi facilities have approximately 8,000 m^2 of floor space and currently house its production facilities with three 200L and four 500L disposable bioreactors. The bioreactors could be used in either concentrated fed-batch mode or perfusion mode. The Company plans to conduct phase 2 expansion of its Yuxi facilities. The Company's Shanghai facilities currently house two 250L

disposable bioreactors, mainly used for manufacturing Phase 1/2 trial materials. Materials for Phase 3 clinical studies are, and in the future for commercial purposes will be, manufactured in the Yuxi facilities.

The Company's manufacturing facilities in Yuxi, Yunnan are commercialization-ready and satisfy the product validation prerequisite for the approval of innovative drug candidates under current regulations in China. The concentrated fed-batch or perfusion technologies used at the Yuxi facilities allow it to generate higher titer and yield than the conventional fed-batch technology, driving the high-end of the industry range. The Company expects the current capacities of Yuxi facilities will support its commercial manufacturing needs in the near future.

The Company is building its in-house commercialization team to support the launch of its first two to three NMPA-approved drug assets, including GB226, which the Company expects to launch in the second half of 2021 subject to NMPA approval. The Company will expand its in-house commercialization team to 150-300 employees by 2021 to cover top-tier hospitals in major cities, complemented by strategic partnerships that penetrate lower-tier cities. The Company may also form strategic partnerships with international biopharmaceutical companies to expand its global footprint.

GB491: a differentiated oral therapy for HR+/HER2- breast cancer

GB491 (Lerociclib, a CDK4/6 inhibitor)

GB491 (Lerociclib) is a novel, potent, selective and potentially best-in-class oral CDK4/6 inhibitor being developed for use either alone or in combination with endocrine therapy/targeted therapies in breast cancer. CDK4/6 inhibitors in combination with endocrine therapy/fulvestrant represent an established treatment for HR+/HER2- advanced or metastatic breast cancer and have demonstrated significant improvements in progression PFS and OS. A recent study also indicates that adding a CDK4/6 inhibitor to standard postsurgery endocrine therapy significantly cut the risk of cancer recurrence in patients with high-risk HR+/HER2- early breast cancer (eBC). GB491 has consistently demonstrated robust efficacy in several preclinical models and clinical trials in HR+ breast cancer.

In addition, currently approved CDK4/6 inhibitors either induce dose-limiting neutropenia requiring a drug holiday, potentially limiting efficacy, or is limited by gastrointestinal toxicity. Preclinical and early clinical data have demonstrated that GB491 is differentiated from other CDK4/6 inhibitors based on its favorable safety and tolerability profile and ability to be dosed continuously with less dose-limiting neutropenia, which is one of the main toxicities associated with CDK4/6 inhibition.

Lerociclib is currently being evaluated by G1 Therapeutics in a Phase 2a clinical trial in combination with fulvestrant for patients with HR+/HER2- breast cancer. The Company in-licensed the rights to develop and commercialize GB491 in the APAC region (excluding Japan) from G1 Therapeutics in June 2020. The Company shall pay to G1 Therapeutics (i) an upfront payment in the amount of US$6mn, (ii) milestone payments upon achievement of certain development and sales milestones in the aggregate amount of US$40mn, and (iii) tiered royalty payments ranging from high single to low double-digits based on aggregate annual net sales of Lerociclib.

The Company plans to initially develop GB491 in HR+/HER2- mBC and eBC, with plans to expand its development of GB491 to multiple other indications such as NSCLC. The Company plans to file an IND application with the NMPA to conduct a PK bridging study of GB491 in Chinese patients. After completing the PK study, the Company plans to initiate clinical studies of GB491 in patients with HR+/HER2- mBC and eBC and other indications.

Preliminary clinical data in estrogen receptor-positive, HER2-negative (ER+/HER2-) breast cancer have demonstrated proof-of-concept of the differentiated clinical profile of lerociclib versus currently marketed CDK4/6 inhibitors, with improved tolerability and less neutropenia. Neutropenia is one of the main toxicities associated with CDK4/6 inhibition.

Lerociclib shows good preliminary efficacy

Lerociclib demonstrated potent inhibition across CDK4, CDK6, and CDK9 *in vitro*. CDK4 binding has been shown to be related to tumor inhibition, while CDK6 binding is related to hematological toxicity. Principal investigators in the trials hypothesized that CDK9 binding might have contributed to the better efficacy (higher ORR) of abemaciclib compared with palbociclib and ribociclib.

Figure 4: Binding affinity of lerociclib

	Lerociclib
Biochemical	
CDK1/cyclinB1 Ki (nmol/L)	2.4
CDK2/cyclinA Ki (nmol/L)	1.5
CDK4/cyclinD1 Ki (nmol/L)	0.001
CDK5/p35 Ki (nmol/L)	0.832
CDK6/cyclinD3 Ki (nmol/L)	0.002
CDK7/cyclinH/MAT1 Ki (nmol/L)	2.4
CDK9/cyclinT Ki (nmol/L)	0.028

Source: Company data, CMBIS

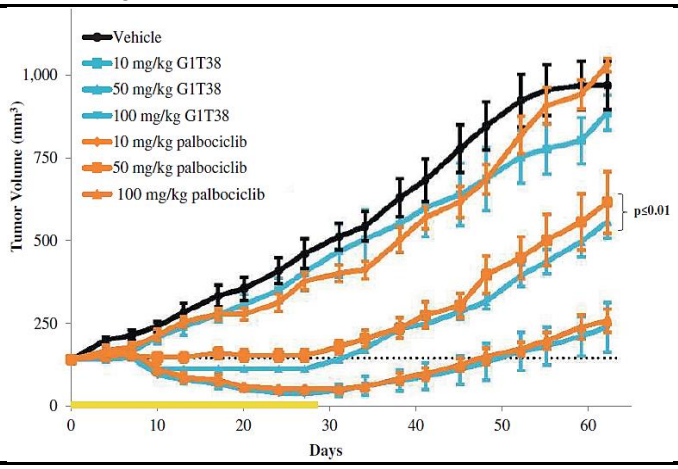
Figure 5: Binding affinity of other CDK4/6 inhibitors

	Abemaciclib	Palbociclib	Ribociclib
Biochemical			
CDK1/cyclinA2 Ki (nmol/L)	330±90	>1,400	>1,400
CDK2/cyclinE1 Ki (nmol/L)	150±60	>2,500	>2,500
CDK4/cyclinD3 Ki (nmol/L)	0.07±0.01	0.26±0.03	0.53±0.08
CDK5/p35 Ki (nmol/L)	86±12	>2,000	>2,000
CDK6/cyclinD1 Ki (nmol/L)	0.52±0.17	0.26±0.07	2.3±0.3
CDK7/cyclinH/MAT1 Ki (nmol/L)	220±10	>2,000	>2,000
CDK9/cyclinT1 Ki (nmol/L)	4.1±1.3	150±10	190±20

Source: Company data, CMBIS

In a preclinical head-to-head study, lerociclib treatment led to equivalent or improved anti-tumor efficacy compared to the first-in-class CDK4/6 inhibitor, palbociclib, in an in vivo ER+ breast cancer xenograft model.

Figure 6: Single agent efficacy of lerociclib in breast cancer



Source: Company data, CMBIS

In December 2019, G1 Therapeutics announced results of its Phase 2a clinical trial in the US investigating lerociclib in combination with fulvestrant for the treatment of HR+/HER2- breast cancer. Lerociclib, dosed without a drug holiday, showed a differentiated safety and tolerability profile than observed in clinical trials with currently marketed CDK4/6 inhibitors.

Patients enrolled in this clinical trial are women of any menopausal status with locally advanced or metastatic HR+/HER2- breast cancer who had progressed during or within 12 months after adjuvant therapy or progressed during or within two months after endocrine therapy for advanced or metastatic disease. Part 1 of this study was an open-label, 3+3, parallel-dose escalation of lerociclib 200mg-850mg QD and 100mg-425mg BID administered continuously. Part 2 of this study was an open-label expansion at lerociclib doses of 400mg QD, 500mg QD, 150mg BID, and 200mg BID administered continuously. Fulvestrant 500 mg was administered on days 1, 15, and 29, then once monthly as per standard of care.

Preliminary efficacy findings were consistent with other CDK4/6 inhibitors used in combination with fulvestrant. As of 7 Oct 2019, 110 trial participants received lerociclib (46 in part 1 and 64 in part 2) at doses ranging from 200-650 mg once daily (QD) and 100-250 mg twice daily (BID). 59 (53.6%) remain on lerociclib treatment. 48 patients (43.6%) discontinued lerociclib treatment due to progressive

disease, two (1.8%) withdrew by choice, and one (0.9%) due to an adverse event (AE). Median (range) duration of lerociclib exposure was 6.0 (1.0-31.0) months.

BID dosing demonstrated an improved safety and tolerability profile compared with QD dosing, with lower rates of gastrointestinal AEs. Overall, the most common lerociclib-related AEs (≥10%) were neutropenia (74.5%), nausea (54.5%), leukopenia (49.1%), diarrhea (45.5%), anemia (30.0%), vomiting (23.6%), thrombocytopenia (22.7%), fatigue (22.7%), and lymphocytopenia (10.0%). Low rates of lerociclib-related stomatitis and alopecia were observed across all dose levels in both dosing schedules. Stomatitis and alopecia were 6.4% and 4.5%, respectively.

Serious AEs considered related to lerociclib were reported in six patients (5.5%). One patient (0.9%) discontinued treatment due to an AE: Grade 4 neutropenia at 200 mg QD; this event resolved. Most common Grade 3/4 laboratory abnormalities were observed in absolute neutrophil (49.1%), leukocyte (35.5%), and lymphocyte (11.8%) counts. No cases of QTcF prolongation (480ms or 60ms increase), or venous thromboembolism occurred at any dose level. Lerociclib dose reduction occurred in 34 patients (30.9%). Continuous lerociclib dosing with fulvestrant resulted in a dose-dependent decline and subsequent plateau of neutrophils at the end of cycle 1 (week 4). Per protocol, no lerociclib dose interruptions or reductions were necessary due to Grade 3 neutropenia without associated infection or fever.

The maximum tolerated dose (MTD) determined in part 1 was 500 mg QD based on 2/6 patients (33.3%) experiencing a DLT at 650 mg QD.

The projected RP2D of 150mg BID or 200mg BID demonstrated an improved tolerability profile relative to QD dosing, including decreased rates of gastrointestinal AEs as well as lower rates of neutropenia. One patient at 150mg BID (5.0%) and four patients at 200mg BID (19.0%) experienced Grade 4 neutropenia; no other Grade 4 AEs were reported at these dose levels.

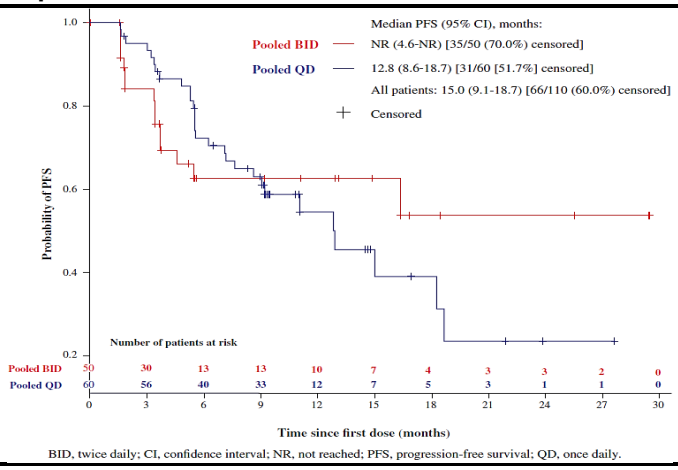
The efficacy data were consistent with those from other CDK4/6 inhibitors used in combination with fulvestrant. Confirmed objective response rate was 21.4% across all dose levels. Clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD] lasting ≥ 24 weeks) was 65.2% across all dose levels. Median PFS across the entire study was 15.0 months: 12.8 months for all QD dose levels combined and not reached for all BID dose levels combined.

Figure 7: Best overall response (confirmed) in patients with measurable disease

	QD					BID				Total		
Patients, n (%)	200 mg (n = 6)	300 mg (n = 3)	400 mg (n = 13)	500 mg (n = 30)	650 mg (n = 6)	100 mg (n = 5)	150 mg (n = 18)	200 mg (n = 19)	250 mg (n = 3)	All QD doses (n = 58)	All BID doses (n = 45)	All doses (N = 103)[a]
CR	0	0	0	0	0	0	0	0	0	0	0	0
PR	1(16.7)	1(33.3)	4(30.8)	9(30.0)	0	1(20.0)	2(11.1)	4(21.1)	0	15(25.9)	7(15.6)	22(21.4)
SD	4(66.7)	1(33.3)	9(69.2)	19(63.3)	5(83.3)	2(40.0)	12(66.7)	12(62.3)	2(66.7)	38(65.5)	28(62.2)	66(64.1)
SD≥24weeks	4(66.7)	1(33.3)	6(46.2)	13(43.3)	2(33.3)	2(40.0)	2(22.2)[c]	4(28.6)[d]	2(66.7)	26(44.8)	10(32.3)[e]	36(40.4)[f]
PD	1(16.7)	1(33.3)	0	2(6.7)	1(16.7)	2(40.0)	4(22.2)	2(10.5)	1(33.3)	5(8.6)	9(20.0)	14(13.6)
NE	0	0	0	0	0	0	0	1(5.3)	0	0	1(20.0)	1(1.0)
Clinical benefit[b]	5(83.3)	2(66.7)	10(76.9)	22(73.3)	2(33.3)	3(60.0)	4(44.4)[c]	8(57.1)[d]	2(66.7)	41(70.7)	17(54.8)[e]	58(65.2)[f]

Source: G1 Therapeutics, Company data, CMBIS
Notes:
a: Seven patients (6.4%) did not have measurable disease or had measurable disease but no post baseline tumor scans.
b: Clinical benefit = CR + PR + SD lasting ≥ 24 weeks. Percentages were calculated by excluding those on treatment who did not have a confirmed objective response and have not made it to the week 24 assessment.
BID, twice daily; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; QD, once daily.

Figure 8: Kaplan-Meier plot for PFS



BID, twice daily; CI, confidence interval; NR, not reached; PFS, progression-free survival; QD, once daily.

Source: Company data, CMBIS

For comparison purpose, in a multicenter, randomized, double-blind, placebo-controlled, Phase 3 trial of fulvestrant with or without palbociclib +/-goserelin in women with HR+/HER2- mBC whose disease progressed after prior endocrine therapy (PALOMA-3) conducted by Pfizer, as of March 2015, among 521 enrolled patients, palbociclib in combination with fulvestrant demonstrated an ORR of 24.6% (95% CI: 19.6-30.2). 31% of the enrolled patients in the metastatic setting have received prior chemotherapy.

Lerociclib has superior safety

Therapeutics with better tolerability are required among intermediate and high-risk patients who receive longer treatment duration. Lerociclib is a potentially best-in-class CDK4/6 inhibitor in terms of tolerability profile, allowing for continuous dosing with fewer dose-limiting toxicities such as neutropenia and potentially less monitoring. For example, based on US FDA label information, physicians need to monitor complete blood counts (CBC), liver function and signs and symptoms of thrombosis and pulmonary embolism in patients prior to or during treatment with Verzenio (abemaciclib) therapy. Less monitoring would mean fewer office visits and medical tests, improving the experience for patients and reducing the burden on physician offices and costs to the healthcare system.

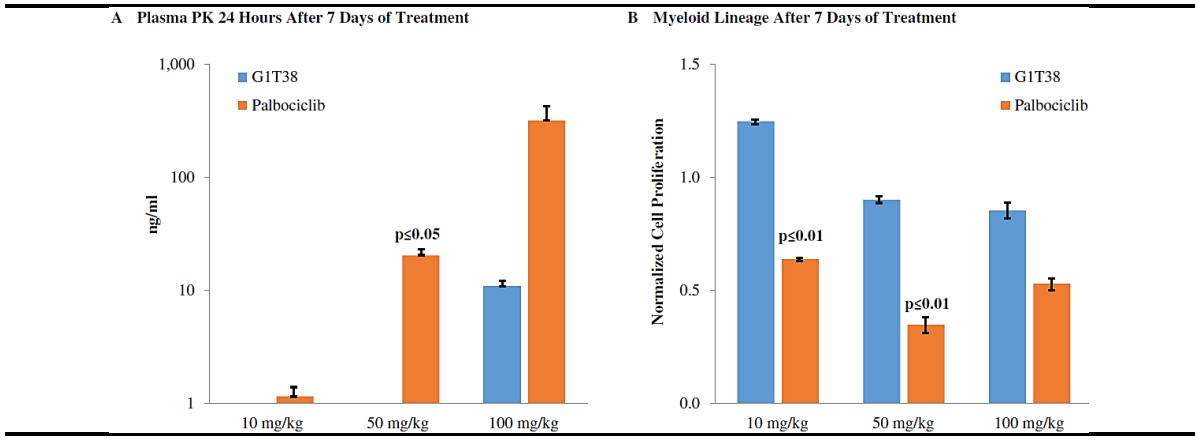
Figure 9: Lerociclib is a potentially best-in-class CDK4/6 inhibitor in terms of safety and side effects

	Dose-limiting neutropenia	Monitoring requirement	Dosing holiday	QT prolongation	DILI	Grade 3/4 diarrhea	VTE
Ibrance®	x	x	x	—	—	—	—
Kisqali®	x	x	x	x	x	—	—
Verzenio®	x	x	—	—	x	x	x
Lerociclib	—	Potential for less monitoring	—	—	—	—	—

Source: G1 Therapeutics, Company data, CMBIS
Notes: DILI=drug-induced liver injury; VTE=venous thromboembolism; x=inferior to lerociclib

Neutropenia is one of the main toxicities associated with CDK4/6 inhibition. Current treatments require frequent blood testing for neutropenia. In a preclinical head-to-head study, in an ER+ breast cancer xenograft model, lerociclib accumulated in mouse xenograft tumors but not plasma, resulting in less inhibition of mouse myeloid progenitors than after palbociclib treatment. This suggests that palbociclib-induced neutropenia may be due to accumulation of the drug resulting in persistent inhibition of CDK4/6 in the bone marrow, thus preventing the recovery of bone marrow proliferation prior to subsequent doses. Also, lerociclib-treated mice showed no differences in myeloid progenitor proliferation in any treatment cohort when compared to vehicle, while palbociclib treatment led to more than 50% reduction in proliferation in both the 50 and 100 mg/kg cohorts. These data indicate that between doses, the longer exposure of palbociclib resulted in drug concentrations that were above the threshold necessary to maintain G1 arrest of bone marrow progenitor cells resulting in sustained inhibition of myeloid progenitors. In contrast, due to the minimal lerociclib compound in the plasma at 24 hours, the bone marrow seems to have more time to recover from CDK4/6 inhibition between doses suggesting that continuous daily dosing may be achievable in cancer patients.

Figure 10: Comparison of myeloid precursor proliferation following G1T38 and palbociclib treatment



Source: Company data, CMBIS

Lerociclib treatment led to comparatively less Grade 3/4 neutropenia and diarrhea. In addition, lerociclib has not caused serious liver toxicity in the clinical trials to date. By contract, based on US FDA label information, both Kisqali (ribociclib) and Verzenio can cause serious liver problems, and blood tests need to be done to check the liver before and during treatment with these two drugs.

Figure 11: AE profiles of lerociclib

Trial	**NCT02983070**	
Phase	Ib/II	
Line setting	Median 2L+	
Treatment	Lerociclib + fulvestrant	
Dosing	150mg BID	
Baseline		
Menopausal status	70% Postmenopausal	
ECOG PS	0-1	
AE (%)	**All**	**Gr 3/4**
Neutropenia	55%	35%
Leukopenia	40%	15%
Nausea	15%	0%
Diarrhea	20%	0%
Anaemia	20%	5%
Fatigue	10%	0%

Source: Company data, CMBIS (Data cutoff: 7 Oct 2019)

Figure 12: AE profiles of other CDK4/6 inhibitors

	Abemaciclib				Palbociclib				Ribociclib			
Trial	**MONARCH-3**		**MONARCH-2**		**PALOMA-2**		**PALOMA-3**		**MONALEESA-2**		**MONALEESA-3**	
Phase	III		III		III		III		III		III	
Line setting	1L		1/2L		1L		Median 2L+		1L		1/2L	
Treatment	Abemaciclib + NSAI		Abemaciclib + fulvestrant		Palbociclib + letrozole		Palbociclib + fulvestrant		Ribociclib + letrozole		Ribociclib + fulvestrant	
Dosing	150mg BID		150mg BID		125mg, 3w on/1w off		125mg, 3w on/1w off		600mg, 3w on/1w off		600mg, 3w on/1w off	
Baseline												
Menopausal status	100% Postmenopausal		84% Postmenopausal		100% Postmenopausal		79% Postmenopausal		100% Postmenopausal		100% Postmenopausal	
ECOG PS	0-1		0-1		0-2 (2<2%)		0-1		0-1		0-1	
AE (%)	**All**	**Gr 3/4**	**All**	**Gr 3/4**	**All**	**Gr 3/4**	**All**	**Gr 3/4**	**All**	**Gr 3/4**	**All**	**Gr 3/4**
Neutropenia	44%	24%	46%	27%	80%	67%	79%	62%	77%	52%	70%	53%
Leukopenia	22%	9%	28%	9%	39%	25%	46%	25%	33%	20%	28%	14%
Nausea	41%	1%	45%	3%	35%	0%	29%	0%	53%	2%	45%	1%
Diarrhea	82%	10%	86%	13%	26%	1%	19%	0%	38%	2%	29%	1%
Anaemia	32%	7%	29%	7%	24%	5%	26%	3%	21%	2%	17%	3%
Fatigue	41%	2%	40%	3%	37%	2%	38%	2%	41%	3%	32%	2%

Source: Company data, CMBIS

Large market opportunity of CDK4/6 inhibitor in China

Breast cancer is one of the top incident cancers in China, with approximately 331 thousand new cases reported in 2019 and 369.9 thousand new cases expected in 2024. Breast cancer is also the most prevalent cancer among women in China. HR+/HER2- breast cancer represents 62.0% breast cancer patients in China, which is 2.8 times the number of HER2+ breast cancer patients. Due to increasing penetration of neo-adjuvant and adjuvant therapies and early diagnosis, the overall five-year survival rate for breast cancer patients in China is over 80%, according to the 2019 annual meeting on breast cancer held by the CSCO.

Approximately 90% of newly diagnosed breast cancer patients are at Stage I-III and approximately 30% of these patients will experience disease recurrence. Adjuvant breast cancer therapy has much bigger market opportunities in China than mBC first-line therapy due to the larger patient base (82.5 thousand vs. 45.3 thousand in China) and longer treatment duration (about 84-120 months vs. about 30 months). Recent clinical data demonstrated that CDK4/6 inhibitors have promising results as HR+/HER2- eBC adjuvant therapy, which are potentially the optimal treatment. Early breast cancer adjuvant therapy is expected to represent a significant segment of the CDK4/6 inhibitor market in the future. In China, the market size of CDK4/6 inhibitors in eBC adjuvant therapy is expected to expand to RMB0.6bn in 2022 and further to RMB12.2bn in 2030, representing a CAGR of 47.1% from 2022 to 2030.

CDK4/6 inhibitors have already been included in the NCCN guidelines as first-line therapy for HR+/HER2- mBC. In China, the market size of CDK4/6 inhibitors in mBC therapy is expected to expand to RMB4.7bn in 2022 and further to RMB10.5bn in 2030, representing a CAGR of 10.8% from 2022 to 2030. Three CDK4/6 inhibitors have been approved globally for advanced and metastatic breast cancer, including Pfizer's Ibrance (palbociclib), Novartis' Kisqali (ribociclib), and Eli Lilly's Verzenio (abemaciclib), collectively with global sales of US$6.0bn. In China, Ibrance has been approved for first-line HR+/HER2- locally advanced or metastatic BC in combination with aromatase inhibitors, with annual sales of approximately RMB415mn in 2019.

Figure 13: Comparison between GB491 and its approved or late-stage competitors in China

Drug name	Sponsors/ collaborators	Phase	Indications	Combination therapy/ monotherapy	First posted date/ NMPA approval date
Palbociclib (Ibrance)	Pfizer	Approved	HR+/HER2- locally advanced or metastatic BC	Combo with aromatase inhibitors	7/31/2018
SHR-6390	Hengrui Medicine	Phase 3	HR+/HER2- local advanced or advanced metastatic breast cancer for female patients	Combo with fulvestrant	4/9/2019
		Phase 3	HR+ and HER2- advanced breast cancer	Combo with aromatase inhibitors	6/17/2019

Source: Company data, CMBIS
Note: The price of Ibrance is RMB29,800/125mg for 21 tablet and RMB1,419.0 per unit. Ibrance is not currently listed in the NRDL. The expiration date of the key patents are 10 Jan 2023.

GB221: an rh-HER2 mAb candidate for metastatic breast cancer

GB221 (an anti-HER2 mAb)

GB221 is the Company's HER2 mAb product candidate for HER2+ metastatic breast cancer (mBC). The Company plans to file the first NDA of GB221 with the NMPA in the second half of 2020.

HER2 is a validated molecular target for cancer therapy. Overexpression of HER2 proteins has been shown to play a critical role in the progression of malignancies, especially in breast cancer. Anti-HER2 biologics have now become a standard therapy for late-stage HER2+ breast cancer, according to the CIC Report. The standard treatment for neo-adjuvant and adjuvant HER2+ breast cancer is chemotherapy in combination with anti-HER2 therapies. For first-line HER2+ late-stage and recurrent breast cancer, trastuzumab, pertuzumab and chemotherapy are generally used together as the standard treatment. For second-line HER2+ late-stage and recurrent breast cancer, T-DM1, trastuzumab in combination with chemotherapy, lapatinib in combination with capecitabine, and trastuzumab in combination with lapatinib are often used as the standard treatment.

Solid clinical data

Currently, the Company is conducting two Phase 3 clinical trials in China to evaluate the safety, efficacy and immunogenicity of (i) GB221 in combination with capecitabine (Xeloda) compared to placebo in combination with capecitabine (Xeloda) in adult patients with HER2+ metastatic breast cancer (the "GB221-003 Study"), and (ii) GB221 in combination with docetaxel (Taxotere) compared to trastuzumab in combination with docetaxel (Taxotere) in adult patients with HER2+ metastatic breast cancer (the "GB221-004 Study"). Study results of the GB221-004 Study are not available yet.

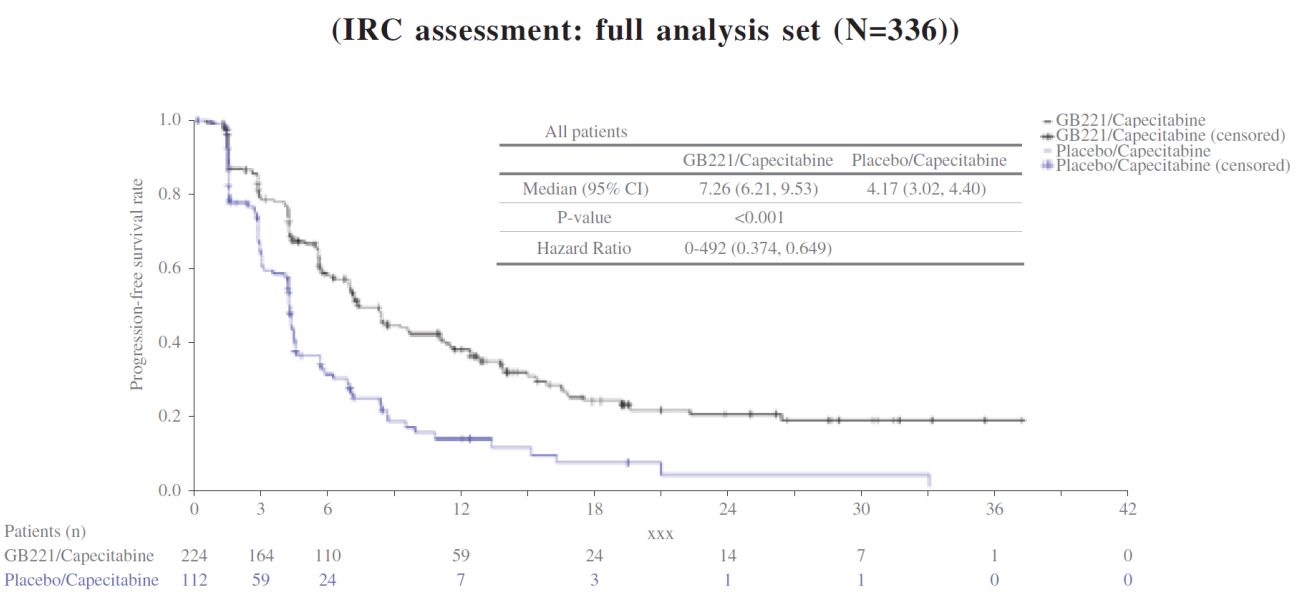
GB221-003 Study

The GB221-003 Study is a randomized, double-blind, multi-center Phase 3 clinical study to evaluate GB221 or placebo in combination with capecitabine in patients with HER2+ relapsed or metastatic breast cancer with at least one measurable target lesion based on RECIST1.1, who have failed previous taxanes and/or anthracyclines but have not been received standard anti-HER2 treatment or capecitabine.

The Company has completed patient enrollment for this study. Based on internal review of the progress of this trial, the Company expects to complete this trial and submit an NDA with the NMPA in the second half of 2020.

The median PFS as assessed by IRC for GB221 in combination with capecitabine versus capecitabine alone was 7.26 months (95% CI: 6.21, 9.53) vs. 4.17 months (95% CI: 3.02, 4.40), and the hazard ratio was 0.49, $p<0.001$, showing that GB221 in combination with capecitabine can significantly reduce the risk of disease progression in HER2+ advanced breast cancer patients who have previously received taxanes and/or anthracyclines as compared with capecitabine alone.

Figure 14: Efficacy analysis of GB221 in combination with capecitabine in HER2+ breast cancer



Source: Company data, CMBIS

TEAEs occurred in 96.9% of the patients being treated with GB221 in combination with capecitabine (N = 224), while TEAEs occurred in 91.1% of the patients receiving capecitabine alone (N = 112). TRAEs occurred in 92.4% of patients receiving GB221 in combination with capecitabine and 79.5% of patients receiving capecitabine alone. Common AEs (≥10%) of GB221 in combination with capecitabine include hematological toxicity, hand-foot syndrome, infusion reactions, liver damage, nausea, and decreased ejection fraction, mostly at grade 1-2, which is consistent with the safety profile reported for Herceptin in combination with capecitabine. No new safety signals have been identified for GB221.

Figure 15: Safety analysis of GB221+capecitabine vs capecitabine alone in HER2+ breast cancer

Adverse events (AEs)	GB221+capecitabine	capecitabine alone
	N=224	N=112
⩾Grade 3 AEs	31.3%	28.6%
Serious adverse events (SAEs)	11.2%	11.6%
AEs leading to GB221/placebo dose discontinuation	4.9%	4.5%
AEs leading to death	0.9%	2.7%

Source: Company data, CMBIS

GB221-004 Study

The Company is conducting the GB221-004 Study for the novel drug registration pathway and plans to submit the results of this study as a post-filing supplement to its NDA submission for the GB221-003 Study. The GB221-004 Study is a randomized, double-blind, multi-center Phase 3 clinical study to evaluate GB221 or trastuzumab in combination with docetaxel in patients with HER2+ breast cancer. The Company plans to enrol a total of 412 patients. As of 27 May 2020, the Company had enrolled 350 patients. The Company expects to complete this trial by 2021.

These patients will be randomized at a 1:1 ratio into two groups: (i) the treatment group will receive the first i.v. administration of GB221 at 8 mg/kg dose level and the remaining at 6 mg/kg q3w plus at least six doses of docetaxel at 75 mg/m2 dose level for three weeks until disease progression,

intolerable toxicity or the end of the 12-month period; and (ii) the control group will receive the first i.v. administration of trastuzumab at 8 mg/kg dose level and the remaining at 6 mg/kg q3w dose level plus at least six doses of docetaxel at 75 mg/m2 dose level for three weeks until disease progression, intolerable toxicity or the end of the 12-month period. The primary endpoint of this study is week-18 ORR as determined based on RECIST1.1.

GB221-005 Study

The Company is conducting the GB221-005 Study for the novel registration pathway. The GB221-005 Study is a randomized, double-blind, single-center Phase 1 clinical study to compare the PK parameters of single dose of GB221 and Herceptin in healthy volunteers. The Company plans to enrol a total of 88 patients. As of 27 Jul 2020, the Company has completed patient enrollment for this trial. The Company expects to complete this trial by the second half of 2020.

These patients will be randomized at a 1:1 ratio into two groups: (i) the treatment group will receive single dose of GB221 intravenously at 6 mg/kg dose level; and (ii) the control group will receive single dose of Herception intravenously at 6 mg/kg dose level. The primary endpoints of this study are C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$.

Large market opportunity for HER2 mAb

Trastuzumab and pertuzumab are monoclonal antibodies that bind to the HER2 protein and thereby cause the cells to cease reproducing. Trastuzumab and pertuzumab given in combination with chemotherapy is the current first-line standard of care for HER2+ metastatic breast cancer. Kadcyla (ado-trastuzumab emtansine, or T-DM1), an ADC, is also used for HER2+ oncology which received NMPA's approval in January 2020. In China, the biologics that have been approved for breast cancer are Roche's Herceptin (trastuzumab), Roche's Perjeta (pertuzumab) and Roche's Kadcyla. Combination therapies of Herceptin and Perjeta are already being used as the first-line standard treatment for HER2+ breast cancer patients in China as per NCCN guidelines.

For breast cancer, as of the fourth round of medical reimbursement negotiations in 2019, a total of four HER2-targeted drugs were included. In 2017, Herceptin and Lapatinib were added into the NRDL through negotiation with price cuts at up to 69.0% and 42.4%, respectively. In 2019, Perjeta and Pyrotinib were successfully included into the new 2020 NRDL through negotiation. As the first-line "gold standard" for HER2+ breast cancer, Herceptin is also the first tumor biologic included in the NRDL. According to the CIC Report, the sales volume of Herceptin increased rapidly from about 100 thousand vials (440mg per vial) before its NRDL listing in 2017 to over 700 thousand vials (440mg per vial) in 2019.

Sales of Herceptin grew from RMB1.7bn in 2015 to RMB5.2bn in 2019, while sales of Perjeta, approved in China in 2018, was RMB560mn in 2019. Medical reimbursement negotiation is expected to become the norm, encouraging more Chinese patients to use anti-tumor biologics.

Market size of HER2+ breast cancer monoclonal antibodies and ADCs in China was RMB0.9bn in 2014 and grew to RMB5.8bn in 2019, representing a CAGR of 44.5% from 2014 to 2019. This market size is expected to grow further to RMB24.2bn in 2030, representing a CAGR of 13.9% from 2019 to 2030.

Several trastuzumab biosimilar drugs from other pharmaceutical companies in China are expected to enter the market in the near future. Among all competing pharmaceutical companies in China, the Company is the only company with a complete set of novel drug candidates having similar modalities as HER2-targeting drug products including Herceptin, Perjeta and Kadcyla that are widely used in HER2+ breast cancer.

The NMPA approved the first trastuzumab-mimic drug from Sunshine Guojian in June 2020 and approved HLX02, a trastuzumab biosimilar from Henlius, in August 2020. Genor Biopharma, Anhui Anke Biotechnology, Shanghai Pharmaceuticals, Bio-thera Solutions and Zhejiang Hisun Pharmaceutical have trastuzumab biosimilar drugs in pipeline. CTTQ Pharma and Qilu Pharmaceuticals have pertuzumab biosimilar drugs in pipeline. RemeGen and Bio-thera Solutions have HER2 ADC drugs in pipeline.

Figure 16: GB221 and its approved or late-stage competitors in China

Drug name	Sponsors/ collaborators	Drug type	Phase	Indications	First posted date/ NMPA approval date
Herceptin (trastuzumab)	Roche	N/A	Approved	HER2 + mBC	2002/9/5
赛普汀 (Inetetamab)	Sunshine Guojian	Novel	Approved	HER2 + mBC	2020/6/19
HLX02	Shanghai Henlius Biotech	Biosimilar	Approved	HER2+ BC	2020/8/14
GB221	**Genor Biopharma**	**Novel**	**Phase 3**	**Chemotherapy failed HER2+ advanced BC**	**2016/9/28**
				HER2+ recurrent or metastatic BC	**2018/4/19**
BAT8001 (Her2 ADC)	Bio-thera Solutions	Novel	Phase 3	HER2+ advanced BC	2018/2/22
HS022	Hisun Pharmaceuticals	Biosimilar	Phase 3	Breast cancer	2018/4/8
Recombinant human HER2 monoclonal antibody	Anhui Anke Biotechnology	Biosimilar	Phase 3	HER2+ BC	2019/5/23
SIBP-01	Shanghai Institute of Biological Products	Biosimilar	Phase 3	HER2+ BC	2019/6/5
RC48 (Her2 ADC)	RemeGen	Novel	Phase 3	HER2 low expression locally advanced or metastatic breast cancer	2020/5/11

Source: Company data, CMBIS

GB226: a recombinant humanized PD-1 mAb for oncology

GB226 (geptanolimab, an anti-PD-1 mAb)

The Company in-licensed the rights to develop, manufacture and commercialize GB226 in China from Crown Bioscience in March 2015. GB226 is an investigational, humanized, IgG4 mAb targeting the programmed cell death-1 receptor (PD-1) on immune cells designed to restore the natural ability of the immune system to recognize and kill cancer cells by selectively blocking the dual ligand (PD-L1 and PD-L2) binding to the PD-1 protein.

The Company is developing GB226 as a monotherapy in PTCL, PMBCL, cervical cancer and ASPS in China. A pivotal Phase 2 clinical trial is ongoing for PMBCL, and an NDA of GB226 for PTCL has been accepted and granted priority review by NMPA. The Company is also developing GB226 in combination with fruquintinib, a small molecule, selective and highly potent inhibitor of VEGFR 1, 2 and 3, for second- and third- line EGFR+ NSCLC and second-line mCRC in China. Genor has submitted NDA for PTCL in July 2020.

The Company is executing a comprehensive clinical trial development plan in China targeting an array of cancer indications for its GB226. The Company has adopted a fast-to-market strategy and a differentiated regulatory pathway for GB226 by conducting clinical trials for indications with few effective treatment options.

2L+ r/r PTCL: There is no NMPA- or FDA- approved PD-(L)1 drugs for PTCL yet. The Company has enrolled a total of 102 patients with ECOG 0-1. An NDA of GB226 for PTCL has been accepted and granted priority review by NMPA.

2L+ r/r PMBCL: The Company is conducting an open-label, single-arm pivotal Phase 2 study in China to evaluate the safety and efficacy of GB226 at 3mg/kg q2w dose level in patients with r/r PMBCL who failed at least two prior systemic treatments, with ECOG 0-1. The primary endpoint is ORR and the secondary endpoints are DOR, OS and PFS. The Company expects to enrol a total of 53 patients. As of 27 May 2020, the Company had recruited 23 patients.

Recurrent or metastatic cervical cancer: As of 2 Apr 2020, GB226 showed promising anti-tumor activities in recurrent or metastatic cervical cancer. Clinical data of 58 patients were included in efficacy analysis, including all patients who received at least one valid efficacy evaluation and patients who had exited the study. GB226 demonstrated an investigator-evaluated ORR of 19.0%.

ASPS: The Company has recruited 37 patients with ECOG 0-1. The Company will plan for further studies based on internal review of the study results.

The Company is evaluating GB226 for the treatment of some of the most prevalent cancer types, such as NSCLC and mCRC. The Company plans to maximize GB226's commercial potential and explore extensive PD-1 backbone combination therapies. The combination therapy of PD-1 and fruquintinib may potentially demonstrate better efficacy than PD-1 monotherapy.

2L EGFR+ NSCLC: According to the CIC report, NSCLC is the cancer with the highest incidence rate in China. More than 900 thousand patients are newly diagnosed as lung cancer annually in China, among which over 80% are diagnosed with NSCLC. Among all EGFR-positive NSCLC patients who receive EGFR therapy as first- or second- line treatment, approximately 47% are also PD-1- positive. These patients will turn to PD-1 therapy after developing resistance to EGFR therapy. Besides, patients who are neither EGFR- nor PD-1- positive also intend to receive PD-1 therapy. The Company is conducting a multi-center, open-label, dose-finding Phase 1b study with extension phase in China to evaluate the safety and tolerability of GB226 at 210mg q2w dose level in combination with fruquintinib (2mg, 4mg or 5mg, q.d., po., 3 weeks-on/1 week-off) in relapsed or metastatic NSCLC patients with EGFR-sensitive mutations who have failed to respond to EGFR-TKI treatment, the

pharmacokinetic characteristics of GB226 and fruquintinib, and the immunogenicity of GB226. The primary endpoints are adverse events, serious adverse events, DLT and maximum tolerated dose and the secondary endpoints are DCR, ORR, OS, PFS, DOR, antidrug antibody and PK parameters. The Company expects to enrol at least 42 patients at about three trial sites. As of 27 May 2020, the Company had recruited nine patients.

2L+ mCRC: According to the CIC report, the incidence of CRC in China reached over 433 thousand cases in China. For patients with drug resistance, second-line treatment is limited. PD-(L)1 monotherapy and combination therapies have already been proven effective in clinical trials for third-line mCRC treatment in the US. The Company is conducting a multi-center, dose escalation Phase 1b study in China to evaluate the safety and tolerability of GB226 at 3mg/kg q2w dose level in combination with fruquintinib (3mg, 4mg or 5mg, q.d., po.,3 weeks-on/1 week-off) in patients with mCRC, the PK characteristics of GB226 in combination therapy and immunogenicity. The primary endpoints are adverse events, dose limited toxicity (DLT) and maximum tolerated dose (MTD) or extended period recommended dose (RDE), and the secondary endpoints are DCR, ORR, OS, PFS, DOR, antidrug antibody and PK parameters. The Company expects to enrol a total of 21 patients at three trial sites. As of 27 May 2020, the Company had recruited seven patients.

In March 2020, the Company submitted an IND for an open-label, multi-center Phase 1b/2 clinical trial of GB226 in combination with lenvatinib for the treatment of patients with HCC. The NMPA confirmed that the study may proceed in June 2020.

Promising clinical trial results

Pivotal phase 2 study in r/r PTCL

The Company has completed a pivotal Phase 2 clinical study to evaluate the efficacy and safety of GB226 for the treatment of Chinese population with r/r PTCL who failed at least one prior systemic treatment. The Company has recruited a total of 102 patients with ECOG 0-1. GB226 is given at 3mg/kg q2w dose level intravenously until disease progression, unacceptable toxicity or the expiration of two years. Primary endpoint is ORR, and secondary endpoints are duration of response (DOR), overall survival (OS), progression-free survival (PFS), disease control rate (DCR), time to response (TTR), safety and immunogenicity.

GB226 showed a promising clinical activity in PTCL patients. Clinical data of 73 patients were included in the efficacy analysis, representing the full analysis set population, which is a trial population as close as possible to the general population for which the test treatment is intended. The efficacy results from this trial are summarized in the following tables. GB226 demonstrated an independent review committee (IRC)-evaluated ORR of 38.4%, whereas the reported ORR of chidamide (HDAC inhibitor) is 28%.

Figure 17: Efficacy analysis of GB226 in r/r PTCL

Overall efficacy	Investigator assessment (N=73) n (%)	IRC assessment (N=73) n (%)
Best overall response (BOR)		
Complete response (CR)	5 (6.8%)	8 (11.0%)
Partial response (PR)	23 (31.5%)	20 (27.4%)
Stable disease (SD)	11 (15.1%)	15 (20.5%)
Progressive disease (PD)	27 (37.0%)	23 (31.5%)
Unevaluable (UE)*	1 (1.4%)	0
Not applicable (NA)#	6 (8.2%)	7 (9.6%)
Objective response rate (ORR) (CR+PR) (95% CI)	**28 (38.4%)**	**28 (38.4%)**
	(27.21%, 50.48%)	**(27.21%, 50.48%)**
Disease control rate (DCR) (CR+PR+SD) (95% CI)	**39 (53.4%)**	**43 (58.9%)**
	(46.37%, 65.20%)	**(46.77%, 70.29%)**
Duration of response (DOR) (months)		
(Minimum, maximum)	(0.03+, 13.83+)	(1.31+, 13.83+)
Median (95% CI)	2.9 (1.5, NR)	7.10 (4.21, NR)
Estimated rate of durable responses		
3 months (95% CI)	0.5 (0.3, 0.7)	0.7 (0.5, 0.9)
6 months (95% CI)	0.4 (0.2, 0.6)	0.5 (0.3, 0.7)
12 months (95% CI)	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)
Time to response (TTR) (months)		
(Minimum, maximum)	(1.18, 9.66)	(0.03+, 11.14+)
Median (95% CI)	1.4 (1.4, 2.7)	4.0 (1.5, NR)
Estimated rate of response		
3 months (95% CI)	0.5 (0.4, 0.6)	0.5 (0.4, 0.7)
6 months (95% CI)	0.4 (0.2, 0.5)	0.4 (0.2, 0.6)
12 months (95% CI)	0.2 (0.0, 0.4)	NR (NR, NR)

Source: Company data, CMBIS
Notes: NA = not applicable (subjects exited the study without conducting at least one valid efficacy evaluation due to adverse events or withdrawal of consent); CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = unevaluable (subjects received imaging scan but the results were not evaluable); IRC = independent review committee; CI = confidence interval

Figure 18: PSF in r/r PTCL

	Investigator assessment (N=73)	IRC assessment (N=73)
Progressive-free survival (months)		
(Minimum, maximum)	(0.30+, 15.18+)	(0.30+, 15.18+)
Median	2.7 (1.4, 2.9)	2.7 (1.5, 4.2)
Progressive-free survival rate		
3 months (95% CI)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)
6 months (95% CI)	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)
12 months (95% CI)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)

Source: Company data, CMBIS
Notes: IRC = independent review committee; CI = confidence interval; PFS = progression-free survival

In sub-group analysis, GB226 demonstrated anti-tumor efficacy across all common subtypes of PTCL and in patients (n = 16) who had previously been treated with chidamide.

Figure 19: GB226 demonstrated anti-tumor efficacy across all common subtypes of PTCL

		Efficacy (IRC assessment)	
Histologic subtypes	Number of patients	ORR N (%)	DCR N (%)
All patients		37 (36.3%)	57 (55.9%)
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	26	4 (15.4%)	11 (42.3%)
Extranodal NK-/T-cell lymphoma, nasal type (ENKTL)	17	10 (58.8%)	13 (76.5%)
ALK-positive anaplastic large cell lymphoma (ALCL ALK+)	5	2 (40.0%)	3 (60.0%)
ALK-negative anaplastic large cell lymphoma (ALCL ALK-)	13	7 (53.8%)	8 (61.5%)
Others	12	5 (41.7%)	8 (66.7%)

Source: Company data, CMBIS
Notes: IRC = independent review committee; CI = confidence interval; PTCL-NOS = PTCL-not otherwise specified; ENKTL = extranodal NK-/T-cell lymphoma, nasal type; ALCL ALK+ = anaplastic lymphoma kinase-positive anaplastic large cell lymphoma; ALCL ALK- = anaplastic lymphoma kinase-negative anaplastic large cell lymphoma

Figure 20: GB226 demonstrated anti-tumor efficacy in PTCL patients who had previously received chidamide

Subgroup	ORR (95% CI)	DCR (95% CI)	Median PFS (months) (95% CI)
Previous exposure to Chidamide			
Yes (N=16)	6 (37.5%) (15.20%, 64.57%)	8 (50.0%) (24.65%, 75.35%)	2.6 (1.2-8.3)
No (N=57)	22 (38.6%) (26.00%, 52.43%)	35 (61.4%) (47.57%, 74.00%)	2.7 (1.4-4.2)

Source: Company data, CMBIS
Notes: ORR = objective response rate; DCR = disease control rate; PFS = progression-free survical; CI = confidence interval

GB226 showed an acceptable safety profile in PTCL patients. Clinical data of 102 patients were included in safety analysis, which include patients who received at least one injection of GB226 and at least one valid safety evaluation.

Figure 21: Safety analysis of GB226 in r/r PTCL

Adverse events (AEs)	Gxplore-002(N=102) n (%)
All treatment emergent adverse events (TEAEs)	94 (92.2%)
≥Grade 3 TEAEs	57 (55.9%)
Treatment-related adverse events (TRAEs)	81 (79.4%)
≥Grade 3 TRAEs	23 (22.5%)
Serious adverse events (SAEs)	40 (39.2%)
Treatment-related SAEs	16 (15.7%)
Immune-relatedadverse events (irAEs)	36 (35.3%)
≥Grade 3 irAEs (irAE)	10 (9.8%)
AEs leading to dose interruption	22 (21.6%)
TRAEs leading to dose interruption	14 (13.7%)
AEs leading to dose discontinuation	17 (16.7%)
TRAES leading to dose discontinuation	9 (8.8%)
AEs leading todeath	12 (11.8%)
TRAEs leading to death	1 (1.0%)

Source: Company data, CMBIS
Notes: (1) TEAE = treatment emergent adverse events; TRAE = treatment related adverse events; SAE = serious adverse events; irAE = immune-related adverse events; CTCAE = common terminology criteria for adverse events (2) Grade according to CTCAE

Figure 22: Summary of ≥10% TEAE of GB226 in r/r PTCL

System organ classes (SOCs) Terminology	Gxplore-002(N=102) n (%)
At least one treatment emergent adverse event	87 (85.3%)
Metabolism and nutrition disorders	42 (41.2%)
Anorexia	15 (14.7%)
Hypokalemia	15 (14.7%)
Hypoproteinemia	12 (11.8%)
General disorders and administration site conditions	40 (39.2%)
Fever	25 (24.5%)
Fatigue	11 (10.8%)
Blood and lymphatic system disorders	33 (32.4%)
Anemia	33 (32.4%)
Respiratory, thoracic and mediastinal disorders	21 (20.6%)
Cough	15 (14.7%)
Infectious and infestations	24 (23.5%)
Upper respiratory infection	15 (14.7%)
Pulmonary infection	11 (10.8%)
Skin and subcutaneous disorders	15 (14.7%)
Pruritus	13 (12.7%)

Source: Company data, CMBIS

Grade≥3 TEAEs that were observed in >5% of patients primarily included anemia (12.7%), reduced lymphocyte count (10.8%), reduced platelet count (9.8%), reduced white blood cell count (9.8%), upper respiratory tract infection (7.8%), death (7.8%), lung infection (6.9%), reduced neutrophil count (6.9%) and fever (5.9%). GB226 mainly showed irAEs, whereas chidamide showed hematological abnormalities. Thrombocytopenia, leucopenia and neutropenia were observed with higher incidence and more severity with chidamide than GB226. 94 patients (92.2%) had treatment emergent antidrug antibody (ADA) to GB226, among whom two patients was ADA-positive at baseline.

Phase 2 study in relapsed/metastatic/unresectable ASPS

The Company is currently conducting an open-label, single-arm, Phase 2 clinical study of GB226 in relapsed/metastatic/unresectable ASPS. The Company has recruited 37 patients with ECOG 0-1. GB226 is given intravenously at 3 mg/kg q2w dose level until disease progression, unacceptable toxicity or the expiration of one year. Primary endpoint is ORR, and secondary endpoints are DOR, OS, PFS and safety.

As of 23 Mar 2020, GB226 showed promising clinical activities in ASPS. Clinical data of 37 patients were included in efficacy analysis, including all patients who received at least one injection of GB226 and at least one valid efficacy evaluation and patients who had exited the study.

The efficacy results from this trial for GB226 as of 23 Mar 2020 are summarized in the following table. GB226 demonstrated an ORR of 40.5%, as compared to the reported ORR of 25% for anlotinib (安罗替尼), which is the standard of care treatment for ASPS.

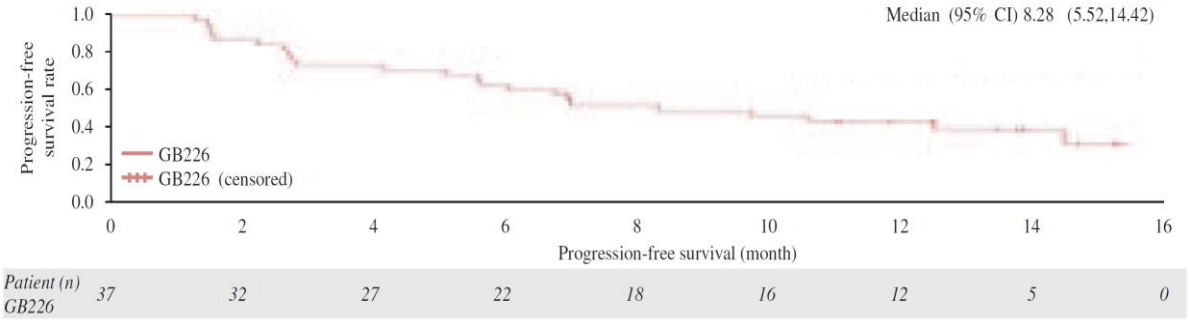
Figure 23: Efficacy analysis of GB226 in ASPS

Overall efficacy	Investigator assessment* (N=37) n (%)	IRC assessment* (N=37) n (%)
Best overall response (BOR)		
Confirmed + unconfirmed completed response (CR)	1 (2.7%)	0
Confirmed CR	0	0
Confirmed + unconfirmed partial response (PR)	14 (37.8%)	14 (37.8%)
Confirmed PR	13 (35.1%)	14 (37.8%)
Stable disease (SD)	17 (45.9%)	18 (48.6%)
Objective response rate (ORR) (CR + PR)#	**15 (40.5%)**	**14 (37.8%)**
(95% CI)	**(24.8%, 57.9%)**	**(22.5%, 55.2%)**
Disease control rate (ORR) (CR + PR + SD)#	**31 (83.8%)**	**32 (86.5%)**
(95% CI)	**(68.0%, 93.8%)**	**(71.2%, 95.5%)**
Duration of response (DOR) (months)		
(Minimum, maximum)	(2.79+, 13.77+)	(2.6+, 13.73+)
Median (95% CI)	NR (6.9, NR)	NR (10.28, NR)
Estimated rate of durable responses		
3 months (95% CI)	100% (100%, 100%)	92.9% (59.1%, 99.0%)
6 months (95% CI)	87.5% (53.9%, 96.2%)	91.7% (59.1%, 99.0%)
Time to response (TTR) (months)		
(Minimum, maximum)	(1.35, 15.38+)	(1.35, 15.38+)
Median (95% CI)	NR (2.9, NR)	NR (4.2, NR)

Data as of 23 Mar 2020
Source: Company data, CMBIS
Notes: (1) BOR = best overall response; CR = complete response; PR = partial response; SD = stable disease; ORR = objective response rate; DOR = duration of response; TTR = time till response; CI = conficence interval; NR = not reached; IRC = independent review committee

The following graph shows the PFS of the 37 patients as of 23 Mar 2020. No death was observed as of 23 Mar 2020 in this trial, and the longest survival period was 18.3 months.

Figure 24: PFS in ASPS



	Investigator assessment	IRC assessment
Number of patients	37	37
Progression-free survival (months)		
(Minimum, maximum)	(1.41, 15.24+)	(1.22, 15.24+)
Median (95% CI)	8.2 (5.6, 14.0)	8.3 (5.5, 14.4)
Estimated progression-free survival rate		
3 months (95% CI)	75.7% (58.5%, 86.5%)	73.0% (55.6%, 84.4%)
6 months (95% CI)	62.2% (44.6%, 75.6%)	59.5% (42.0%, 73.2%)

Source: Company data, CMBIS
Notes: CI = conficence interval; NR = not reached; IRC = independent review committee

In sub-group analysis, as of 23 Mar 2020, GB226 demonstrated anti-tumor efficacy in both first-line and second-line or higher ASPS patients and in 33.3% of ASPS patients who had failed anlotinib treatment.

Figure 25: GB226 demonstrated anti-tumor efficacy in both first-line and second-line or higher ASPS patients and in ASPS patients who had failed anlotinib treatment

Subgroup	ORR (95% CI)		DCR (95% CI)	
Lines of therapy				
First therapy (N=14)	5 (35.7%)	(12.8%, 64.9%)	14 (100.0%)	(76.8%, 100.0%)
First line and above (N=23)	9 (39.1%)	(19.7%, 61.5%)	18 (78.3%)	(56.3%, 92.5%)
Previous exposure to Anlotinib				
Yes (N=9)	3 (33.3%)	(7.5%, 70.1%)	5 (55.6%)	(21.2%, 86.3%)
No (N=28)	11 (39.3%)	(21.5%, 59.4%)	27 (96.4%)	(81.7%, 99.9%)

Data as of 6 Sep 2019
Source: Company data, CMBIS
Notes: CI = confidence interval; IRC = independent review committee; NR = not reached; 95% CI was calculated by Clopper-Pearson method for ORR and DCR

As of 23 Mar 2020, GB226 showed an acceptable safety profile in ASPS. Clinical data of 37 patients were included in safety analysis, including all patients who received at least one injection of GB226 and at least one valid safety evaluation. The average exposure period among all 37 patients was 48 weeks, ranging from 8.1 weeks to 69.6 weeks. 83.8% of these patients had received GB226 for 24 weeks or longer, and 48.6% had received GB226 for 52 weeks or longer.

Figure 26: Safety analysis of GB226 in ASPS

Adverse events (AEs)	Gxplore-005 (N=37) n (%)
All treatment emergent adverse events (TEAEs)	36 (97.3%)
Treatment-related adverse events (TRAEs)	31 (83.8%)
Treatment emergent serious adverse events (SAEs)	7 (18.9%)
Treatment-related SAEs	3 (8.1%)
Immune-related adverse events (irAEs)	18 (48.6%)
≥Grade 3 TEAEs	8 (21.6%)
≥Grade 3 TRAEs	4 (10.8%)
AEs leading to dose interruption	14 (37.8%)
TRAEs leading to dose interruption	10 (27.0%)
AEs leading to dose discontinuation	2 (5.4%)
TRAEs leading to dose discontinuation	2 (5.4%)
AEs leading to death	0
TRAEs leading to death	0

Source: Company data, CMBIS
Notes: (1) TEAE = treatment emergent adverse events; TRAE = treatment related adverse events; SAE = serious adverse events; irAE = immune-related adverse events; CTCAE = common terminology criteria for adverse events (2) Grade according to CTCAE

Figure 27: Summary of ≥10% TEAE of GB226 in ASPS

System Organ Classes (SOCs) Terminology	Gxplore-005 (N=37) n (%)
At least one treatment emergent adverse event	36 (97.3%)
Skin and subcutaneous disorders	17 (45.9%)
Skin rash	7 (18.9%)
Infectious and infestations	17 (45.9%)
Upper respiratory infection	11 (29.7%)
General disorders and administration site conditions	15 (40.5%)
Fever	8 (21.6%)
Influenza-like illness	4 (10.8%)
Metabolism and nutrition disorders	9 (24.3%)
Hyperglycemia	5 (13.5%)
Hyperuricemia	4 (10.8%)
Blood and lymphatic system disorders	9 (24.3%)
Anemia	7 (18.9%)
Endocrine disorders	8 (21.6%)
Hypothyroidism	7 (18.9%)

Source: Company data, CMBIS

Grade ≥ 3 TEAEs primarily included elevated lipase (N=2, 5.4%). 17 patients had at least one immune-related AE, which primarily included hypothyroidism (N=7; 18.9%) and rash (N=6; 16.2%).

Phase 2 study in recurrent or metastatic cervical cancer

The Company is currently conducting a multi-center, prospective, open-label, single-arm Phase 2 clinical study of GB226 in PD-1-positive recurrent or metastatic cervical cancer patients who failed at least one prior platinum-based chemotherapy. The Company expects to enrol a total of 80 patients at about 20 trial sites with ECOG 0-1. GB226 is given intravenously at 3 mg/kg q2w dose level until disease progression, unacceptable toxicity or the expiration of two years. Primary endpoint is ORR, and secondary endpoints are DOR, OS, PFS, DCR, TTR, safety and ADA.

As of 2 Apr 2020, GB226 showed promising anti-tumor activities in recurrent or metastatic cervical cancer. Clinical data of 58 patients were included in efficacy analysis, including all patients who received at least one valid efficacy evaluation and patients who had exited the study.

The efficacy results from this trial for GB226 as of 2 Apr 2020 are summarized in the following table. GB226 demonstrated an investigator-evaluated ORR of 19.0%.

Figure 28: Efficacy analysis of GB226 in recurrent or metastatic cervical cancer

Overall efficacy	Investigator assessment (N=58) n(%)
Best overall response (BOR)	
Complete response (CR)	0
Unconfirmed + confirmed partial response (PR)	11 (19.0%)
Confirmed partial response (PR)	8 (13.8%)
Stable disease (SD)	10 (17.2%)
Progressive disease (PD)	29 (50.0%)
Not evaluable (NE)	3 (5.2%)
Not applicable (NA)	5 (8.6%)

Source: Company data, CMBIS
Notes: BOR = best overall response; CR = complete response; PR = partial response; SD = stable disease; ORR = objective response rate; NE = not evaluable

Large market potential for anti-PD-1 mAb

There is a significant commercial opportunity in China for PD-(L)1 class of drugs. According to the CIC Report, the incidence of all cancers in China increased from 3.8mn in 2014 to 4.5mn in 2019. The top ten types of cancers by incidence in 2019 accounted for 77.7% of the total incidence, reaching 3.5mn. Lung cancer was the most common cancer in China with 886 thousand new patients in 2019. Certain subtypes of gastrointestinal cancers, especially gastric cancer, have higher incidence rates in China than in the US. Driven by a combination of factors such as unhealthy lifestyle and aging population, it is estimated that the incidence of all cancers in China will reach 5.0mn in 2023. Among all types of cancers, lung, stomach, colorectal, liver, breast and esophageal cancers are the six most common cancers in China and respectively accounted for approximately 916.4 thousand, 500.3 thousand, 433.8 thousand, 434.4 thousand, 330.5 thousand and 332.8 thousand of the total incidences in China in 2019.

Currently available clinical data suggest that some of the most prevalent cancers in China, such as lung, stomach, colorectal, liver and esophageal cancers, are responsive to the PD-(L)1 class of drugs. Taking into account of the other cancer types (such as bladder, melanoma and kidney cancers) that are also responsive to the PD-(L)1 class, the overall annual incidence of cancers potentially responsive to PD-(L)1 antibodies in China was approximately 3.1mn in 2019, according to the CIC Report.

Figure 29: Approved PD-1 antibodies in China

Drug name	Sponsors/ collaborators	Indications	NMPA approval date	Price (RMB)	Medical reimbursement	Expiration date(s) of key patent(s)
Opdivo (nivolumab)	Bristol-Myers Squibb	EGFR/ALK negative locally advanced or metastatic NSCLC	2018/6/15	9,260/100mg/10ml 4,591/40mg/10ml	No	July 2023 - June 2027
		recurrent or metastatic head and neck squamous cell carcinoma	2019/9/30			
Keytruda (pembrolizumab)	Merck	unresectable or metastatic melanoma	2018/7/26	17,918/100mg/4ml	No	June 2027 - June 2028
		EGFR/ALK negative metastatic nonsquamous NSCLC	2019/3/29			
		EGFR/ALK negative metastatic NSCLC	2019/10/24			
		metastatic squamous NSCLC	2019/11/27			
		Esophageal cancer	2020/6/19			
Tuoyi (toripalimab)	Junshi	unresectable, metastatic malignant melanoma	2018/12/17	7,200/240mg/6ml	No	NA
Tyvyt (sintilimab)	Innovent	refractory Hodgkin lymphoma	2018/12/27	2,843/100mg/10ml	Yes	September 2036 - August 2037
Airuika (camrelizumab)	Hengrui	refractory Hodgkin lymphoma	2019/5/29	19,800/200mg/vial	No	November 2034 - December 2035
		liver cancer	2020/3/6			
		Late stage esophageal squamous cell carcinoma	2020/6/19			
		Late stage nonsquamous NSCLC	2020/6/19			
Baizean (tislelizumab)	BeiGene	r/r classical Hodgkin's lymphoma (cHL)	2019/12/27	10,688/100mg/vial	No	September 2033 - June 2034
		Locally advanced or metastatic urothelial carcinoma	2020/4/11			

Source: Company data, CMBIS
Note: NMPA Approval Date is for the first indication; (ii) Medical reimbursement for Tyvyt is only for r/r cHL treatment

Two PD-L1 antibodies have been approved in China. Roche's Tecentriq (atezolizumab) was approved by the NMPA on 13 Feb 2020 for advanced NSCLC and AstraZeneca's Imfinizi (durvalumab) was approved by the NMPA on 9 Dec 2019 for advanced NSCLC. Several companies have anti-PD-(L)1 drug candidates with an NDA application under review by the NMPA for the first indications, including Gloria Pharmaceuticals' GLS-010 and Akeso's AK105. According to the CIC Report, the market size for PD-(L)1 antibodies in China is expected to grow from RMB6.1bn in 2019 to RMB65.5bn in 2030, representing a CAGR of 24.1%.

According to the CIC Report, the sales in China in 2019 were RMB2,270mn for Keytruda, RMB1,000mn for Opdivo, RMB1,016mn for Tyvyt, RMB958mn for Airuika and RMB774mn for Tuoyi.

The PD-(L)1 antibody drug in China has been rapidly growing. The Company has adopted a differentiated clinical development strategy in terms of targeting oncology indications with few effective treatment options, including PTCL, PMBCL, cervical cancer and ASPS. PTCL is a major subtype of NHL in China. PTCL and ASPS are novel indications for which the FDA has not yet approved any PD-(L)1 antibody drugs. According to the CIC Report, the incidence and mortality of NHL in China has been rising annually. In 2019, incidence of NHL in China reached 90.4 thousand people, representing a CAGR of 3.9% from 2014 to 2019, and the mortality of NHL in China reached 45.4 thousand people, representing a CAGR of 3.5% from 2014 to 2019.

PTCL is often an invasive cancer that develops from white blood cells called T-lymphocytes, or T-cells. Epidaza (chidamide), an HDAC inhibitor, has been approved in China for PTCL. Before 2014,

chemotherapies were the main treatments for PTCL. The treatment for PTCL is limited globally, and Epidaza is the only approved drug for first-line PTCL therapy in China. But due to its limited efficacy, it is normally used in second-line therapy. There is currently no immuno-therapies approved in China for the treatment of PTCL. In China, there are only two PD-(L)1 drugs targeting PTCL, including the Company's GB226, which is under Phase 2 pivotal trial, and AK104 from Akeso, a Phase 1b/2 trial of which was initiated in January 2020.

PMBCL has low incidence but strong invasiveness. In 2019, the incidence of PMBCL in China reached 3.6 thousand cases, representing a CAGR of 3.9% from that in 2014 at 3.0 thousand cases. About 75% of PMBCL patients have bulky disease with a tumor mass exceeding 10 cm. However, few drugs have been developed to treat PMBCL. Rituximab in combination with chemotherapy is a feasible treatment regimen for PMBCL, and pembrolizumab is a feasible treatment regimen for relapsed PMBCL, according to the NCCN guidelines. The only PD-(L)1 drug marketed for PMBCL globally is Keytruda, which was approved in June 2018. In China, the only biologic drug that has been approved for PMBCL is Roche's Rituxan (rituximab), which targets CD20.

Cervical cancer is the second most commonly occurring cancer in women. In 2019, the incidence of cervical cancer in China reached 116 thousand cases, representing a CAGR of 2.5% from that in 2014 at 102 thousand cases. It is expected that in 2030 the incidence number will increase to 125 thousand cases. The relapsed rate for cervical cancer is relatively high at about 35-40%. The treatment options for relapsed/metastatic cervical cancer patients are currently limited. Main treatments for advanced cervical cancer is radiotherapy such as external beam radiation therapy with adjuvant chemotherapy. Chemotherapy mainly adopts platinum-containing monotherapy or combination therapy. According to the CSCO guidelines for cervical cancer, bevacizumab is recommended to be used in both first- and second- line treatments. Several targeted biologics are under clinical trials for relapsed/metastatic cervical cancer globally, such as Avastin (bevacizumab) and PD-(L)1 drugs. There is currently no approved biologic drug for cervical cancer in China so far. PD-(L)1 drugs have great potential in second-line r/r cervical cancer treatment. PD-(L)1 drugs targeting r/r cervical cancer are expected to be approved in 2022 and experience a significant growth in the near future.

ASPS is a cancer with mutations in the ASPL-TFE3 gene. ASPS is of great significance because of its high metastatic rate of 79%. The treatment scheme for ASPS is limited at present with a main focus on neo-adjuvant therapy. ASPS has fewer treatment options than angiosarcomas and solitary fibrous tumor (SFT) due to its insensitivity to cytotoxic drugs, according to the NCCN guidelines. More ASPS treatments are in need. No PD-(L)1 drug has been approved for ASPS so far. Keytruda is under Phase 2 clinical trial for ASPS registered with the FDA. In China, only CTTQ Pharma's Focus V (anlotinib), which targets RTK, has been approved for ASPS.

In addition to monotherapies, the Company is developing GB226 in combination with other therapies for various oncology indications, including NSCLC and mCRC.

NSCLC is the cancer with the highest incidence rate in China. More than 900 thousand patients are newly diagnosed as lung cancer annually in China, among which over 80% are diagnosed with NSCLC. In 2019, the incidence of NSCLC in China reached 733.1 thousand cases, representing a CAGR of 3.2% from that in 2014 at 624.8 thousand cases.

There are various treatment plans for NSCLC. Currently, patients with advanced NSCLC are divided into EGFR/ALK-positive and EGFR/ALK-negative groups. EGFR/ALK-negative patients are treated with immunotherapy if they are positive for PD-L1. About 50% of patients with advanced non-squamous NSCLC fall under this category. Keytruda has already been approved as first-line treatment for this indication, with the vast majority of other PD-(L)1 drugs also being developed for this indication. EGFR is the most common genetic mutation in NSCLC patients in China, and its proportion in non-squamous NSCLC patients is about 44%. According to the treatment guidelines, these patients are directly treated with small molecule EGFR tyrosine kinase inhibitors (EGFR TKI inhibitors). The first-

and second- generation EGFR TKI inhibitors that have been approved in China include erlotinib, gefitinib and afatinib. Currently, the world's potential best-in-class third-generation EGFR TKI inhibitor, Tagrisso (osimitinib), has been approved in China for first-line treatment of patients with advanced EGFR mutation-positive NSCLC. Tagrisso will gradually replace other EGFR TKI inhibitors, but patients still lack effective later-line treatments after Tagrisso-resistance.

The effect of first-line immunotherapy in patients with EGFR mutations is not optimal, because of the overall low level of PD-L1 expression in patients. However, the JCO study indicated that PD-L1 expression significantly increases with the development of resistance to EGFR TKI inhibitors, so immunotherapy may still be used as a treatment option for EGFR mutation-positive advanced NSCLC patients after the development of resistance to EGFR TKI inhibitors. There is currently no immunotherapy drug approved for the treatment after the development of resistance to EGFR TKI inhibitors, so this group of patients with advanced EGFR mutation-positive NSCLC urgently need a later-line treatment after drug resistance. In China, the Company is among the only two domestic companies currently conducting clinical trials for EGFR mutation-positive NSCLC patients after EGFR TKI inhibitors treatment failure.

Since being approved as first-line treatment in September 2019, Tagrisso has become the recommended first-line treatment for Chinese patients with EGFR mutation-positive NSCLC, according to the treatment guidelines. After that, the vast majority of new EGFR mutation positive NSCLC patients will use Tagrisso as first-line treatment. The clinical trial of GB226 is the only trial in China that specifically targets patients with EGFR mutation-positive NSCLC after treatment with Tagrisso has failed, and the Company's clinical trial design has been optimized for Tagrisso resistance. GB226 is taking the lead in the market and may become the first Chinese immunotherapy drug approved for the treatment of patients with advanced EGFR mutation-positive NSCLC after Tagrisso resistance.

CRC is the cancer developed from the colon or rectum. In 2019, the incidence of CRC in China reached near 434 thousand cases, representing a CAGR of 3.2% from that in 2014 at 370 thousand cases. It is expected that this number will reach over 570 thousand in 2030. The treatment options for mCRC are limited to combination therapies of bevacizumab with chemotherapy or cetuximab with chemotherapy. Although these therapies have been approved as first-line treatment for mCRC patients, for patients with drug resistance, second-line treatment is limited, according to the NCCN guidelines. PD-(L)1 monotherapy and combination therapies have already been proven effective in clinical trials for third-line mCRC treatment in the US. Currently, there are over 10 Phase 2/3 PD-(L)1 drugs clinical trials ongoing targeting mCRC registered with the FDA, including Opdivo and Keytruda. In China, the only biologics that have been approved for mCRC in China are Roche's VEGF-targeting Avastin (bevacizumab), Merck's EGFR-targeting Erbitux (cetuximab) and Qilu Pharmaceutical's Ankeda (bevacizumab biosimilar). In China, PD-(L)1 drug clinical trials registered for mCRC are limited, including only four candidates. With the approval of PD-(L)1 therapy for mCRC by the FDA, the application and approval progress is expected to be accelerated. PD-(L)1 therapy is expected to become the standard third-line therapy for mCRC patients in China in 2021, according to the CIC Report.

Figure 30: Comparison between GB226 and its approved or late-stage competitors in China

Drug name	Sponsors/ collaborators	Phase	Indications	First posted date (for drugs under development)/ approval date (for approved drugs)
PTCL				
GB226	**Genor Biopharma**	**Phase 2**	**r/r PTCL**	**2018/4/27**
AK104	Akeso	Phase 1b/2	r/r PTCL	2020/1/13
PMBCL				
GB226	**Genor Biopharma**	**Phase 2**	**PMBCL**	**2018/8/19**
TQB2450	Chiatai Tianqing	Phase 2	PMBCL	2019/5/29
ASPS				
GB226	**Genor Biopharma**	**Phase 2**	**ASPS**	**2018/8/9**
Cervical Cancer				
Durvalumab	AstraZeneca	Phase 3	Locally advanced cervical cancer	2020/4/9
GB226	**Genor Biopharma**	**Phase 2**	**PD-1-positive relapsed or metastatic cervical cancer that fails platinum-based chemotherapy**	**2019/3/8**
GLS-010	Harbin Gloria, Wuxi AppTec	Phase 2	Relapsed or metastatic cervical cancer	2019/5/15
HLX10 (in combination with chemotherapy)	Shanghai Henlius Biotech	Phase 2	Advanced cervical cancer	2019/12/6
Recombinant PD-L1 mAb	Zhaoke Oncology	Phase 1b/2	Cervical cancer	2018/7/2
EGFR mutation-positive NSCLC				
Opdivo	BMS	Phase 3	Advanced or metastatic EGFR mutation-positive and T790M negative NSCLC with first line EGFR-TKI treatment failure	2017/6/29
JS001 (in combination with pemetrexed platinum-based chemotherapy)	Junshi	Phase 3	EGFR mutation positive NSCLC with EGFR-TKI treatment failure	2019/4/19
GB226	**Genor Biopharma**	**Phase 1**	**Recurrent or metastatic NSCLC with EGFR-TKI treatment failure**	**2018/11/27**
mCRC				
KN035	Alphamab	Phase 2	Advanced CRC	2018/7/25
Opdivo (in combination with ipilimumab)	BMS	Phase 2	dMMR/MSI-H relapsed or metastatic CRC	2019/12/18
SCT-I10A (in combination with SCRT200)	Sino Cell Tech	Phase 1b	Advanced CRC	2020/3/18
GB226 (in combination with bevacizumab and chemotherapy)	**Genor Biopharma**	**Phase 1**	**mCRC**	**2019/1/7**
GB226 (in combination with fruquintinib)	**Genor Biopharma**	**Phase 1**	**mCRC**	**2019/1/8**

Source: Company data, CMBIS

GB492 (IMSA101): a STING agonist drug candidate for solid tumors

GB492 (IMSA101)

GB492 is the Company's STING agonist drug candidate for solid tumors. In preclinical studies, IMSA101 demonstrated effective inhibition of tumor growth alone and in combination with checkpoint inhibitors, including tumors resistant to PD-(L)1. Preliminary data of several early stage clinical trials suggest that STING agonist in combination with PD-1 might be efficacious in treating solid tumors, including head and neck squamous cell carcinoma (HNSCC) immune-oncology treatment-naive TNBC, immune-oncology-treated MM and thyroid carcinoma. STING agonists have also been shown to be generally well tolerated in these early stage trials. Two Phase 2 combination studies of STING agonist and PD-1 are currently undergoing, both in first-line setting HNSCC.

The Company in-licensed the rights to development, manufacture and commercialize GB492 in the APAC region (excluding Japan) from ImmuneSensor Therapeutics in June 2020. IMSA101 is currently undergoing a Phase 1/2 clinical trial alone or in combination with ICI conducted by ImmuneSensor Therapeutics in the US. The Company plans to evaluate GB492 in combination with GB226 in patients with solid tumors. The Company believes that there is exciting potential for the application of STING modulators in combination with immune checkpoint blockade (ICB) therapy for oncology indications, for non-responders or post-responsders to ICB therapy, and for tumors resistant to current ICB therapy.

IMSA101 is currently undergoing an open-label clinical trial conducted by ImmuneSensor Therapeutics with a dose escalation stage (Phase 1) and a dose expansion stage (Phase 2a) for evaluating its safety and efficacy alone or in combination with an ICI. Phase 1 of this study will enrol about 45 patients across five sites, and Phase 2a of this study will enrol about 95 patients. The primary endpoints will be the RP2Ds as monotherapy and in combination with an ICI. The secondary endpoints will be safety and tolerability administered via intratumoral (IT) injection, preliminary signals of anti-tumor activity, and PK by IT injection. Patients will receive IMSA101 via IT injection on Day 1 of Weeks 1, 2, and 3 of Cycle 1 (i.e., weekly dosing 3 out of 4 weeks) and on Day 1 of Weeks 1 and 3 (bi-weekly dosing) of subsequent cycles. Combination dosing of IMSA101 with an ICI will be initiated when a given dose level and the next higher dose level are confirmed as safe, and the dose level has demonstrated PD activity. Eligible patients for the combination therapy arm will have had Stable Disease (evaluated based on RECIST) for at least four consecutive cycles of an approved ICI. Dose escalation for combination therapy will proceed on a 3+3 basis, consistent with escalation in monotherapy arm. The Company plans to evaluate GB492 in combination with GB226 in solid tumors.

HNSCC and triple-negative breast cancer (TNBC) have limited treatment options with over 106 thousand annual incidence in China combined in 2019. Studies have shown that immunotherapy has some effects in advanced stage patients of both types of cancer. Around 67% of HNSCC patients and 55% of TNBC patients have PD-(L)1 expression and may benefit from immunotherapy. STING agonist, as an immune stimulatory therapy, may further increase the response to ICIs in these patients. The combination use of STING agonist and ICIs has the potential to become a new treatment option for these patients and address the unmet medical needs. Global leading biopharmaceutical companies with a focus on immune-oncology, such as MSD and BMS, have already started STING agonist trial in combination with PD-1 inhibitors. In China, there is currently no approved or pipeline STING agonists in clinical trials. The China market size of STING agonist is expected to reach RMB0.1bn in 2025 and further expand to RMB4.0bn in 2030, representing a CAGR of 108.3% from 2025 to 2030.

GB242: a biosimilar product candidate to infliximab for RA

GB242 (infliximab biosimilar)

GB242 is the Company's biosimilar product candidate to infliximab, which is sold under the trade name Remicade in China. The Company is currently conducting a Phase 3 study of GB242 in RA patients in China and expects to file an NDA with the NMPA in the second half of 2020. The Company also submitted an NDA to the NMPA for GB242 in moderate to severe RA and other infliximab's approved indications in Nov 2020.

Infliximab is a medication used to treat a number of autoimmune diseases, including CD, UC, RA, AS and PsA. Infliximab was approved for medical use in the US in 1998. Infliximab biosimilars have been approved in the European Union, Japan and the US from 2013 to 2019. Worldwide sales of infliximab, including the originator and biosimilars, were US$6.9bn in 2019. The China market size of infliximab was RMB1.3bn in 2019 and is expected to grow to RMB3.7bn by 2023 and reach RMB8.1bn by 2030, representing a CAGR of 17.8% from 2019 to 2030, according to the CIC Report. The prevalence of rheumatoid arthritis in China was approximately 5.9mn cases in 2019. It is expected that biosimilars will represent 64.2% market share of infliximab in 2030. Infliximab is the only TNF- α biologic approved for UC in China.

Infliximab is the only chimeric TNF-α mAb currently marketed in China, which was approved by the NMPA in 2006. Infliximab is also the only TNF-α mAb approved in China for UC. There is one other infliximab biosimilar drug candidate for which an NDA has been submitted with the NMPA. Remicade was included in the NRDL in 2019. As a biosimilar to Remicade, GB242 will also have access to the NRDL, subject to negotiation with the NMPA. Besides GB242, there are two other infliximab biosimilar drug candidates under Phase 3 clinical trials in China, including Zhejiang Hisun's HS626 for plaque psoriasis and Parexel's CT-913 for active RA.

Figure 31: Comparison between GB242 and its late-stage competitors in China

Drug name	Sponsors/ collaborators	Phase	Indications	First posted date/ NMPA approval date
CMAB008	Mabpharm	NDA	Moderate to severe active RA	2019/12/30
GB242	**Genor Biopharma**	**NDA**	**RA**	**2017/7/28**
HS626	Zhejiang Hisun Pharmaceutical	Phase 3	Plaque psoriasis	2018/4/8
CT-P13	Celltrion	Phase 3	Active RA	2018/10/30

Source: Company data, CMBIS

The Company is conducting a multi-center, randomized, double-blind, in parallel Phase 3 clinical trial in China to evaluate the safety and efficacy of GB242 compared to Remicade at a dose level of 3 mg/kg administered intravenously in adult patients with RA. The Company has completed enrolment of 570 patients in this trial. Primary endpoint of the study is equivalent efficacy of ACR20 at week 30.

The Company has completed enrolment of 570 patients for the Phase 3 trial. If the data from this trial establishes biosimilarity between GB242 and Remicade, the Company submitted an NDA to the NMPA for GB242 in moderate to severe RA and other infliximab's approved indications in Nov 2020.

In addition to RA, the Company also plans to apply for regulatory approval for the CD, UC, AS and PsA. According to the Biosimiliar Guidelines, if clinical similarity has been demonstrated in the comparative studies, extrapolation to other indications of the reference product could be considered. Assuming that it achieves favourable biosimiliarity and safety results for GB242 with respect to the RA indication, the Company expects to be able to expand GB242 indications to CD, UC, AS and PsA without the need of full-length clinical trials. As GB242's reference drug, Remicade, is approved in China for RA, CD, UC, AS and PsA, conducting Phase 3 clinical trials for the RA indication has enabled the Company to seek NDA approval for all five indications for Remicade.

GB223: a fully humanized mAb drug candidate for Giant-cell Tumor of Bone (GCTB) and Postmenopausal Osteoporosis (PMO)

GB223 (RANKL mAb)

GB223 is a fully humanized mAb against receptor activator of nuclear factor kappa-B ligand (RANKL) that the Company is developing for the treatment of giant-cell tumor of bone and postmenopausal osteoporosis. The Company in-licensed GB223 from Abcom Biopharmaceutical (北京安保康生物医药科技有限公司) for development in China.

Historically, the only treatment option for patients with GCTB has been surgery. However, patients who undergo surgery often experience high rate of disease recurrence or devastating consequences, such as amputation. Further, about 25-30% of patients with GCTB have to undergo joint replacements.

Bisphosphonates are the most widely used drugs (about 70%) for treating osteoporosis by preventing bone resorption, but bisphosphonates may impose a high risk of atypical femur fractures over five years. Calcitonin is used in about 20% of patients and functions by preventing bone resorption, but calcitonin may lead to an increased risk of malignancy. Biologics are used in about 7% of patients, including Amgen's Prolia, a RANKL inhibitor, which was approved by the NMPA in June 2020 and parathyroid hormone and PTH-related analogue. Parathyroid hormone and PTH-related analogue may increase the risk of osteosarcoma. Selective estrogen receptor modulators are only available for female patients and function by preventing bone resorption.

Amgen's Xgeva (地舒单抗), a RANKL mAb, is currently the only FDA-approved antibody drug and the undoubted first-line treatment option for patients whose GCTB cannot be surgically removed or for when surgery is likely to result in severe morbidity, such as loss of limb or joint removal. GCTB often occurs in young adults, especially among those between 20 and 40 years old. Surgery is the major treatment for grade I-III GCTB. The recurrent rate of grade I-II GCTB is 12-65%.

According to the results of the first Chinese osteoporosis epidemiological survey disclosed by National Health Commission, osteoporosis has become a significant health problem for middle and old aged people in China, which is especially prevalent among middle and old aged women. Due to the relatively serious aging trend, the CAGR of osteoporosis patients in China is higher than the global average in the past five years. The prevalence of osteoporosis in China grew from 83.4mn in 2014 to 101.0mn in 2019, representing a CAGR of 3.9%.

Amgen's Prolia (地舒单抗) was approved by the FDA in 2010 for PMO. Prolia had global sales of US$1,030mn in 2014, which grew to US$2,672mn in 2019, according to the CIC Report. Recent study shows that about 30% of the osteoporosis patients are available for RANKL biologic therapies. Amgen's Prolia was approved by the NMPA in June 2020 for PMO. There are several RANKL antibody candidates under Phase 3 clinical trials, including Qilu Pharma's QL1206, and Luye Pharma's LY06006.

The first RANKL biologic, namely, Xgeva, was approved under overseas fast-track scheme without local clinical trial data by the NMPA in May 2019 for GCTB. The listing price of Xgeva is RMB5,298/100mg, and it is not included in the NRDL yet. Expiration dates of key patents of Xgeva are from June 2022 to November 2023.

Competition in the therapeutic markets to which GB223 belongs is fierce given the abundance of existing competing drugs and drug candidates that continue to increase competition in the market. The Company plans to compete with other drug candidates based on its novel molecule and potentially better efficacy.

Figure 32: Comparison between GB223 and its competitors in China

Drug name	Sponsors/ collaborators	Drug type	Phase	Indications	First posted date/ NMPA approval date
Bone Metastases from Tumors and GCTB					
QL1206	Qilu Pharma Group	Biosimilar	Phase 3	Bone metastases from solid tumors	2019/10/30
MW032	Shanghai Mabwell	Novel	Phase 3	Bone metastases from breast cancer	2020/3/18
JMT103	JMT Bio	Biosimilar	Phase 1	Bone metastases from solid tumors and GCTB	2018/3/27
			Phase 1b/2	Unresectable or surgery is not feasible GCTB	2020/2/20
HS629	Zhejiang Hisun pharmaceutical	Biosimilar	Phase 1	The prevention of skeletal-related events in patients with bone metastases from solid tumors	2018/4/12
LZM004	Livzon Pharmaceutical Group	Biosimilar	Phase 1	Bone metastases from solid tumors and GCTB	2018/8/15
GB223	**Genor Biopharma**	**Novel**	**Phase 1**	**The prevention of skeletal-related events in patients with bone metastases from solid tumors**	**2019/1/17**
LY01011	Luye Pharma Group	Biosimilar	Phase 1	The prevention of skeletal-related events in patients with bone metastases from solid tumors	2019/4/10 2019/12/2
HL05	Hualan Bio	Biosimilar	Phase 1	The prevention of skeletal-related events in patients with bone metastases from solid tumors	2020/2/26
PMO					
QL1206	Qilu Pharmaceutical	Biosimilar	Phase 3	PMO at high risk for fracture	2019/6/5
LY06006	Luye Pharma	Biosimilar	Phase 3	PMO at high risk for fracture	2019/6/14
MW031	Shanghai Mabwell	Novel	Phase 3	PMO at high risk for fracture	2019/11/4
KN012	Alphamab	Biosimilar	Phase 1	PMO	2018/7/27
JMT103	JMT Bio	Biosimilar	Phase 1	Osteoporosis	2018/7/30
GB223	**Genor Biopharma**	**Novel**	**Phase 1**	**PMO**	**2018/11/14**
SHR-1222	Hengrui Medicine	Biosimilar	Phase 1	Osteoporosis	2019/2/19
CMAB807	Mabpharm	Biosimilar	Phase 1	PMO	2019/4/24
QL1206	Qilu Pharmaceutical	Biosimilar	Phase 1	PMO at high risk for fracture	2019/11/18

Source: Company data, CMBIS

The Company's IND application was approved by the NMPA in December 2017 in accordance with novel drug development pathway. The Company is currently conducting the dose escalation stage of a randomized, double-blind, placebo-controlled Phase 1 study to evaluate the safety, tolerability and PK profiles of single dose of GB223 in 44 healthy subjects. As of 27 May 2020, the Company had enrolled 38 patients. These patients were divided into five cohorts, with two patients in each cohort receiving placebo and the remaining patients in each cohort receiving single-dose subcutaneous injection of GB223 at 7 mg, 21 mg, 63 mg, 119 mg and 140 mg dose levels, respectively. The next dose group may be initiated only after the safety and tolerability are confirmed within four or eight weeks after the previous dose is given. Primary endpoints of this study are safety and PK/PD parameters, and secondary endpoint is ADA.

The Company expects to obtain preliminary data from the Phase 1 clinical trial by the end of 2020 and plans to file with the NMPA to conduct Phase 2 clinical trials of GB223 in PMO and GCTB afterwards.

GB222: a biosimilar product candidate to bevacizumab

GB222 (Bevacizumab biosimilar)

GB222 is the Company's biosimilar product candidate to bevacizumab, which is sold under the trade name Avastin in China. The Company is currently developing GB222 for glioblastomas (GBM), with plans to extrapolate other approved indications of bevacizumab including mCRC and NSCLC.

The Company's IND application for GB222 was approved by the NMPA in September 2016, and it is pursuing the biosimilar regulatory development pathway based on the demonstrated similarity to the reference product in the CMC and pre-clinical studies. The Company has completed a randomized, double-blind, parallel-controlled Phase 1 study to assess the PK, safety, tolerance and immunogenicity of a single 1 mg/kg dose of GB222 compared to bevacizumab in 84 healthy volunteers. Primary endpoint was AUC0-t, and secondary endpoints were Cmax, AUC0-inf, and immunogenicity. For each of AUC0-inf and AUC0-t, the 90% CI for the ratio of GB222 to Avastin were fully contained within 80% to 125%, confirming the bioequivalence between GB222 and Avastin, so the Company concluded that the PK profile of GB222 was similar to that of Avastin. GB222 was also well tolerated in healthy male volunteers. If data from the Phase 1 clinical trial established preliminary bio-similarity between GB222 and Avastin, the Company plans to submit an IND filing with the NMPA for initiating a Phase 2 clinical confirmation trial by 2021.

Bevacizumab has been approved for advanced r/r NSCLC and mCRC in China and has been included in the NRDL. The National Health Commission (NHC) has listed bevacizumab as one of the combined radiotherapy drugs for r/r GBM, but it has not been approved by the NMPA for GBM. According to the CIC Report, the China sales of bevacizumab were RMB1.0bn in 2014 and grew to RMB5.9bn in 2019, representing a CAGR of 42.6%. The China sales of bevacizumab are expected to further grow to RMB13.7bn in 2030, representing a CAGR of 15.5% from 2019 to 2030. Qilu Pharmaceutical's Ankeda was approved by the NMPA in 9 Dec 2019, which is China's first bevacizumab biosimilar. As of the Latest Practicable Date, there are 14 other bevacizumab biosimilar drug candidates in Phase 3 clinical trials in China.

CRC is one of the most common cancers in China, with about 433.8 thousand new incidences in 2019. The incidence number is expected to increase to about 570.8 thousand in 2030, according to the CIC Report. 30% of CRC patients were under advanced/metastatic stage when first diagnosed. The first line treatment for mCRC is bevacizumab combo with chemotherapy or cetuximab combo with chemotherapy. Both bevacizumab and cetuximab were approved in China. Besides mCRC, bevacizumab was also approved for the treatment of r/r NSCLC. Glioblastoma (GBM) is another potential market for bevacizumab, though there is no bevacizumab currently under late stage clinical development for GBM in China, according to the CIC Report.

CRC is the cancer developed from the colon or rectum. In 2019, the incidence of CRC in China reached near 434 thousand cases, representing a CAGR of 3.2% from that in 2014 at 370 thousand cases. It is expected that this number will reach over 570 thousand in 2030. The treatment options for mCRC are limited to combination therapies of bevacizumab with chemotherapy or cetuximab with chemotherapy. Although these therapies have been approved as first-line treatment for mCRC patients, for patients with drug resistance, second-line treatment is limited, according to the NCCN guidelines.

Avastin is the best-selling drug among all anti-VEGF monoclonal antibodies. According to the CIC Report, worldwide sales of Avastin were CHF7,073mn (US$7.3bn) in 2019. The sales of Avastin in China were about RMB2.8bn in 2019.

GB224: a fully humanized mAb against IL-6 for RA

GB224 (IL-6 mAb)

GB224 is a novel, fully humanized, highly potent mAb highly selective to IL-6 that the Company is developing for RA. The Company is conducting a dose escalation Phase 1 clinical study of GB224 in healthy adult subjects and another Phase 1 clinical study in RA patients.

Current therapies for RA in China include traditional Chinese medicine, corticosteroids, and DMARDs, including immunosuppressants and targeted therapies such as TNF- α inhibitors. Tocilizumab is currently the only IL-6 biologic approved in China targeting autoimmune disease.

Competition in the RA market to which GB224 belongs is fierce given the abundance of existing competing drugs and drug candidates that continue to increase competition in the market, whereas competition in the UC and CD markets is less fierce.

As of 27 May 2020, the Company had enrolled 52 subjects for the Phase 1 clinical trial in healthy subjects and expect to obtain preliminary data from this trial by the second half of 2020. As of the same date, the Company had enrolled one patient for the Phase 1 clinical trial in RA patients, and the Company expects to enroll a total of 24 patients for this trial.

Figure 33: Comparison between GB224 and its approved or late-stage competitors in China

Drug name	Sponsors/ collaborators	Phase	Indications	First posted date/ NMPA approval date
Actemra (tocilizumab)	Roche	Approved	Systemic juvenile idiopathic arthritis	2017/9/25
		Phase 3	RA	2017/3/13
BAT1806	Bio-Thera Solutions	Phase 3	RA	2019/2/11
CMAB806	Mabpharm	Phase 3	Moderate to severe RA	2019/4/19
LZM008	Livzon Mabpharm	Phase 3	RA	2019/6/27
GB224	**Genor BioPharma**	**Phase 1**	**Moderate to severe RA**	**2018/8/9**
CMAB806	Mabpharm	Phase 1	RA, systemic juvenile idiopathic arthritis	2018/8/29
QX003S	Jiangsu Quan Xin Biomedical	Phase 1	Moderate to severe RA	2019/1/15
IA001	Shanghai Destiny Biotech	Phase 1	RA, systemic juvenile idiopathic arthritis	2020/1/14

Source: Company data, CMBIS
Note: Actemra's price is RMB1,925/200mg, and Actemra is not listed in the NRDL yet. Expiration dates of key patents of Actemra were from April 2012 to March 2016

There is currently no cure for RA. However, clinical studies indicate that remission of symptoms is more likely when treatment begins early with medications. The types of medications recommended by physicians depend on the severity and duration of the patient's symptoms. Current symptom relieving therapies mainly include: (i) nonsteroidal anti-inflammatory drugs (NSAIDs) which relieve pain and reduce inflammation, including ibuprofen (Advil, Motrin IB) and naproxen sodium (Aleve); (ii) steroids, such as prednisone, which are often prescribed to relieve acute symptoms including inflammation and pain and to slow joint damage; (iii) DMARDs, which slow the progression of RA and save the joints and other tissues from permanent damage, including methotrexate (Trexall, Otrexup, others), leflunomide (Arava), hydroxychloroquine (Plaquenil) and sulfasalazine (Azulfidine); and (iv) biologic agents, which constitute a new class of DMARDs and target parts of the immune system that trigger inflammation that causes joint and tissue damage, including abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), baricitinib (Olumiant), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rituxan), sarilumab (Kevzara), tocilizumab

(Actemra) and tofacitinib (Xeljanz). Biologic DMARDs are usually most effective when paired with a nonbiologic DMARD, such as methotrexate.

However, current therapies cause various side effects in RA patients. For example, NSAIDs may cause severe digestive tract problems, stomach irritation, heart problems, and liver and kidney damage. Steroids may cause thinning of bones, weight gain, high blood pressure, and diabetes. DMARDs may cause liver damage, bone marrow suppression and severe lung infections. Biologic agents may increase the risk of infections due to their immunosuppressing effects and may cause severe side effects such as neutropenia. Higher doses of tofacitinib (Xeljanz) have also been found to increase the risk of blood clots in the lungs in RA patients.

Other early-stage pipelines

GB235: a recombinant humanized HER2 mAb for breast cancer

GB235 is a recombinant humanized HER2 antibody that the Company is developing for the treatment of breast cancer. The Company owns worldwide rights to GB235. The Company's IND application for a Phase 1 clinical trial of GB235 in HER2+ mBC patients was approved by the NMPA in February 2018. Similar to GB221, GB235 binds to HER2 and blocks the signaling pathways mediated by HER2 that lead to tumor growth.

GB235 binds to HER2 extracellular subdomain III, and in the Company's pre-clinical studies, GB235 did not demonstrate competitive binding to HER2 against Herceptin or Perjeta. Trastuzumab (Herceptin) binds to HER2 extracellular subdomain IV whereas pertuzumab (Perjeta) binds to subdomain II. GB235 is also able to inhibit HER3 downstream PI3K-AKT signaling pathway and MAPK signaling pathway. The Company's pre-clinical studies also demonstrated that GB235 in combination with GB221 (Trastuzumab biosimilar) possessed more potent antitumor effect in vitro in Heregulin- α-mediated tumor cells and did not develop similar drug resistance as GB235 or GB221 monotherapy. In the HER2-positive NCI-N87 xenograft, GB221 monotherapy (20 mg/kg, Trastuzumab biosimilar) displayed poor ability in tumor growth inhibition. Notably, GB235 combined with GB221 exhibited significant antitumor activity in NCI-N87 xenograft, whereas GB221 alone displayed only partial effect. For mice bearing of gastric patient-derived tumor xenograft, the model GA0060 showed no response to GB221 (10 mg/kg, Trastuzumab biosimilar) monotherapy. In contrast, tumor growth was significantly suppressed in nude mice treated with combinatorial treatment with GB235 plus GB221 in comparison to mice treated with GB221 alone. Collectively, the results demonstrate that the addition of GB235 to GB221 treatment sensitizes Trastuzumab-resistant cancer cells to GB221.

GB251: a HER2-directed ADC drug candidate for breast cancer

GB251 is a HER2-directed ADC drug candidate that the Company is developing to treat breast cancer. ADCs are molecules consisting of a recombinant mAb covalently bound to a cytotoxic drug (called drug payload or warheads) via a synthetic linker. ADCs combine the advantage of antibodies in binding a specific target and the cytotoxic capability of a chemotherapeutic drug. The Company is collaborating with NewBio Therapeutics (上海新理念生物医药科技有限公司) to develop GB251.

A stable linker between the antibody and the cytotoxic drug is crucial for the ADC integrity in circulation. After antibody binding to the specific antigen on the (cancer) cell surface, the ADC gets internalized and the cytotoxic drug is released intracellularly where it can exert its effect. GB251 is an ADC composed of GB221 (trastuzumab), MMAE and innovative linkers.

In the Company's pre-clinical studies, GB251 demonstrated inhibitory effects on the growth of several types of HER2+ tumor cells in vitro, including among others, SK-Br3, JIMT-1 and BT474. GB251 has also demonstrated similar inhibitory effects on tumor growth in several types of tumor-bearing mouse models at significantly lower doses than T-DM1. Moreover, in both rats and monkeys, serum Cmax of MMAE was significantly lower in animals dosed with GB251 than those dosed with the corresponding levels of MMAE, suggesting that the serum circulating levels of MMAE, and thereby its toxicity, could be reduced if administered in ADC form. The Company's IND application for GB251 was approved by the NMPA in April 2018. The Company plans to conduct a randomized, open-label, multi-center Phase 1a clinical trial in China to evaluate the safety, tolerability, PK/PD and immunogenicity of GB251 in HER2+ metastatic breast cancer patients. The Company plans to enrol a total of 68 patients, who will be randomized into ten arms at 0.25 mg/kg, 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 2.5 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg and 5 mg/kg. After determining the appropriate dosage from this Phase 1a trial, the Company plans to conduct a randomized, open-label, multi-center, in-parallel Phase 1b/2 clinical trial in China to evaluate the safety and efficacy of GB251 in HER2+ metastatic breast cancer patients. The Company plans to enrol a total of 216 patients, who will be randomized at 1:1:1 ratio into

three arms to receive: (i) GB251, (ii) GB251 and (iii) capecitabine and lapatinib. The primary endpoint is PFS and the secondary endpoints are week-6 ORR, OS, safety, PK and immunogenicity.

GB232: A TNF-α mAb product candidate for RA

GB232 is a novel TNF-α mAb that the Company is developing for autoimmune diseases such as RA. The Company owns worldwide rights to GB232. Similar to adalimumab, GB232 is a fully humanized mAb that can bind to TNF- α. Adalimumab has been approved by the EMA and the FDA for the treatment of RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and psoriasis when conventional therapies are not sufficiently effective. Worldwide sales of adalimumab exceeded US$19.2bn in 2019. Adalimumab (sold under the trade name Humira by AbbVie) and golimumab (sold under the trade name Simponi by Johnson & Johnson) were approved by the NMPA in China as a treatment for RA, ankylosing spondylitis and psoriasis. Besides, Bio-Thera's Geleli (adalimumab biosimilar) and Hisun's Anjianning (adalimumab biosimilar) were also approved by the NMPA in 2019. Besides the Company's GB232, there is one other adalimumab biosimilar drug candidate in Phase 3 clinical trials in China.

Bi-specific antibodies

Compared with existing monoclonal antibodies, bi-specific antibodies are designed to enable improved efficacy and enable novel and unique mechanisms of actions to treat diseases which cannot be treated by mAb drugs. Bi-specific antibodies are antibodies that can simultaneously recognize two different epitopes or antigens. Bi-specific antibodies can be developed with dual-targeting of receptors and/or ligands that simultaneously block multiple identified signaling pathways, thereby inducing biological effects previously unattainable with monospecific mAbs and increasing tumor-specific targeting and efficacy. BsAbs are expected to achieve potentially enhanced anti-tumor efficacy through synergistic signaling inhibition effects, acceleration of tumor cell degradation and enhancement of immune response modulation. BsAbs can also provide improved tumor-targeting specificity by recognizing two functionally-complementary tumor-associated antigens. Therefore, bi-specific antibodies creates additional therapeutic options for treating diseases that do not respond sufficiently to monoclonal antibodies.

CD3×CD20 (GB261)

The Company is developing a CD3×CD20 bi-specific antibody for the treatment of non-Hodgkin lymphoma (NHL). GB261 simultaneously recognizes two different epitopes on CD3 and CD20 receptors. GB261 has strong T-cell activation efficacy but relatively low CD3 binding affinity to avoid cytokine storm. Meanwhile, GB261 is differentiated from other CD3×CD20 antibodies in that it maintains ADCC/CDC function, which only kills cancer cells but not T-cells or other normal cells. This feature enables GB261 to target cancer cells with better potency. GB261 was also designed to have low immunogenicity. The Company believes that all of these features will enable GB261 to bring clinical benefits to patients. According to the CIC Report, three other CD3×CD20 bi-specific antibody drug candidates are under Phase 1/2 clinical trials for oncology indications registered with the FDA. Currently, GB261 is under CMC development, and the Company expects to file an IND application with the NMPA in 1H21, and further explore global development opportunities.

PD-L1×CD55

The Company is developing a PD-L1×CD55 bi-specific antibody for the treatment of solid tumors, including pancreatic cancer. This bi-specific antibody simultaneously inhibits receptor/ligand binding to PD-L1 and CD55. The Company's PD-L1×CD55 bi-specific antibody (GB262) has a novel mechanism of action. PD-L1 is a PD-1 receptor overexpressed on cancer cells to repress T-cell activation, and CD55 is a complement regulatory protein overexpressed on cancer cells to inhibit complement function. Therefore, simultaneous binding to both PD-L1 and CD55 is expected to remove cancer cell inhibition on both T-cell activation and complement activation. Furthermore, CD55 is a

quick internalizing antigen, whereas PD-L1 is a slow internalizing antigen, so the parental CD55 mono-specific antibody has strong internalizing ability, whereas the parental PD-L1 mono-specific antibody has almost no internalizing ability. The advantages of this new feature for PD-L1-based mechanism of action is that the blocking of PD1/PD-L1 interaction by a PD-L1 mono-specific antibody is affected by the on/off rate of the PD-L1 mono-specific antibody, but when the PD-L1×CD55 bi-specific antibody triggers PD-L1 internalization, PD-L1 on cancer cell surface is “wiped off,” thereby more completely blocking PD1/PD-L1 interaction. Similarly, the downregulation of CD55 on target cell surface powerfully releases cancer cell repression on complement-dependent cytotoxicity and induces cancer cell lysis. Cell-based data with PD-L1×CD55 bi-specific antibody is favourable and the Company expects to initiate animal study soon.

EGFR×c-Met

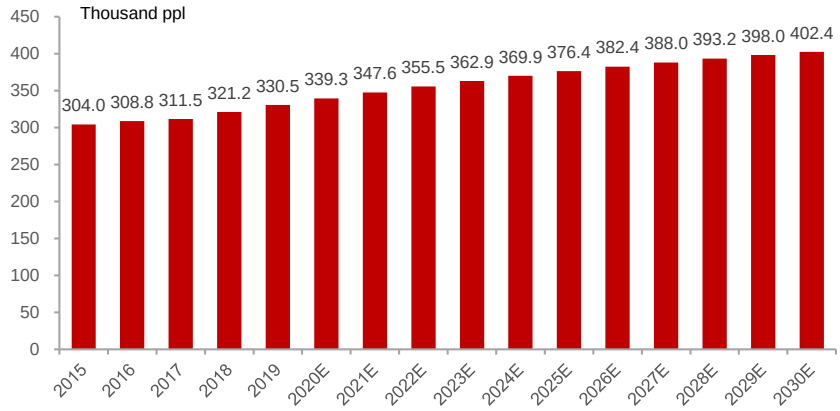
The Company is developing an EGFR×c-Met bi-specific antibody for the treatment of Tagrisso relapsed NSCLC. This bi-specific antibody simultaneously inhibits ligand binding to EGFR and c-Met and contains the same EGFR-binding arm as that of JNJ372 but a new c-Met-binding arm that blocks c-Met/HGF interaction similarly to that of JNJ372. A significant relationship between EGFR and c-Met signaling was recognized through the studies on cancer therapy outcomes. C-Met is a critical player in developing resistance to targeted therapies, including therapies directed at EGFR. EGFR and downstream genetic mutations such as KRAS, histologic transformation, and the activation of alternative pathways, which includes the c-Met signaling pathway, have been identified as mechanisms of resistance to EGFR-targeted therapies. Consequently, blocking one receptor tends to upregulate the other, leading to resistance to single-agent treatment. Amplification of c-Met and/or high levels of HGF ligand expression have been observed in NSCLC patients with intrinsic or acquired resistance to tyrosine kinase inhibitors of EGFR, including erlotinib and gefitinib. Conversely, c-Met amplified lung cancer cells exposed to c-Met-inhibiting agents for a prolonged period develop resistance via the EGFR pathway. Because of the signaling crosstalk between EGFR and c-Met, inhibition of both receptors in combination may lead to improved outcomes for patients with c-Met- and EGFR- driven cancers. Additionally, concurrent inhibition may overcome or delay therapeutic resistance compared to the blockade of just one pathway.

CDK4/6 Inhibitor Market in China

Overview of breast cancer market

Breast cancer is the most common cancer in Chinese women, with 331 thousand new incidence cases in 2019 which may increase to 402 thousand in 2030E.

Figure 34: Incidence of breast cancer in China



Source: CIC, CMBIS

The status of the hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) in a breast cancer tumor defines the four most common types of breast cancer. HR and HER2 can either be present, or positive (HR+, HER2+), or absent, or negative (HR-, HER2-), in the tumor. HR+/HER2- is the most common subtype among the four. HR+/HER2- breast cancer represents 62.0% of all breast cancer patients in China, which is 2.8 times the number of HER2+ breast cancer patients (22.4%), with 11.2% being HR+ and 11.2% being HR-. The number of TNBC patients represents the remaining 15.6% of all breast cancer patients in China.

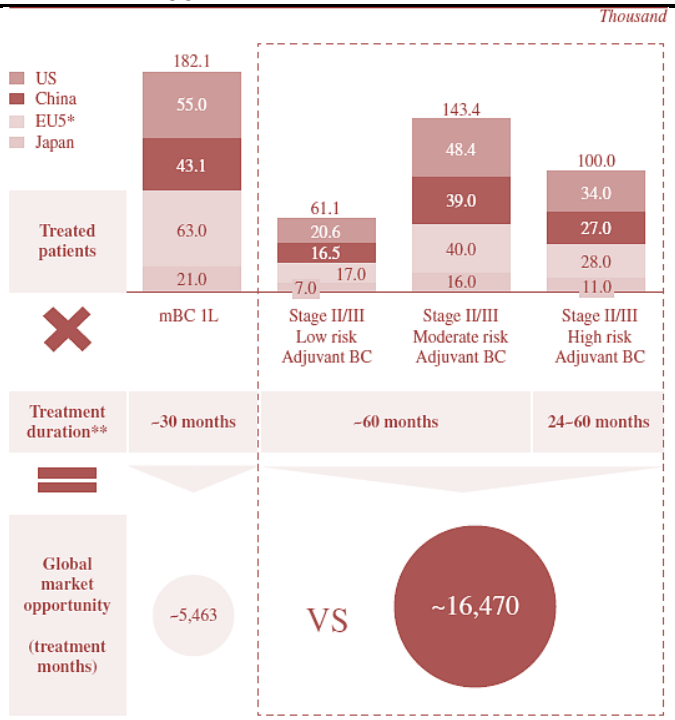
Figure 35: Treatment path of breast cancer by subtype

Treatment	Neoadjuvant	Adjuvant	1L	2L
HER2+	Trastuzumab + pertuzumab + Chemo	Chemo + Trastuzumab	Pertuzumab + trastuzumab + docetaxel	T-DM1
	Endocrine therapy (if also HR+)	Chemo + Trastuzumab + Pertuzumab + ET (if also HR+)	Pertuzumab + trastuzumab + paclitaxel	Trastuzumab + lapatinib
HR+	CDK4/6i + ET	CDK4/6i + ET	CDK4/6i + Aromatase inhibitor	CDK4/6i + fulvestrant
	CDK4/6i + ET + AKTi	Chemo + ET	CDK4/6i + Fulvestrant	Everolimus + ET
TNBC	Chemo	Chemo	PARPi / AKTi + Chemo	PI3Ki + fulvestrant
	PD-(L)1 + Chemo	PD-(L)1 + Chemo	PD-(L)1 + Chemo	ADC

Source: Expert interview, CIC, CMBIS
Notes: 1L = first-line; 2L = second-line; CDK4/6i = CDK4/6 inhibitor; ET = endocrine therapy; AKTi = AKT inhibitor; PARPi = poly ADP ribose polymerase inhibitor; PI3Ki = phosphoinositide 3-kinase inhibitor; ADC = antibody-drug conjugate; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer.

CDK4/6 inhibitor has already been included in the NCCN guidelines as first-line therapy for HR+/HER2- mBC. In addition, ASCO study shows that constant adjuvant therapy lasting for five years may significantly reduce the risk of distant recurrence rate for HR+ post-operative BC patients. For high risk post-operative BC patients, the adjuvant therapy may last for ten years. A recent successful study shows that CDK4/6 inhibitor also has promising results as HR+/HER2- eBC adjuvant therapy. Adjuvant BC therapy has much bigger market opportunities than mBC first-line therapy due to the larger patient base and longer treatment duration. The below diagram sets forth the comparison of the market opportunities of HR+/HER2- early stage adjuvant BC therapy and mBC first-line therapy in 2030.

Figure 36: Comparison of HR+/HER2- BC early stage adjuvant therapy and metastatic first-line therapy in 2030



Source: CIC, CMBIS
Note: * EU5 Countries represents France, Germany, Italy, Spain and the United Kingdom
** Ideal treatment duration

There are three approved CDK4/6 inhibitors globally, all of them target top line treatment of HR+/HER2- mBC.

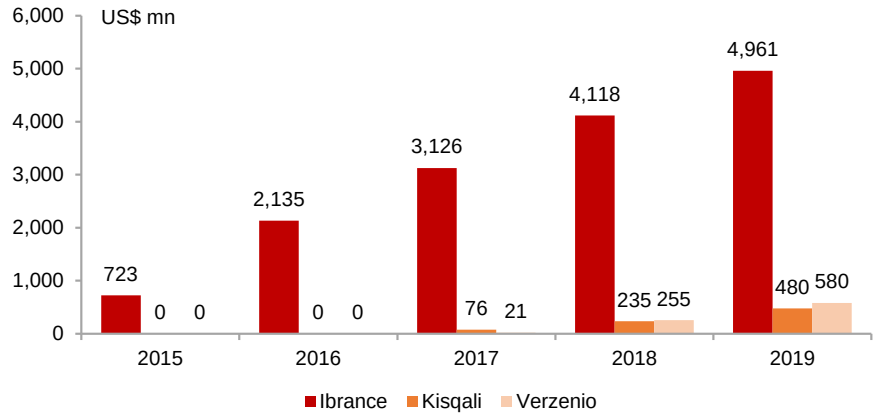
Figure 37: FDA-approved CDK4/6 inhibitors

Trade name (Generic name)	Company	Indication	Approval date	Price
Ibrance (Palbociclib)	Pfizer	Advanced breast cancer	Feb 3, 2015	US$ 13,007 for 21 tablet US$ 619.4 per unit
		First-line HR+, HER2-metastatic breast cancer	Mar 31, 2017	
Kisqali (ribociclib)	Novartis	HR+/HER2-metastatic breast cancer	Mar 13, 2017	US$ 5,539 for 21 tablet US$ 263.8 per unit
		HR+/HER2-advanced breast cancer	Jul 18, 2018	
Verzenio (abemaciclib)	Eli Lilly	Certain advanced or metastatic breast cancers	Sep 28, 2017	US$ 3,239.9 for 14 tablet US$ 231.4 per unit

Source: CIC, CMBIS

Worldwide, Ibrance recorded US$4,961mn sales in 2019, followed by Verzenio with US$580mn sales and Kisqali with US$480mn sales.

Figure 38: Global sales of approved CDK4/6 inhibitors



Source: Annual reports, CIC, CMBIS

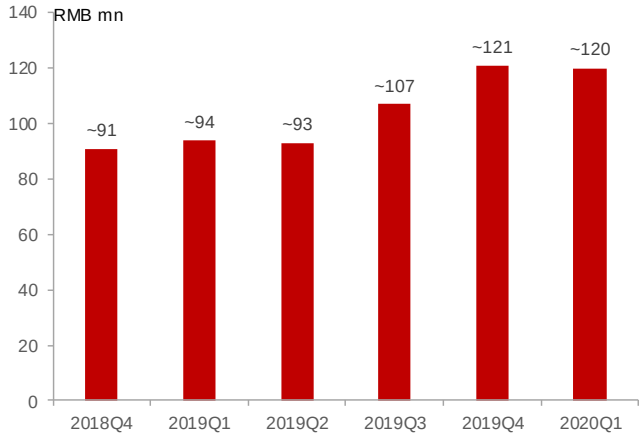
Ibrance (palbociclib) is the only CDK4/6 inhibitor approved in China. It was approved by the NMPA in July 2018 as a first-line combination therapy for HR+/HER2- locally advanced or metastatic breast cancer. The sales performance of Ibrance was impressive. It generated about RMB625mnn sales in China the first six quarters after its approval, with over RMB400mn sales in 2019.

Figure 39: Approved CDK4/6 inhibitors in China

Trade name (Generic name)	Indication	Approval date	Price (RMB)	NRDL coverage	Patient assistance program	Treatment frequency	Annual spending* (RMB)
Ibrance (愛博新) (Palbociclib)	1L combo with aromatase inhibitors for HR+ HER2- locally advanced or metastatic BC	31 Jul 2018	29,800/125mg for 21 tablets, 1,419.0 per unit	No	4+3, Buy 4 cycles treatment get 3 free	Every 28 days	221,371

Source: CIC, CMBIS

Figure 40: Quarterly sales of approved CDK4/6 inhibitors in China

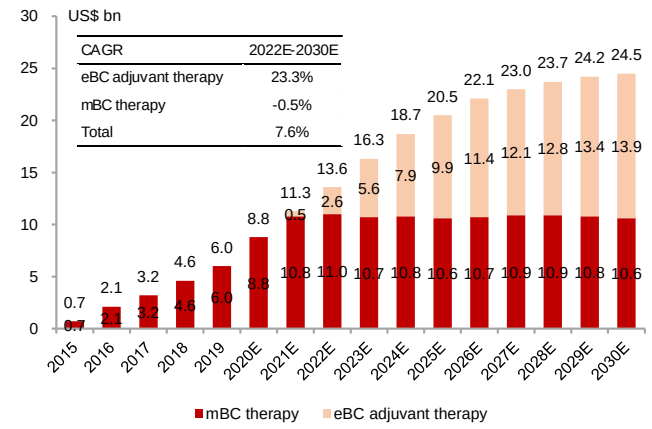


Source: CIC, CMBIS
Note: *applying standard therapy cycle, for each month, take 1 pill per day for 21 days then stop 7 days; using 13 cycles annually

Market size of CDK4/6 inhibitors in breast cancer

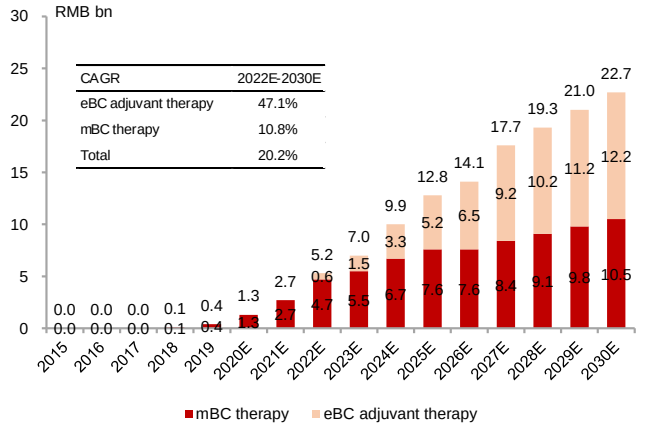
It is expected that eBC adjuvant therapy will represent a significant segment of the CDK4/6 inhibitor market in the future. According to CIC, the market size of CDK4/6 inhibitors for HR+/HER2- breast cancer globally may increase to US$24.5bn by 2030E and the market size in China may rise to RMB22.7bn in 2030E.

Figure 41: Global market sizes of CDK4/6 inhibitor in HR+/HER2- breast cancer



Source: CIC, CMBIS

Figure 42: Market sizes of CDK4/6 inhibitor HR+/HER2- in breast cancer in China



Source: CIC, CMBIS

On 16 Jun 2020, Eli Lilly announced that Verzenio (abemaciclib) in combination with standard adjuvant endocrine therapy has met the primary endpoint of invasive disease-free survival, significantly decreasing the risk of breast cancer recurrence or death compared to standard adjuvant endocrine therapy alone. These results are from a pre-planned interim analysis of the Phase 3 MONARCH-E study making Verzenio the only CDK4/6 inhibitor to demonstrate a statistically significant reduction in the risk of cancer recurrence for people with high risk HR+, HER2- early breast cancer. The promising result strengthens the position of CDK4/6i in eBC adjuvant therapy.

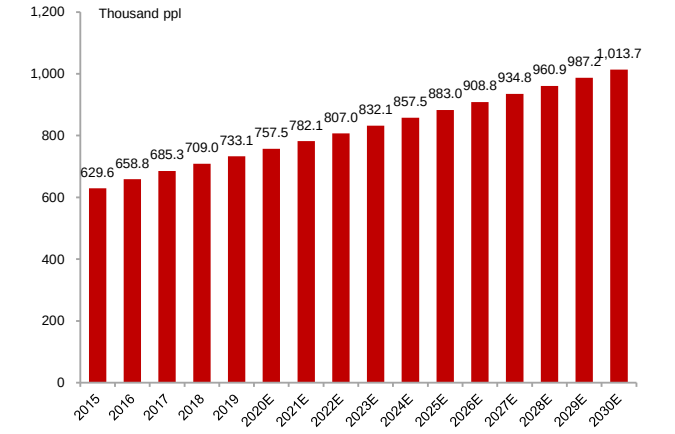
Currently, there is no NMPA-registered CDK4/6 inhibitor pipeline drugs for eBC adjuvant therapy.

Overview of non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is another market that CDK4/6 inhibitors may penetrate. NSCLC is the most common cancer in China, with over 733 thousand new incidence in 2019. EGFR mutation in NSCLC is particularly common in Asian population, especially in Chinese population, which indicates a massive market potential for drugs targeting the patient pool. About 80% of the NSCLC patients were initially diagnosed as late stage patients, with about half of them were EGFR positive in China.

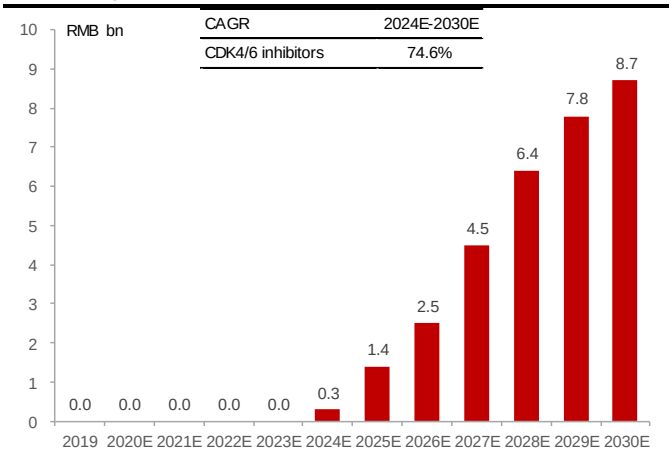
Tagrisso (osimeritinib) was approved for first line therapy for EGFR positive late stage NSCLC patients in China. There are also clinical trials initiated in which CDK4/6 inhibitors are being combo used with osimeritinib to further improve the first line therapy for EGFR positive late stage NSCLC patients. Combo use of CDK4/6 inhibitors and osimertinib has the potential to prolong the time to disease progression by overcoming resistance mechanisms. NSCLC is another potential therapeutic area for CDK4/6 inhibitor.

Figure 43: Incidence of NSCLC in China



Source: CIC, CMBIS

Figure 44: Market size of CDK4/6 inhibitor in NSCLC in China, 2019-2030E



Source: CIC, CMBIS

Several CDK4/6 inhibitors are under early clinical trials for NSCLC globally.

Figure 45: CDK4/6 inhibitor pipeline for NSCLC globally as of 22 Jun 2020

Drug	Company	Indication	Phase	First post date	Combo/mono
Palbociclib	Pfizer	Advanced KRAS mutant NSCLC	Phase 1/2	5/30/2017	Combo with MEKi (MEK162)
G1T38	G1 therapeutics	EGFR mutation-positive metastatic NSCLC	Phase 1/2	3/7/2018	Combo with osimertinib
SHR6390	Hengrui Medicine	Advanced NSCLC	Phase 1/2	7/26/2018	Combo with PD-1 (SHR-1210)

Source: CIC, CMBIS

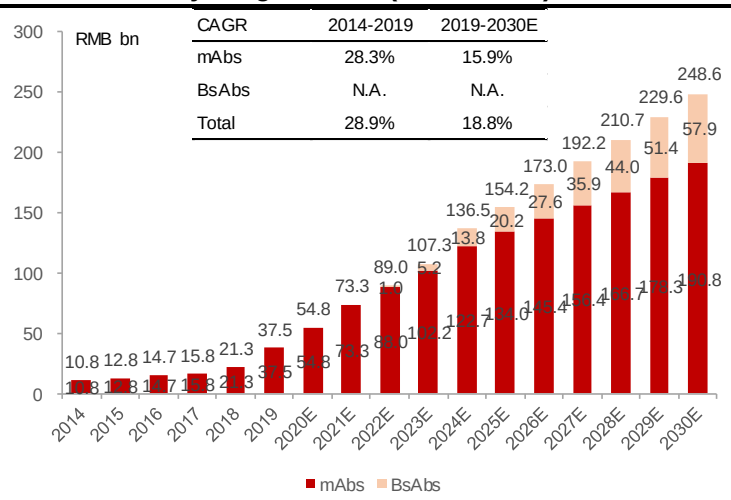
Overview of antibody drug market in China

Market size of antibody drugs in China

Antibody drugs include monoclonal antibodies (also known as naked monoclonal antibodies), bi-specific antibodies and antibody-drug conjugate (ADCs, also known as conjugated monoclonal antibodies). Antibody drugs are the largest category of therapeutic biologics, which have generally shown higher efficacy and lower toxicity in treating cancers than traditional therapies such as chemotherapy and radiotherapy. Antibodies target tumor selective antigens with a high degree of target specificity, which reduces off-target toxicity and side effects, and have gained increasing acceptance among patients and doctors. In recent years, combination therapies of two or more monoclonal antibodies, as well as monoclonal antibody-based therapy in combination with targeted small-molecule drugs and chemotherapies and ADCs, have been increasingly used. In addition, research and development on bi-specific antibody drugs is also gaining popularity. ADCs, which benefit from the high specificity of monoclonal antibodies and carry potent cytotoxic compound selectively to antigen-expressing tumor cells, also witness continuous development.

Antibody drugs are widely used in different therapeutic areas, including oncology, autoimmune disease, neurology and osteoporosis. Oncology is the largest therapeutic area of antibody drugs, accounting for approximately 85.6% of the total antibody drug market in China in 2019.

Figure 46: China antibody drugs market (2014-2030E)



Source: CIC, CMBIS

Market size of monoclonal antibody in China

Monoclonal antibodies are antibodies made by identical immune cells that are all clones of a unique parent cell and recognize the same part of a target molecule. Monoclonal antibodies can work in different ways. Most monoclonal antibodies target antigens on cancer cells, but some work by binding to antigens on other non-cancerous cells or even free-floating proteins. There are four different ways in which monoclonal antibodies can be made, namely, murine, chimeric, humanized and human. Compared with chemotherapy drugs, naked monoclonal antibodies tend to have fewer serious side effects.

The China monoclonal antibody market increased at a CAGR of 28.3% from RMB10.8bn in 2014 to RMB37.5bn in 2019 and is estimated to increase at a CAGR of 15.9% to RMB190.8bn in 2030. Monoclonal antibodies are widely used in different therapeutic areas, including oncology, autoimmune disease, neurology and ophthalmology. Oncology and autoimmune disease are the two largest

therapeutic areas of monoclonal antibodies, accounting for approximately 85.6% and 8.8% of the total monoclonal antibody market in 2019, respectively.

Monoclonal antibodies in general have PK characteristics including slow clearance, long half-life, and limited tissue distribution. The long half-life offers the advantage of less frequent dosing in patients as compared to small molecules. Also, compared with chemotherapy drugs, monoclonal antibodies tend to have fewer serious side effects. As a result, the market share of monoclonal antibodies in oncology treatment is expected to experience a rapid growth in China from less than 20.0% market share in oncology drug market in 2019 to over 40% market share in 2030.

Overview of bi-specific antibody market

A bi-specific antibody is used to describe a large family of molecules designed to recognize two different epitopes or antigens. Bi-specific antibodies can bridge therapeutics (e.g., T cells, drugs) and targets (e.g., tumour) or regulate two different pathogenic mediators. Bi-specific antibodies with defined specificities do not occur naturally in the human body and are mainly produced by three methods, namely, chemical conjugation, quadroma technology and genetic approaches. As of 22 Jun 2020, there are 97 ongoing (does not include completed, suspended and terminated trials) bi-specific antibodies clinical trials globally, among which 31 trials are evaluating drug candidates targeting immune checkpoint pathways.

Figure 47: Comparison of major formats BsAbs

	Asymmetric IgG-like BsAbs	Fc-less BsAbs	Bispecific sdAb fusion protein
Structure			
Characteristic	• Asymmetric bispecific IgG molecules possess an asymmetric architecture due to the presence of, at least, different Fv regions. Depending on the method of preparation and origin of heavy and light chains, they may furthermore differ in the constant regions of the heavy or light chain. Due to the Fc region, asymmetric BsAbs which target two or more epitopes has a higher serum half-life and ADCC function.	• Fc-less BsAbs lack Fc-mediated effector functions, such as antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement fixation, and FcRn-mediated recycling, which is responsible for the long serum half-life. Fc-less BsAbs contain scFv2, taFv, diabody, Fab fusion protein, etc. Molecular weight of them varies, which depends on the number of domains and the binding/tandem type.	• A single-domain antibody (sdAb) is an antibody fragment consisting of a single monomeric variable antibody domain with a molecular weight of only 12-15 kDa. It is more statble in structure compared with other traditional antibodies. It can be used to make bispecific molecules by a tandem or fusion with other molecules such as Fc domain. The comparatively low molecular mass of the fusion proteins formed by sdAbs and Fc region leads to an enhanced tissue penetration than common BsAbs.

Source: CIC, CMBIS

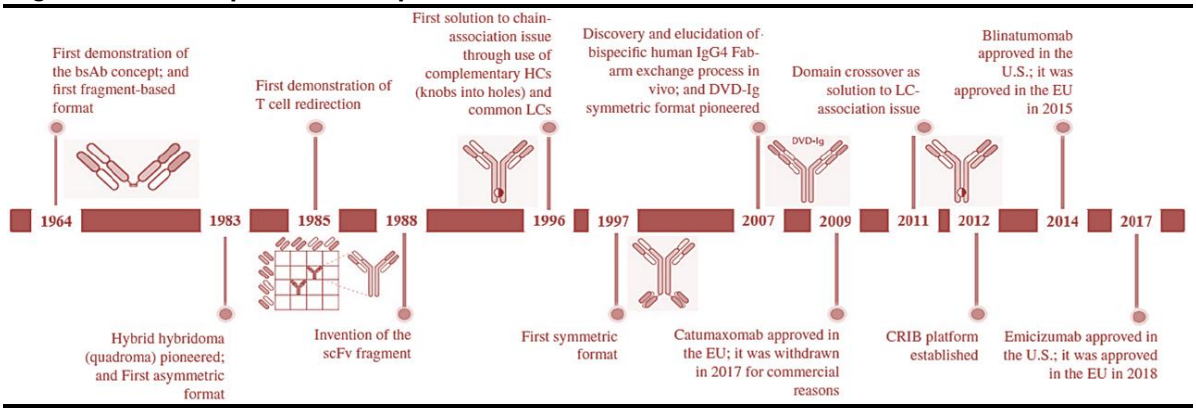
There are diverse formats of bi-specific antibodies, and one major group of bi-specific IgG molecules is asymmetric. This asymmetric IgG-like format retains the traditional monoclonal antibody structure of two Fab arms and one Fc region, but with a capability to bind different targets. Fc-less bi-specific antibody with a smaller size has a higher permeability to reach antigens usually unavailable to conventional antibodies, but the absence of Fc region makes the Fc-less bi-specific antibody lack of ADCC function and with a short serum half-time. Bi-specific single-domain antibody fusion protein can be fused with other molecules such as Fc domain or human serum albumin to extend half-life with a full antigen binding capability.

Numerous efforts have been made to engineer bi-specific antibodies, which has resulted in the generation of more than several dozens of bi-specific antibody formats. Many bi-specific antibodies have been engineered by linking antibody fragments, such as single-chain variable fragments (scFv), antigen-binding fragments (Fab), and heavy (VH) and light chain (VL) variable domains, as well as their appendages to IgG-format monoclonal antibodies. However, these formats, deviating from the conventional IgG structure, often suffer from poor physicochemical properties, such as low solubility

and aggregation, difficulties in large-scale manufacturing, poor pharmacokinetics, and potential immunogenicity. To improve the developability, bi-specific antibodies in the formats of intact IgG or IgG-like (containing an Fc) architectures have been extensively developed. A common approach is to generate Fc heterodimers, with the goal of high heterodimerization yield, while retaining biophysical and biological properties of the wild-type Fc. The platform that can develop Fc-based bi-specific antibodies by Fc heterodimers engineering techniques is called Fc-based bi-specific antibody platforms.

Nowadays, Fc-based bi-specific antibody platforms are major bi-specific antibody platforms around the globe. Various Fc engineering techniques are used in bi-specific antibody development, and bi-specific antibodies developed from Fc-based platforms can be optimized for industry-scale manufacturing. More importantly, these antibodies often show high stability, long serum half-life, low immunogenicity, as well as immune effector functions.

Figure 48: Development of bi-specific antibodies



Source: CIC, CMBIS

Bi-specific antibodies activate new activities by binding two different target molecules in three ways: bridging two cell types (in-trans binding), binding two targets on one cell (in-cis binding), or binding two distinct epitopes on the same target. Therefore, the selection of two targets is particularly important. Nowadays, CD3, PD-1, HER2, CD19 and BCMA are five popular targets selected by global pharmaceutical companies to design bi-specific antibodies. Many bi-specific antibodies select CD3 to recruit and activate T cells, while the other target is mostly tumor antigens. In the past two years, bi-specific antibody candidates against immune checkpoints (PD-L1, PD-1, CTLA-4, etc) have increased significantly as well.

Compared with existing monoclonal antibodies, bi-specific antibodies improve drug efficacy and can act as cytotoxic effector cell redirectors and engage tumour-associated antigens and immune cells, thereby redirecting immune cell cytotoxicity to antigen-expressing tumour cells. Similarly, bi-specific antibodies localize the pharmacological effects on immune responses to a tumour area, which improves efficacy as well as reduces the adverse effects possibly brought by systemic immunomodulation. In addition, bi-specific antibodies place targets into close proximity to trigger contacts between cells and initiate anti-tumour activities, resulting in effective cell killing. By designing two Fabs separately, bi-specific antibodies are able to identify different epitopes which are both present on tumours. The dual specificity of bi-specific antibodies creates additional therapeutic options for treating diseases that do not respond sufficiently to monoclonal antibodies. Bi-specific antibodies can also exhibit dual immunomodulation by recruiting two immune cells at a time, resulting in the blockade of inhibitory targets and depletion of suppressive cells.

Triomab (catumaxomab) (targeting CD3 and EpCAM) is a tri-functional bi-specific antibody for the treatment of cancerous ascites.

Blinatumomab (targeting CD3 and CD19) is used in the treatment of acute b-lymphoblastic leukaemia, and its superior clinical results have renewed interest and investment in bi-specific antibodies.

Emicizumab is used for the treatment of patients with haemophilia A who had developed resistance to other treatments. It binds to both the activated coagulation factors IX and X, mediating the activation of the latter. This is normally the function of coagulation factor VIII, which is missing in haemophilia A patients.

Figure 49: Major approved bi-specific antibodies globally

Biomarker	Approved drug	Company	Indications	First approval	Global sales in 2019 (US$ mn)
CD3xEpCAM	Removab (Catumaxomab)	Trion	• Malignant ascites in patients with EpCAM-positive carcinomas	2009.04	N/A*
CD3xCD19	Blincyto (Blinatumomab)	Amgen	• B-cell acute lymphoblastic leukemia • Relapse or refractory B-cell acute lymphoblastic leukemia	2014.12	312.0
Activated factor IX, factor X	Hemlibra (Emicizumab)	Roche	• Hemophilia A	2017.11	1,427.0

Source: CIC, CMBIS
Note: *In 2013, Removab was voluntarily withdrawn from the US market. On 2 Jun 2017, the European Commission withdrew the marketing authorization for Removab in the EU.

The below tables set forth the clinical stage bi-specific antibody candidates targeting CD3×CD20 and EGFR×c-Met globally. There are no clinical stage bi-specific antibody candidates targeting the same targets in China.

Figure 50: Clinical stage bi-specific antibody candidates targeting CD3×CD20 and EGFR×c-Met globally

CD3×CD20 bi-specific pipelines globally, as of March 2020

Drug name	Sponsor/collaborators	Indications	Phase	First posted date
REGN1979	Regeneron Pharmaceuticals	B-cell non-Hodgkin lymphoma	Phase II	2019/3/25
REGN1979	Regeneron Pharmaceuticals	NHL, chronic lymphocytic leukemia	Phase I	2014/11/14
REGN1979	Regeneron Pharmaceuticals	Lymphoma	Phase I	2016/1/11

EGFR×c-MET bi-specific pipelines globally, as of May 2020

Drug name	Sponsor/collaborators	Indications	Phase	First posted date
EMB-01	EpimAb	Neoplasms, NSCLC	Phase I/II	2019/1/9
JNJ-61186372 combo with Lazertinib	Janssen	Advanced NSCLC	Phase I	2019/9/4
JNJ-61186372	Janssen	NSCLC	Phase I	2015/11/20

Source: CIC, CMBIS

Overview of Oncology Antibody Drugs Market in China

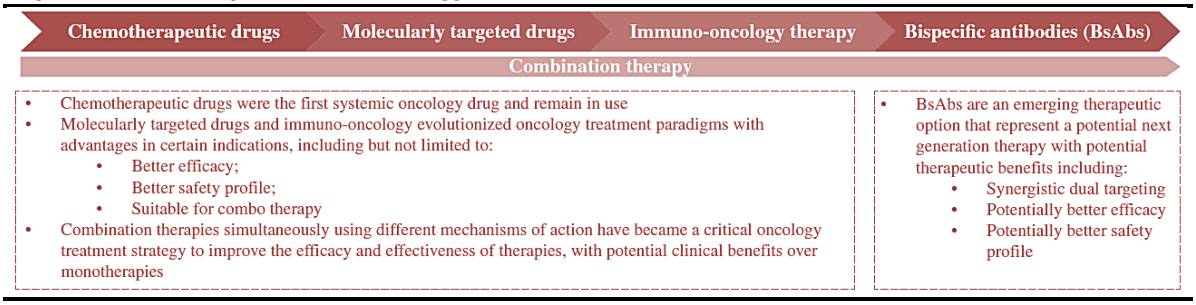
China oncology market

Oncology treatments have undergone significant development over the years, with chemotherapeutic drugs, targeted small molecule drugs and monoclonal antibodies becoming the major oncology treatments available to date. Chemotherapeutic drugs are the first systemic drugs to treat cancer. Although widely used in a broad range of indications, they frequently cause severe side effects. Since the early 2000s, there has been major progress in developing targeted small molecule drugs and monoclonal antibodies, which have revolutionized oncology treatments, many of which have become

global blockbuster drugs. Targeted small molecule drugs generally interfere with specific intracellular signaling that drives tumor growth and metastasis. Monoclonal antibodies are the largest category of antibody drug market and are used in targeted therapy and immuno-oncology therapy, which target tumor-selective antigens with a high degree of target specificity, reducing off-target toxicity and side effects.

Different types of oncology drugs can be used in combination treatments to achieve better therapeutic effects. In recent years, combination therapies of two or more monoclonal antibodies, as well as monoclonal antibody-based therapy in combination with chemotherapeutic drugs and targeted small molecule drugs, have been increasingly used. In addition, research and development on bi-specific antibody drugs is also gaining popularity.

Figure 51: Development of oncology treatments



Source: CIC, CMBIS

The oncology treatment market is directly correlated to patient population. From 2014 to 2019, total cancer incidence in China increased from 3.8mn to 4.5mn. Cancer incidence in China is projected to reach 5.8mn by 2030.

Figure 52: Cancer incidence in China, by cancer types, 2014-2030E

Thousand patients

Cancer types	2014	2015	2016	2017	2018	2019	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E	CAGR 2014-2019	CAGR 2019-2030E
Lung	781.0	787.0	823.6	856.6	886.3	916.4	946.8	977.7	1,008.8	1,040.2	1,071.8	1,103.8	1,136.0	1,168.5	1,201.2	1,234.1	1,267.1	3.2%	3.0%
Stomach	410.0	403.0	435.1	459.5	482.5	500.3	514.1	525.0	533.6	542.1	550.5	558.9	567.2	575.4	583.6	591.7	599.8	4.1%	1.7%
Colon and rectum	370.0	388.0	399.2	410.6	422.1	433.8	445.6	457.5	469.6	481.8	494.1	506.6	519.1	531.9	544.7	557.7	570.8	3.2%	2.5%
Liver	365.0	370.0	389.5	406.6	421.5	434.4	447.5	460.6	473.8	487.1	500.4	513.8	527.2	540.7	554.2	567.8	581.3	3.5%	2.7%
Breast	279.0	304.0	308.8	311.5	321.2	330.5	339.3	347.6	355.5	362.9	369.9	376.4	382.4	388.0	393.2	398.0	402.4	3.4%	1.8%
Esophagus	258.0	246.0	272.3	295.5	315.6	332.8	347.4	359.6	370.9	381.3	390.9	399.6	407.5	414.7	421.2	427.0	432.2	5.2%	2.4%
Thyroid	170.0	201.0	202.4	203.7	206.6	209.5	212.3	215.0	217.6	220.2	222.7	225.2	227.6	229.9	232.1	234.2	236.3	4.3%	1.1%
Brain, CNS	101.0	106.0	109.9	112.8	115.7	118.3	120.8	123.1	125.2	127.2	129.0	130.6	132.2	133.5	134.8	135.9	136.9	3.2%	1.3%
Cervix	102.0	111.0	112.3	113.4	114.6	115.7	116.7	117.8	118.8	119.7	120.6	121.5	122.3	123.1	123.9	124.7	125.4	2.6%	0.7%
Pancreas	92.0	95.0	98.5	101.7	105.0	108.4	111.8	115.3	118.8	122.4	126.1	129.8	133.6	137.4	141.4	145.3	149.4	3.3%	3.0%
Top 10 Incidence	**2,928.0**	**3,011.0**	**3,151.6**	**3,271.9**	**3,391.1**	**3,500.1**	**3,602.3**	**3,699.2**	**3,792.6**	**3,884.9**	**3,976.0**	**4,066.2**	**4,155.1**	**4,243.1**	**4,330.3**	**4,416.4**	**4,501.6**	**3.6%**	**2.3%**
Bladder	78.0	81.4	84.6	87.9	89.7	94.4	97.7	101.1	104.4	107.7	111.1	114.4	117.8	121.1	124.4	127.7	131.0	3.9%	3.0%
Gallbladder	52.0	54.3	56.4	58.6	60.1	63.1	65.4	67.7	70.1	72.5	74.9	77.4	79.9	82.4	84.9	87.5	90.1	3.9%	3.3%
Ovary	51.0	53.1	55.0	55.5	56.7	57.9	59.0	60.0	61.0	61.9	62.8	63.6	64.3	65.0	65.7	66.2	66.8	2.6%	1.3%
Soft tissue sarcoma	46.9	47.9	48.9	49.9	50.9	51.9	52.9	53.9	54.9	55.9	56.9	57.9	58.9	59.9	60.9	61.9	62.9	2.0%	1.8%
Nasopharynx	45.0	46.6	47.4	47.6	48.0	50.3	51.2	52.0	52.9	53.7	54.5	55.3	56.0	56.7	57.4	58.1	58.8	2.3%	1.4%
Melanoma	7.0	7.3	7.6	7.9	7.9	8.3	8.5	8.7	8.9	9.1	9.3	9.4	9.6	9.8	10.0	10.1	10.3	3.5%	2.0%
Others	**596.1**	**627.4**	**638.9**	**648.6**	**664.7**	**680.8**	**697.0**	**713.1**	**729.1**	**745.0**	**760.8**	**776.4**	**792.2**	**807.7**	**822.9**	**838.2**	**853.1**	**2.7%**	**2.1%**
All cancer types	**3,804.0**	**3,929.0**	**4,090.4**	**4,227.9**	**4,369.1**	**4,506.8**	**4,634.0**	**4,755.7**	**4,873.9**	**4,990.7**	**5,106.3**	**5,220.6**	**5,333.8**	**5,445.7**	**5,556.5**	**5,666.1**	**5,774.6**	**3.4%**	**2.3%**

Source: NCCR, WHO, CIC, CMBIS

According to the CIC Report, the aggregate incidence of the ten most prevalent cancer types in China accounted for 77.7% of the total cancer incidence, reaching 3.5mn in 2019. Lung, colorectal and breast cancers are among the most prevalent cancer types in China. The oncology antibody drug market size

for each specific indication is expected to be correlated to the relevant patient population and survival rate.

Figure 53: 5-year relative survival rates* of top 5 cancers in terms of incidence in China, by cancer type

Cancer types	China, 2012-2015
Lung	19.7%
Stomach	35.1%
Colon and rectum	56.9%
Liver	12.1%
Breast	82.0%

Source: The Lancet, CIC, CMBIS
Note: * 5-year relative survival rated describe the percentage of patients with a disease alive five years after the disease is diagnosed, divided by the percentage of the general population of corresponding sex and age alive after five years. The figures of China are calculated on the basis of people diagnosed with cancer between 2012 and 2015.

Overview of immune checkpoint inhibitors against PD-(L)1 in China

Immuno-oncology therapy represents a transformational advancement of the oncology treatment paradigm. Immuno-oncology therapy stimulates the patient's own immune system to generate or augment anti-tumor immune responses to fight against cancer cells. Major types of immuno-oncology therapies include immune checkpoint inhibitors, cytokines, adoptive T-cell therapies and cancer vaccines. In recent years, immune checkpoint inhibitors have garnered attention as one of the most promising types of immuno-oncology therapies. Immune checkpoint inhibitors in the form of monoclonal antibodies against three validated targets, i.e., PD-1, PD-L1 and CTLA-4, are among the major immune-oncology therapies. Currently available clinical data suggest that almost all of the 10 most prevalent cancer types in China and the US proved to be the most responsive to immune checkpoint inhibitors.

PD-(L)1 inhibitors act through interfering with the PD-1/PD-L1 pathway, which prevents T-cells from attacking tumor cells within the tumor microenvironment. In the cancer disease state, the use of an inhibitor that blocks the interaction between PD-L1 and the PD-1 receptor can prevent certain tumor cells from evading the immune system. PD-(L)1 inhibitors are increasingly used for the treatment of many types of cancer and have been proven to have a better efficacy profile and fewer side effects in a number of cancer indications.

To date, there are eight PD-(L)1 inhibitors approved in China. All of these are monoclonal antibodies. The following table sets forth the details of the eight approved PD-(L)1 inhibitors in China as of 22 Jun 2020. The CDE released guidance in February 2018 on the requirements for NDA submissions of PD-(L)1 drug candidates, specifically for data from single-arm trials on r/r advanced cancers without standard-of-care therapies. A pre-NDA meeting is required before the NDA submission, and a rolling NDA submission will be accepted for PD-(L)1 therapies.

Figure 54: Approved PD-(L)1 inhibitors by the NMPA

Trade name (Generic name)	Company	Immune checkpoint	Number of indications	Indications	Treatment line	Approval date
Opdivo (Nivolumab)	BMS	PD-1	2	EGFR/ALK negative locally advanced or metastatic NSCLC	2L	Jun 15, 2018
				Recurrent or metastatic head and neck squamous cell carcinoma	2L	Sep 30, 2019
Keytruda (Pembrolizumab)	MSD	PD-1	5	Unresectable or metastatic melanoma	2L	Jul 26, 2018
				EGFR/ALK negative metastatic non-squamous NSCLC	1L (with combo)	Mar 28, 2019
				EGFR/ALK negative metastatic NSCLC	1L	Sep 30, 2019
				Metastatic squamous NSCLC	1L (with combo)	Nov 27, 2019
				Esophageal cancer	2L	Jun 19, 2019
拓益 (Toripalimab)	Junshi	PD-1	1	Unresectable, metastatic malignant melanoma	≥2L	Dec 17, 2018
达伯舒 (Sintilimab)	Innovent	PD-1	1	Refractory Hodgkin's lymphoma	3L	Dec 27, 2018
艾瑞卡 (Camrelizumab)	Hengrui	PD-1	4	Refractory Hodgkin's lymphoma	3L	May 29, 2019
				Liver cancer	2L	Mar 7, 2020
				Late stage esophageal squamous cell carcinoma	2L	Jun 19, 2019
				Late stage non-squamous NSCLC	1L (with combo)	Jun 19, 2019
百泽安 (Tislelizumab)	BeiGene	PD-1	2	Refractory or relapsed classical Hodgkin's lymphoma	3L	Dec 28, 2019
				Late stage or metastatic Urothelial carcinoma	2L	Apr10, 2020
Imfinzi (Durvalumab)	AstraZeneca	PD-L1	1	Advanced NSCLC	2L	Dec 9, 2019
Tecentriq (Atezolizumab)	Roche	PD-L1	1	SCLC	1L (with combo)	Feb 13, 2020

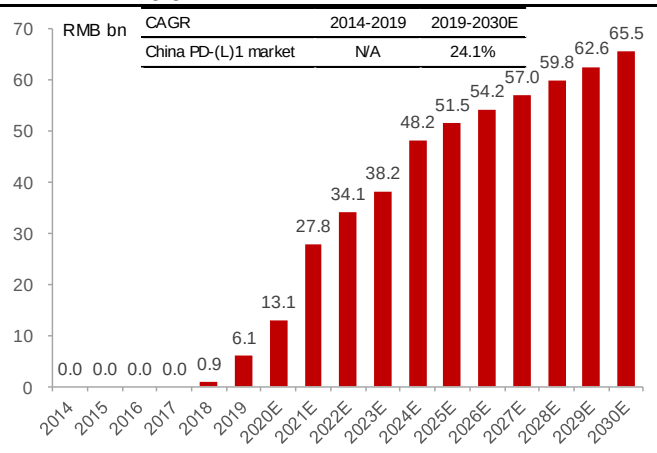
Source: CDE, CIC, CMBIS

In 2019, Innovent's Tyvyt (sintilimab) was included in the NRDL. It was the first PD-1 inhibitor included into the NRDL and had a considerable price reduction of 63.7% from RMB7,838 to RMB2,843 per 100 mg after NRDL inclusion.

Market size of PD-(L)1 inhibitors in China

The first two blockbuster PD-1 inhibitors, Opdivo and Keytruda, were approved by the NMPA in June and July 2018, respectively. Currently, there are six PD-1 inhibitors and two PD-L1 inhibitors in China market and 29 more PD-(L)1 inhibitors under clinical trials, including 14 PD-1 inhibitors and 15 PD-L1 inhibitors. Considering the growing cancer patient population eligible for PD-(L)1 inhibitor treatment in line with expanding indications as well as the increasing accessibility, affordability and acceptance among patients and physicians of PD-(L)1 inhibitors, the total market size of PD-(L)1 inhibitors in China is projected to grow from RMB6.1bn in 2019 to RMB65.5bn in 2030, representing a CAGR of 24.1%.

Figure 55: China PD-(L)1 inhibitor market, 2014-2030E



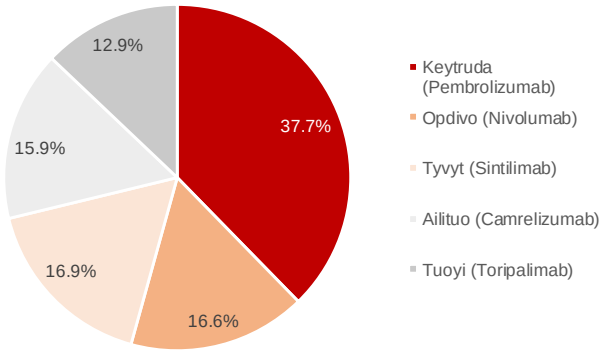
Source: CIC, CMBIS

Combination therapies with immune checkpoint inhibitors as components are expected to improve the response rate and durability of monotherapies of the inhibitors, leading to potentially better efficacy for

approved indications and efficacy in cancer types currently without effective treatments. As of 22 Jun 2019, there were 61 clinical trials with a PD-(L)1 inhibitor as a component in a combination therapy in China. The development of combination therapy increases the market potential for PD-(L)1 inhibitors.

As of 22 Jun 2020, six PD-1 inhibitors were approved in China, namely, BMS's Opdivo, Merck's Keytruda, Junshi's Tuoyi, Innovent's Tyvyt, Hengrui's Ailituo and BeiGene's Baizean, and two PD-L1 inhibitors were approved in China, namely, AstraZeneca's Imfinzi and Roche's Tecentriq.

Figure 56: Market share of PD-1 inhibitors in China, in terms of sales revenue, 2019

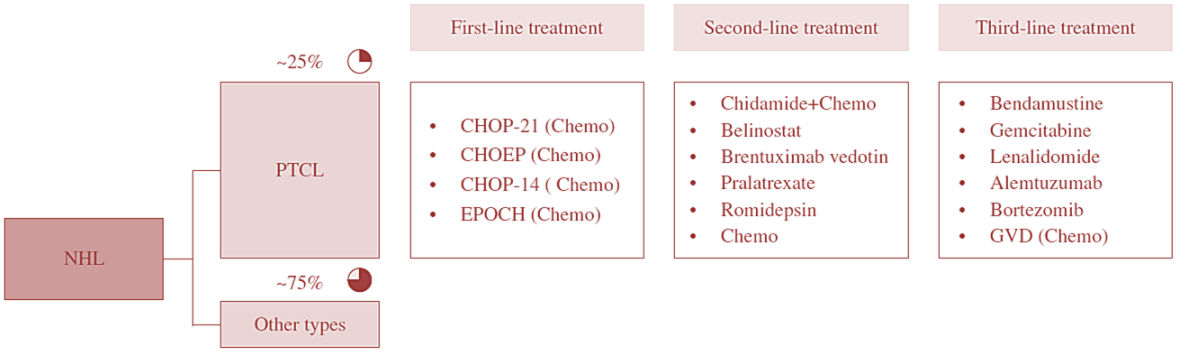


Source: CIC, CMBIS

PTCL

PTCL is a fast-growing cancer that develops from T-cells, accounting for approximately 25% of the total NHL incidence in China. In 2019, the incidence of PTCL in China reached 22.6 thousand cases. Before 2014, chemotherapies were the main treatments for PTCL. The approval of Epidaza, an HDAC inhibitor, has enriched the targeted therapies for PTCL in China. However, there is currently no immuno-therapy approved in China for PTCL.

Figure 57: Treatment path of PTCL



Source: CSCO, CIC, CMBIS

PTCL is often an invasive cancer that develops from white blood cells called T-lymphocytes, or T-cells. Epidaza (chidamide), an HDAC inhibitor, has been approved in China for PTCL. Before 2014, chemotherapies were the main treatments for PTCL. The treatment for PTCL is limited globally, and Epidaza is the only approval drug for first-line PTCL therapy in China. But due to its limited efficacy, it is normally used in second-line therapy.

The table below summarizes the PD-(L)1 inhibitor pipeline for PTCL registered with the NMPA as of 22 Jun 2020.

Figure 58: PD-(L)1 inhibitor pipeline for PTCL registered with the NMPA

Drug name	Target	Sponsor/ collaborators	Indications	Phase	First posted date
GB226	PD-1	Genor Biopharma	Relapsed and refractory PTCL	NDA	2020/7/21
AK104*	PD-1/CTLA-4	Akesobio	Relapsed and refractory PTCL	Phase Ib/II	2020/1/13

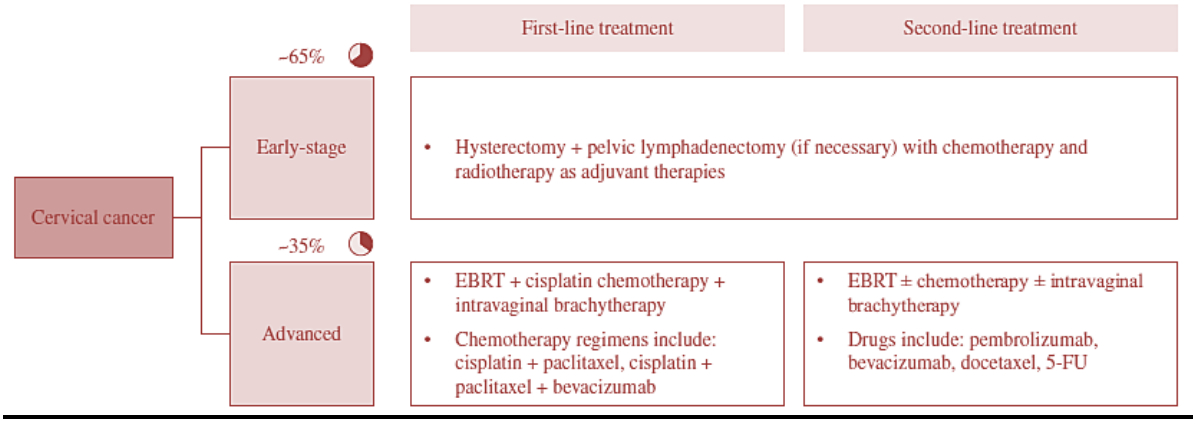
Source: CDE, CIC, CMBIS
Note: *AK104 is a PD-1/CTLA-4 BsAb

There is currently no immuno-therapies approved in China for the treatment of PTCL. In China, there are only two PD-(L)1 drugs targeting PTCL, including GB226, which is under Phase 2 pivotal trial, and AK104 from Akeso, a Phase 1b/2 trial of which was initiated in January 2020.

Cervical Cancer

Cervical cancer is the second most frequent cancer in women. The main treatment for advanced cervical cancer is radiotherapy such as external beam radiation therapy (EBRT) with adjuvant chemotherapy. Chemotherapy mainly adopts platinum-containing monotherapy or combination therapy. According to the CSCO guidelines for cervical cancer, bevacizumab is recommended to be used in both first- and second- line treatments.

Figure 59: Treatment path of cervical cancer



Source: CSCO, CIC, CMBIS

The table below summarizes the PD-(L)1 inhibitor pipeline for cervical cancer registered with the NMPA as of 22 Jun 2020.

Figure 60: PD-(L)1 inhibitor pipeline for cervical cancer registered with the NMPA as of 22 Jun 2020

Drug name	Target	Sponsor/ collaborators	Indications	Phase	First posted date
Durvalumab	PD-L1	AstraZeneca	Locally advanced cervical cancer	Phase Ⅲ	2020/4/9
GB226	PD-1	Genor Biopharma	PD-L1 positive relapsed or metastatic cervical cancer that fails platinum-based chemotherapy	Phase Ⅱ	2018/12/19
				Phase Ⅱ	2019/3/8
GLS-010	PD-1	Harbin Gloria Pharmaceutical	Relapsed or metastatic cervical cancer	Phase Ⅱ	2019/5/15
HLX10	PD-1	Shanghai Henlius Biotech	Advanced cervical cancer	Phase Ⅱ	2019/12/6
Recombinant PD-L1 monoclonal antibody	PD-L1	Zhaoke Oncology	Cervical cancer	Phase Ⅰ	2018/7/2

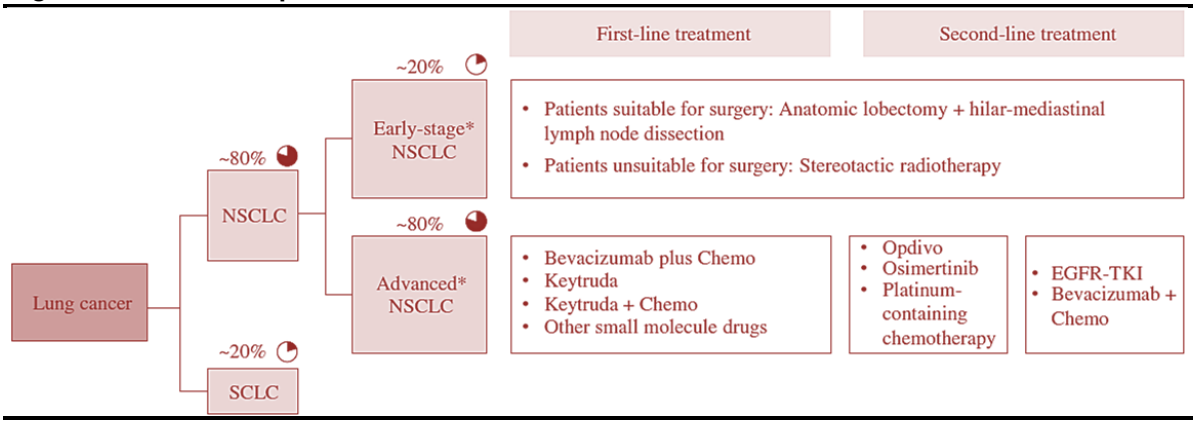
Source: CDE, CIC, CMBIS

NSCLC

NSCLC is the most common cancer in China. More than 916 thousand patients were newly diagnosed with lung cancer in 2019, and over 80% of them were diagnosed with NSCLC. The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These subtypes are grouped together as NSCLC because their treatment and prognoses are often similar.

There are various treatment plans for NSCLC. Among late stage NSCLC patients positive for specific driver genes, such as EGFR+, ALK+ and ROS1+, targeted therapy is the standard first-line treatment for these patients. For the remaining late stage NSCLC patients (about 50% of all late stage NSCLC), immuno-therapy is the first-line treatment plan. Keytruda is already used in these patients. Current research shows that for NSCLC patients positive for specific driver genes, immune-therapy may still play an important role in second- and third- line treatments.

Figure 61: Treatment path of NSCLC



Source: CSCO,CIC, CMBIS
Note: *Early stage: stage I and stage II; advanced stage: stage III and stage IV

The table below summarizes the PD-(L)1 inhibitor pipeline for EGFR+ NSCLC registered with the NMPA as of 22 Jun 2020.

Figure 62: PD-(L)1 inhibitor pipeline for EGFR+ NSCLC registered with the NMPA as of 22 Jun 2020

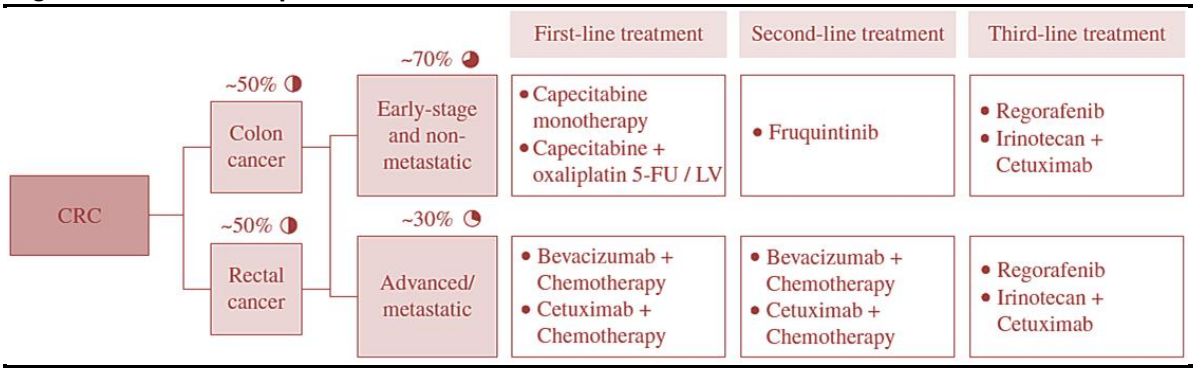
Drug name	Target	Sponsor/ collaborators	Indications	Phase	First posted date
Opdivo	PD-1	BMS	Advanced or metastatic EGFR-mutated and T790M negative NSCLC w ith first line EGFR-TKI treatment failure	Phase Ⅲ	2017/6/29
Keytruda	PD-1	MSD	EGFR-mutated and TKI-resistant metastatic NSCLC	Phase Ⅲ	2018/10/22
JS001*	PD-1	Junshi Biomedical	EGFR-mutated NSCLC w ith EGFRTKI treatment failure	Phase Ⅲ	2019/4/19
			Advanced or relapse EGFR-mutated and T790M negative NSCLC w ith EGFR-TKI treatment failure	Phase Ⅱ	2018/3/6
GB226**	PD-1	Genor Biopharma	Recurrent or metastatic NSCLC w ith EGFR-TKI treatment failure	Phase Ⅰ	2018/11/27

Source: CDE, CIC, CMBIS
Notes: * Combination with chemotherapy
** Combination with fruquintinib

mCRC

Colorectal cancer is also named colon cancer or rectal cancer, depending on where the disease starts. About 30% of colorectal cancers are metastatic colorectal cancer (mCRC). According to the CSCO guidelines for mCRC, bevacizumab plus chemotherapy is recommended to be used in both first- and second- line treatments. Besides, PD-(L)1 therapy in third-line mCRC treatment has already been proven effective in clinical trials in the US. In China, the PD-(L)1 drug clinical trials registered for mCRC are limited, with only four candidates. It is expected that with the approval of PD-(L)1 therapy by the FDA, the approval speed for mCRC in China might speed up.

Figure 63: Treatment path of mCRC



Source: CSCO, CIC, CMBIS

The table below summarizes the PD-(L)1 inhibitor pipeline for mCRC registered with the NMPA as of 22 Jun 2020.

Figure 64: PD-(L)1 inhibitor pipeline for mCRC registered with the NMPA as of 22 Jun 2020

Drug name	Target	Sponsor/ collaborators	Indications	Phase	First posted date
KN035	PD-L1	Alphamab	Advanced colorectal cancer	Phase Ⅱ	2018/7/25
Opdivo*	PD-1	BMS	Treated recurrent or metastatic colorectal cancer	Phase Ⅱ	2019/12/18
GB226**	PD-L1	Genor Biopharma	Metastatic colorectal cancer	Phase Ⅰ	2019/1/7
GB226***			Metastatic colorectal cancer	Phase Ⅰ	2019/1/8
SCT-I10A****	PD-1	Sinocelltech	Advanced esophageal squamous cell carcinoma and colorectal cancer	Phase Ⅰ	2020/3/18

Source: CDE, CIC, CMBIS
Notes: * Combination with Ipilimumab; ** Combination with fruquintinib; *** Combination with chemotherapy; **** Combination with SCT200 or combination with SCT200 and chemotherapy

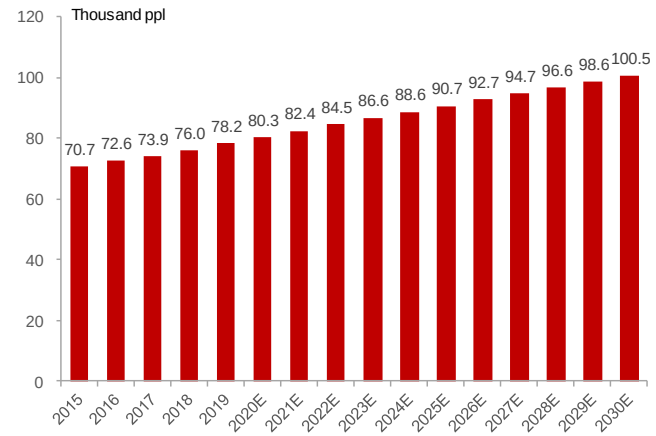
Overview of STING agonist market

STING (also known as TMEM173, MITA, ERIS, and MPYS) is an endoplasmic reticulum (ER) dimeric adaptor protein with 42 kDa 379 amino acids. It contains a transmembrane region (TM1-4, aa 1-154), a cyclic dinucleotide (CDN)-binding domain (CBD, aa 155-341) and a C-terminal tail (CTT, aa 342-379). STING is expressed in various endothelial and epithelial cells, as well as in hematopoietic cells, such as T cells, macrophages and DCs, and acts as a master regulator of type I interferon (IFN) production and the innate immune system. In tumor settings, STING is the major mediator of innate immune sensing of cancerous cells. cGAS, STING and TBK1 are the key effectors involved in host defense, and the cGAS–STING–TBK1 axis is now appreciated as the major signaling pathway in the immune response across different species. Multiple studies show that STING agonist may be used as a new immune stimulatory therapy and enhance the efficacy of cancer immunity cycle.

For instance, HNSCC and TNBC have limited treatment options with over 106 thousand annual incidence in China combined in 2019. Studies have shown that immunotherapy shows some effect in advanced stage patients of both types of cancer. Around 67% of HNSCC patients and 55% of TNBC patients have PD-(L)1 expression and may benefits from immunotherapy.

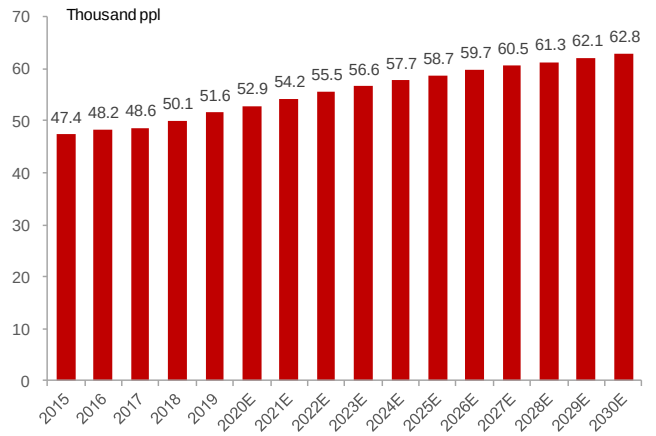
The following diagrams set forth HNSCC and TNBC incidence in China from 2015 to 2019 and the estimated market size from 2020 to 2030.

Figure 65: Incidence of HNSCC in China



Source: CIC, CMBIS

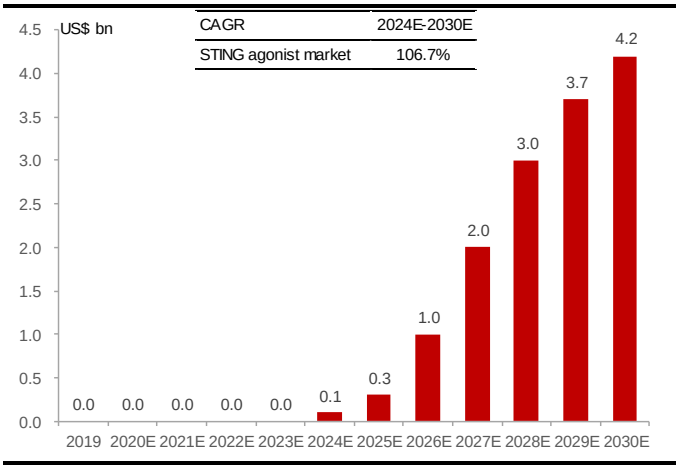
Figure 66: Incidence of TNBC in China



Source: CIC, CMBIS

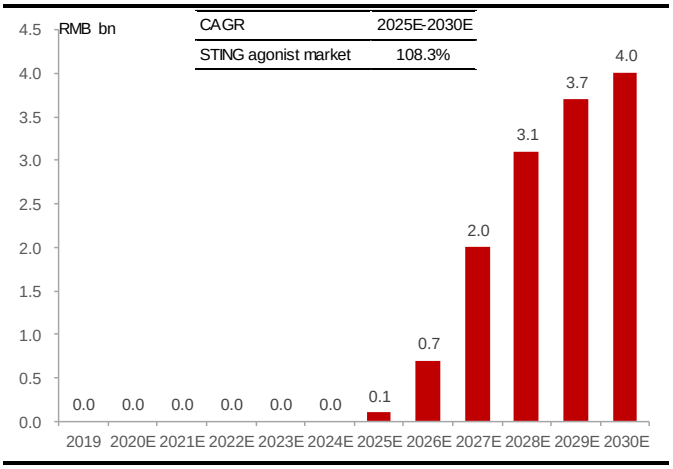
STING agonist, as an immune stimulatory therapy, may further increase the response of immune checkpoint inhibitors for these patients. Combo use of STING agonist and immune checkpoint inhibitors has the opportunity to be the new treatment options for these patients and fulfill unmet medical needs. The below diagram illustrates the market size of STING agonist globally and in China, respectively, in 2019 and the estimated market size from 2020 to 2030.

Figure 67: Global market sizes of STING agonist, 2019-2030E



Source: CIC, CMBIS

Figure 68: Market sizes of STING agonist in China, 2019-2030E



Source: CIC, CMBIS

Global leading biopharma companies in immune-oncology area such as MSD and BMS already started STING agonist combination trials with in-house PD-1 inhibitors. Currently, there is no NMPA-registered STING agonist pipeline drugs in China.

Figure 69: Global STING agonist pipeline as of 22 Jun 2020

Drug	Company	Indication	Phase	First posted date	NCT number	Combo/mono
MK-1454	MSD	HNSCC	Phase 2	1/7/2020	NCT04220866	combo with Keytruda
		Solid tumors, lymphoma	Phase 1	1/4/2017	NCT03010176	combo with Keytruda
BMS-986301	BMS	Advanced solid cancers	Phase 1	5/21/2019	NCT03956680	combo with Opdivo or Ipilimumab
IMSA101	ImmuneSensor Therapeutics/Genor	Solid tumor	Phase 1/2	7/15/2019	NCT04020185	combo with ICI*
MIW815/ ADU-S100	Aduro Biotech	Metastatic/recurrent head and neck cancer	Phase 2	5/3/2019	NCT03937141	combo with Keytruda
		Advanced/metastatic solid tumors or lymphomas	Phase 1	2/5/2016	NCT02675439	combo with Ipilimumab
		Solid tumors and lymphomas	Phase 1	6/1/2017	NCT03172936	combo with PDR001 (PD-1)
SB11285	Spring Bank Pharmaceuticals	Melanoma, HNSCC, solid tumor	Phase 1	9/20/2019	NCT04096638	combo with Opdivo
GSK3745417	GSK	Neoplasms	Phase 1	2/18/2019	NCT03843359	combo with Keytruda
E7766	Eisai	Urinary bladder neoplasms	Phase 1	9/30/2019	NCT04109092	mono
		Lymphoma advanced solid tumors	Phase 1	10/30/2019	NCT04144140	mono

Source: FDA, clinicaltrials.gov, CIC, CMBIS
Note: * Immune checkpoint inhibitors

Overview of HER2 antibody market

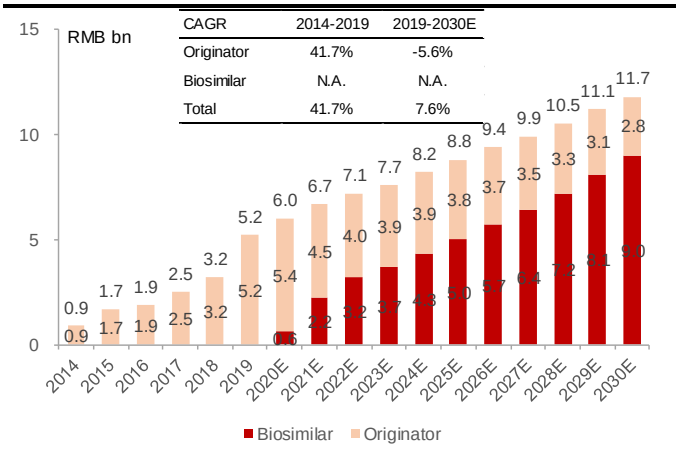
Incidence of breast cancer in China increased from 304 thousand in 2015 to 331 thousand in 2019 and is projected to reach 402 thousand in 2030. Approximately 90% of newly diagnosed breast cancer patients are under Stages I to III, about 30% of whom will experience a recurrence. The discovery of HER2 biomarker has great significance for the diagnosis and treatment of breast cancer. HER2 is a validated molecular target for cancer therapy. Over-expression of HER2 proteins has been shown to play a critical role in the progression of malignancies, especially breast cancer. The level of overexpression of HER2 in tumors can be classified into HER2 High, HER2 Intermediate and HER2 Low by reference to immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) standards. Cancers with HER2 High expression are expected to be the most sensitive to anti-HER2 monoclonal antibodies. The ratio of HER2 high expression patients in breast cancer ranges from 15% to 30%.

Anti-HER2 monoclonal antibodies and ADCs have now become a standard therapy for breast cancer. There are two anti-HER2 monoclonal antibodies, namely Trastuzumab and Pertuzumab, and two ADCs, T-DM1 and trastuzumab deruxtecan, that are being used for breast cancer. Herceptin (Trastuzumab), Perjeta (Pertuzumab), Kadcyla (T-DM1), and Enhertu (trastuzumab deruxtecan) were approved in the US in 1998, 2012, 2013, and 2019, respectively. Herceptin, Perjeta and Kadcyla were approved in China in 2002, 2018 and 2020, respectively.

Kadcyla was designed to deliver emtansine, which disrupts the way cells grow, to cancer cells in a targeted way by attaching emtansine to Herceptin. In this way, the emtansine carried by Herceptin is less toxic to healthy cells and more effective in treating cancer cells. It is projected that more ADCs will be developed in the future and ADCs will make up a more important part of anti-HER2 antibody drugs.

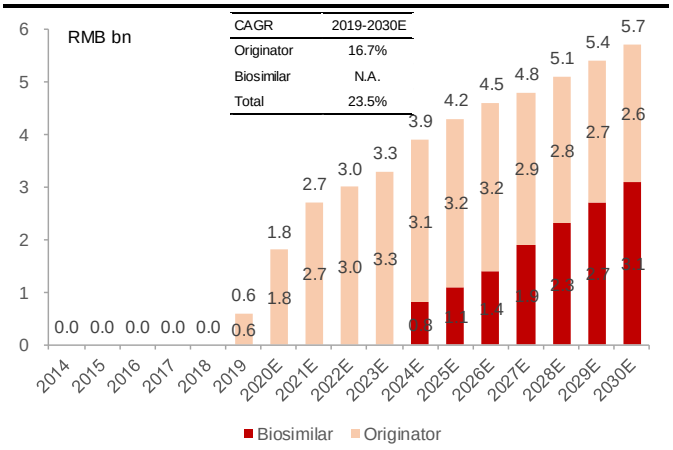
In 2019, the sales revenue of anti-HER2 monoclonal antibodies and ADCs reached CHF$4.9bn in the US, and the sales revenue of Herceptin and Perjeta reached RMB5.8bn in China.

Figure 70: Market size of China Trastuzumab market, 2014-2030E



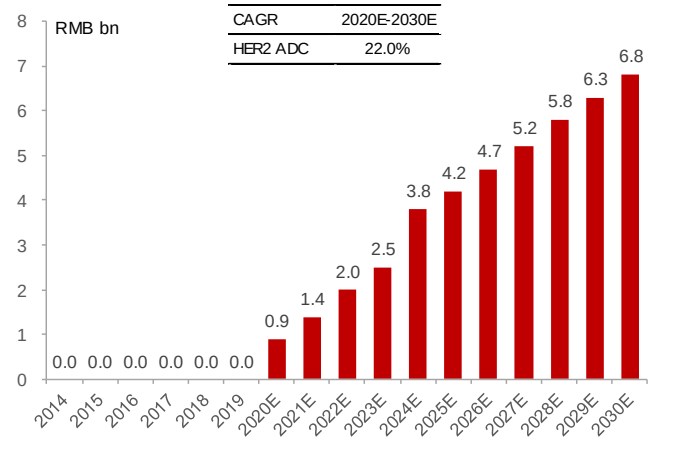
Source: CIC, CMBIS

Figure 71: Market size of China Pertuzumab market, 2014-2030E



Source: CIC, CMBIS

Figure 72: Market size of China HER2 ADC market, 2014-2030E



Source: CIC, CMBIS

Herceptin and Perjeta were approved in China in 2002 and 2018, respectively, and were included in the NRDL in 2017 and 2019, respectively. Kadcyla was approved in China in January 2020. Currently,

combination therapies of Herceptin and Perjeta are the first-line standard treatment for HER2+ breast cancer patients. In June 2020, Inetetamab (赛普汀) from Shanghai Sunshine Guojian became the first approved domestic novel drug in China.

Figure 73: Comparison between GB221 and its approved or late-stage competitors in China

Drug name	Sponsor/ collaborators	Indications	Phase	First posted date
Herceptin (trastuzumab)	Roche	N/A	Approved	2002/9/5
Cipterbin (Inetetamab)	Sunshine Guojian	Novel	Approved	2020/6/19
HLX02	Shanghai Henlius Biotech	HER2-overexpressed metastatic breast cancer	Approved	2020/8/12
GB221	Genor Biopharma	HER2-positive advanced breast cancer	Phase 3	2016/9/28
		HER2-positive recurrent or metastatic breast cancer	Phase 3	2018/4/19
BAT8001 (Her2 ADC)	Bio-Thera Solutions	HER2-positive advanced breast cancer	Phase 3	2018/2/22
HS022	Zhejiang Hisun Biomaterials	Breast cancer	Phase 3	2018/4/8
Trastuzumab	Hualan Bio	HER2-positive metastatic breast cancer	Phase 3	2019/4/26
Recombinant human HER2 monoclonal antibody	Anhui Anke Biotechnology (Group)	HER2-positive breast cancer	Phase 3	2019/5/23
SIBP-01	Shanghai Pharmaceuticals Holding	HER2-positive breast cancer	Phase 3	2019/6/5
RC48 (Her2 ADC)	RemeGen	HER2 low expression locally advanced or metastatic breast cancer	Phase 3	2020/5/11

Source: CDE, CIC, CMBIS

In 2017, Herceptin was added into the NRDL through negotiation with discount up to 69.0%, and the price decreased from RMB24,500 per 440 mg to RMB7,600 per 440 mg. After the 2019 NRDL negotiation, the price of Herceptin further decreased to RMB5,500 per 440 mg. In 2019, Perjeta was successfully included into the 2020 NRDL through negotiation. The price of Perjeta decreased by 73.6% from RMB18,800 per 420 mg to RMB4,955 after NRDL inclusion.

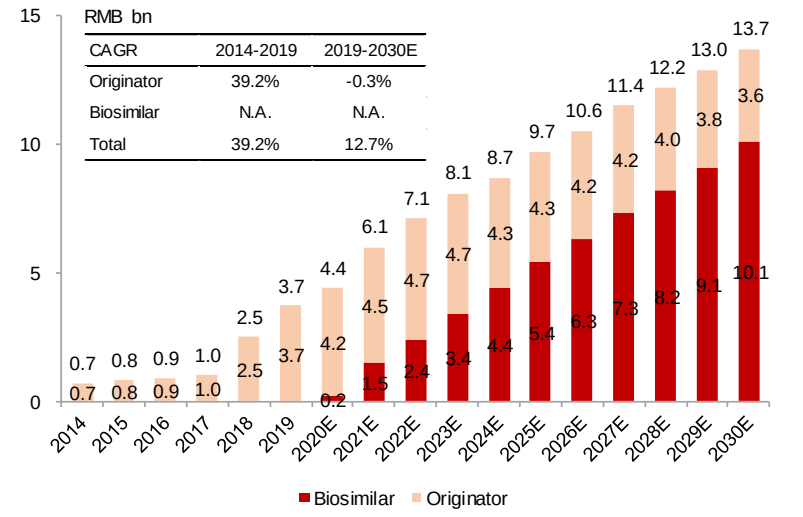
The list prices of Herceptin, Perjeta, Kadcyla and Enhertu in the US are US$1,636.5 per 150 mg, US$5,534.4 per 420 mg, US$3,302.8 per 100 mg and US$2,406.5 per 100 mg, respectively.

The sales volume of Herceptin in China increased rapidly after it was added into NRDL. In 2017, the sales volume of Herceptin was around 100 thousand vail (440mg/vail) annually, while in 2019, the sales volume increased to over near 1,000 thousand vail annually (440mg/vail).

Overview of bevacizumab market in China

The market size of bevacizumab in China may increase from RMB4.0bn in 2019 to RMB14.1bn in 2030, according to CIC.

Figure 74: China bevacizumab market, 2014-2030E



Source: CIC, CMBIS

Bevacizumab is widely used in the treatment of different cancers, including NSCLC, mCRC, GBM and RCC. For late stage non-squamous NSCLC patients, bevacizumab is the drug for first-line treatment. RAS mutation is present in roughly 45% of patients with mCRC, and NRAS mutation occur in about 5% of mCRC cases. For these mCRC patients, bevacizumab is also the drug for first-line treatment.

Currently, there is no available monoclonal antibody approved for GBM in China. In the US, Avastin was approved for recurrent GBM by the FDA in 2017.

Overview of RANKL monoclonal antibodies

The cell surface receptor named RANK (for receptor activator of NFkB) prods osteoclast precursor cells to develop into fully differentiated osteoclasts when RANK is activated by its cognate partner RANK ligand (RANKL). RANKL is produced by osteoblasts and is one of many signaling molecules that facilitate the cross-talk between osteoblasts and osteoclasts and coordinate bone remodeling. Osteoprotegerin (OPG), another protein released by osteoblasts, can also bind to RANKL, acting as a decoy to prevent RANK and RANKL from coming into contact. Anti-RANKL drugs inhibit the maturation of osteoclasts by binding to RANKL, which mimics the natural action of OPG. This protects the bone from degradation and helps to treat osteoporosis.

Prolia and Xgeva represent the first generation anti-RANKL agents, both containing the same active ingredient, denosumab. Prolia is approved for osteoporosis in women after menopause who are at high risk for bone fracture or cannot use other osteoporosis medicine or for whom other osteoporosis medicines did not work well. Xgeva is used to prevent bone fracture, spinal cord compression, or the need for radiation or surgery to bone in patients with multiple myeloma and in patients with bone metastases from solid tumors. They were both approved by the FDA in 2010. In May 2019, Xgeva was approved by the NMPA for the use of unresectable GCTB.

GCTB is a common primary bone tumor in China, accounting for about 11.6% of primary bone tumors, and is often considered benign. However, it is a problematic disease due to its strong local invasiveness, high potential for malignancy, high rate of local recurrence and possibility to metastasize. Patients with GCTB normally have a long survival time. If resectable, surgery is the most important

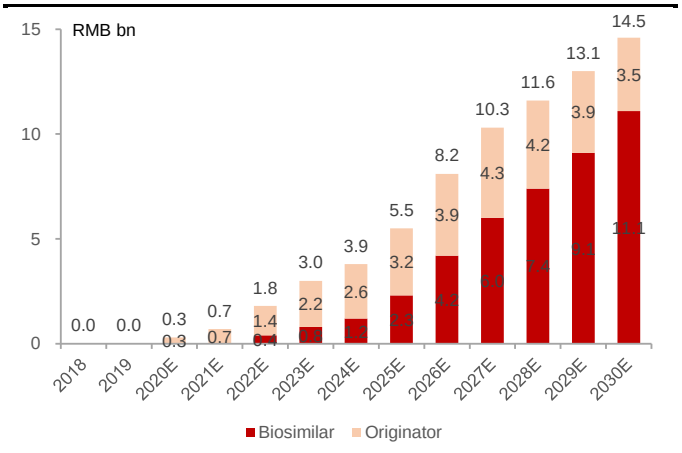
treatment method for GCTB. For unresectable, recurrent or metastatic GCTB, pharmacologic therapy is a mainstream treatment method. In June 2013, the FDA approved denosumab for unresectable GCTB. In May 2019, the NMPA approved denosumab for unresectable GCTB under the overseas fast-track scheme without local clinical trial data.

Osteoporosis is the most common bone disease, characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures. Two categories of osteoporosis have been identified: primary osteoporosis and secondary osteoporosis. Primary osteoporosis includes PMO (type I), senile osteoporosis (type II), and idiopathic osteoporosis (including adolescent type).

PMO is an age-related disease, which generally develops after natural or surgical menopause, when estrogen levels drop precipitously. These changes lead to bone loss, usually in the trabecular (spongy) bone inside the hard cortical bone. According to the results of the first Chinese osteoporosis epidemiological survey disclosed by the National Health Commission, osteoporosis has become a significant health problem for middle and old aged people in China, especially among middle and old aged women. Prevalence rate of osteoporosis is estimated at 19.2% in people over 50 years old, and prevalence rate in women over 50 years old is 32.1%, which is much higher than the 6% prevalence rate in men of the same age.

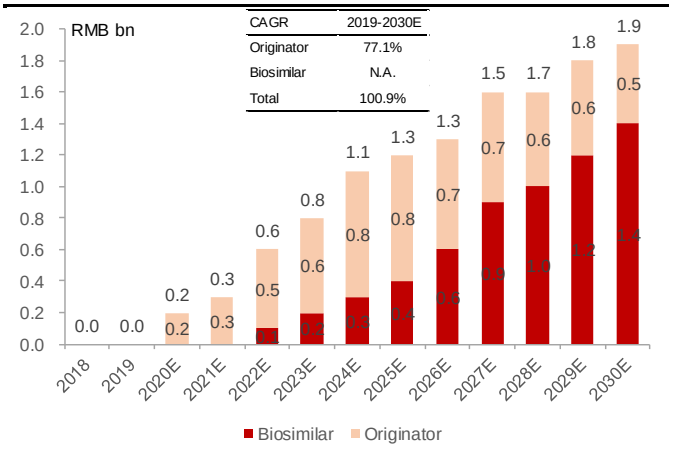
Bisphosphonates are the most widely used drugs for treating osteoporosis by preventing bone resorption. On 19 Jun 2020, Prolia became the first antibody drug approved for PMO treatment by NMPA.

Figure 75: Market size of China Denosumab (PMO) market, 2014-2030E



Source: CIC, CMBIS

Figure 76: Market size of China Denosumab (GCTB and bone metastases from solid tumor) market, 2014-2030E



Source: CIC, CMBIS

Figure 77: NMPA-registered denosumab pipeline targeted osteoporosis (as of 22 Jun 2020)

Drug name	Sponsor/ collaborators	Drug type	Indications	Phase	First posted date
QL1206	Qilu Pharmaceutical	Biosimilar	PMO at high risk for fracture	Phase 3	2019/6/5
LY06006	Luye Pharma	Biosimilar	PMO at high risk for fracture	Phase 3	2019/6/14
MW031	Shanghai Mabwell	Biosimilar	PMO at high risk for fracture	Phase 3	2019/11/4
KN012	Alphamab	Biosimilar	PMO	Phase 1	2018/7/27
JMT103	JMT Bio	Biosimilar	Osteoporosis	Phase 1	2018/7/30
GB223	Genor Biopharma	Novel	PMO	Phase 1	2018/11/14
SHR-1222	Hengrui Medicine	Biosimilar	Osteoporosis	Phase 1	2019/2/19
CMAB807	Mabpharm	Biosimilar	PMO	Phase 1	2019/4/24
QL1206	Qilu Pharmaceutical	Biosimilar	PMO at high risk for fracture	Phase 1	2019/11/18

Source: CDE, CIC, CMBIS

Figure 78: NMPA-registered denosumab pipeline targeted bone metastases from tumors and GCTB (as of 22 Jun 2020)

Drug name	Sponsor/ collaborators	Drug type	Indications	Phase	First posted date
QL1206	Qilu Pharma Group	Biosimilar	Bone metastases from solid tumors	Phase 3	2019/10/30
MW032	Shanghai Mabwell	Novel	Bone metastases from breast cancer	Phase 3	2020/3/18
JMT103	JMT Bio	Biosimilar	Bone metastases from solid tumors and GCTB	Phase 1	2018/3/27
			Unresectable or surgery is not feasible GCTB	Phase 1b/2	2020/2/20
HS629	Zhejiang Hisun pharmaceutical	Biosimilar	The prevention of skeletal-related events in patients with bone metastases from solid tumors	Phase 1	2018/4/12
LZM004	Livzon Pharmaceutical Group	Biosimilar	Bone metastases from solid tumors and GCTB	Phase 1	2018/8/15
GB223	Genor Biopharma	Novel	The prevention of skeletal-related events in patients with bone metastases from solid tumors	Phase 1	2019/1/17
LY01011	Luye Pharma Group	Biosimilar	The prevention of skeletal-related events in patients with bone metastases from solid tumors	Phase 1	2019/4/10 2019/12/2
HL05	Hualan Bio	Biosimilar	The prevention of skeletal-related events in patients with bone metastases from solid tumors	Phase 1	2020/2/26

Source: CDE, CIC, CMBIS

China's aging population, increased expenditure on health per capita and R&D on biosimilars will drive the growth of the osteoporosis market. China's population has been aging at an increasingly faster speed over the past 10 years. The number of people over age 50 has increased from 388mn in 2014 to 453mn in 2018. Since osteoporosis is more prevalent among the elderly, the increasing elderly population is expected to drive the growth of the osteoporosis market.

GCTB is a common primary intermediate tumor of the bone, especially among East Asians. Globally, GCTB accounts for approximately 4-5% of all primary bone tumors. But GCTB is comparatively more common in China, occupying 20% of all primary bone tumors. Although most GCTB tumors are benign, they often result in the complete destruction of the affected bones, leading to bone fracture, joint dysfunction or amputation, if not diagnosed timely and treated properly.

Currently, common treatments of GCTB are mainly surgery and radiotherapy in China. Surgery is the primary treatment for GCTB, with a high recurrence rate of 15-45% after the curettage. When tumors recur, they become more difficult to treat and more likely to spread to other parts of the body. Radiotherapy can control the growth of the tumor to a certain degree, but it can also induce

complications and potential risks of sarcomatoid malignancy. Denosumab, as an effective alternative, brings benefits to patients who suffer from GCTB, especially for those with unresectable or where surgical resection is likely to result in severe morbidity.

Overview of antibody drug market for autoimmune disease in China

Autoimmune diseases are caused by the immune system's responses to its own tissue components. They are usually chronic diseases with long disease courses. They usually involve complex performances, and multiple systems and organs are affected. Major autoimmune diseases include psoriasis (Ps), rheumatoid arthritis (RA), ankylosing spondylitis (AS), ulcerative colitis (UC) and Crohn's disease (CD).

Tumor necrosis factor-alpha (TNF- α) is a potent pathological cytokine involved in inflammatory and immune responses, which can bind to TNF receptor 1 (TNFR1) or TNF receptor 2 (TNFR2). It exists in numerous forms, both monomeric and trimeric, as well as soluble and transmembrane. Upon binding to its receptors, TNF triggers the activation of multiple pathways, including the NFkB and MAPK pathways, which leads to the production of numerous inflammatory cytokines and may also trigger the TNF-induced apoptotic pathway. TNF- α inhibitors bind to the TNF cytokine and inhibit its interaction with TNF receptors.

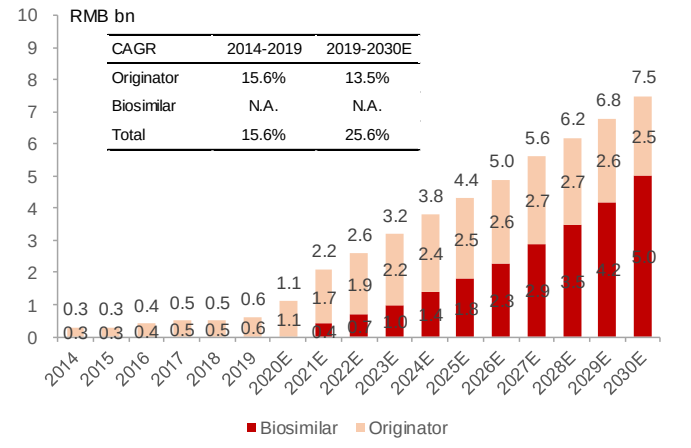
As of 22 Jun 2020, four TNF- α monoclonal antibodies were approved in China, namely, infliximab, adalimumab, certolizumab and golimumab.

Infliximab is a TNF- α blocker and a chimeric monoclonal IgG1 antibody composed of human constant (75%) and murine variable (25%) regions. Infliximab was first approved by the FDA in 1998 under the market name "Remicade" as an intravenous injection. It was first approved by the NMPA in 2006.

RA is a long-term autoimmune disorder that primarily affects the joints. It is caused by the body's immune system attacking the joints, resulting in inflammation and thickening of the joint capsule. Prevalence of RA amounts to approximately 5.9mn in China in 2019.

Inflammatory bowel disease, or IBD, mainly includes UC and CD. UC is a chronic disease that causes inflammation and ulceration of the colon and rectum. The main symptoms include abdominal pain and diarrhea with bloody stools. CD is a disease of unknown etiology, characterized by transmural inflammation of the gastrointestinal tract, which may involve the whole digestive tract or any part of the digestive tract from the mouth to the perianal area. Prevalence of UC and CD amounted to 182 thousand and 28 thousand, respectively, in China as of 31 Dec 2019.

Figure 79: China infliximab market, 2014-2030E



Source: CIC, CMBIS

Figure 80: Infliximab biosimilar pipeline registered with the NMPA that were at late stage

Drug name	Sponsor/ collaborators	Indications	Phase	First posted date
GB242	Genor Biopharma	RA	NDA	2017/7/28
CMAB008	Mabpharm	Moderate to severe active RA	Phase III	2017/9/15
HS626	Zhejiang Hisun pharmaceutical	Plaque psoriasis	Phase III	2018/4/8
CT-P13	Celltrion	Active RA	Phase III	2018/10/30

Source: CDE, CIC, CMBIS

Remicade were included in the NRDL in November 2019. The price of Remicade in NRDL decreased by 66.8% from the original market price of RMB6,047 per 100 mg to RMB2,007 after NRDL inclusion.

Financial Analysis

Drugs sales to start from 2021E

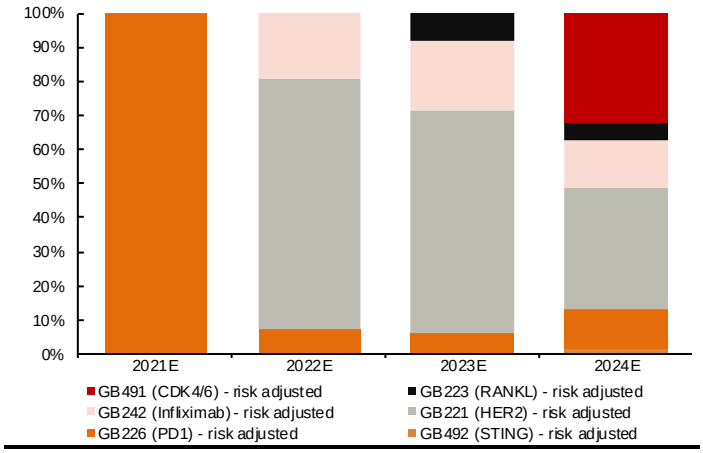
We forecast drug sales to start from 2021E and expect risk-adjusted revenue of RMB643mn/ RMB882mn/ RMB1,895mn in FY2022E/23E/24E. The most advanced drugs include GB226, GB221 and GB242. GB226 is expected to be approved by NMPA in 2021E, and GB221 and GB242 are expected to be approved by NMPA in 2022E. We also forecast GB223 to receive NMPA's approval in 2023E. GB491 and GB492 were expected to launch in China by 2024E. Furthermore, to factor in the risk in drug development, we apply different probability of success (PoS) to our sales forecasts.

Figure 81: Risk-adjusted revenue forecasts (2021-2024E)

(YE 31 Dec) RMB mn	2021E	2022E	2023E	2024E
GB491 (CDK4/6) - risk adjusted	0	0	0	610
YoY	*N/A*	*N/A*	*N/A*	*N/A*
GB226 (PD1) - risk adjusted	23	46	54	216
YoY	*N/A*	*96%*	*17%*	*303%*
GB221 (HER2) - risk adjusted	0	473	575	678
YoY	*N/A*	*N/A*	*22%*	*18%*
GB242 (Infliximab) -risk adjusted	0	124	185	260
YoY	*N/A*	*N/A*	*49%*	*41%*
GB223 (RANKL) - risk adjusted	0	0	69	100
YoY	*N/A*	*N/A*	*N/A*	*45%*
GB492 (STING) - risk adjusted	0	0	0	31
YoY growth	*N/A*	*N/A*	*N/A*	*N/A*
Total Revenue	**23**	**643**	**882**	**1,895**
YoY	*N/A*	*2650%*	*37%*	*115%*

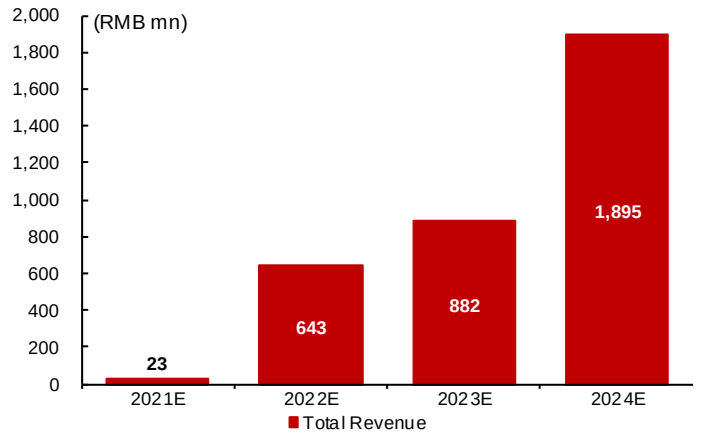
Source: Company data, CMBIS estimates

Figure 82: Revenue breakdown (2021-2024E)



Source: Company data, CMBIS estimates

Figure 83: Total revenue forecasts (2021-2024E)



Source: Company data, CMBIS estimates

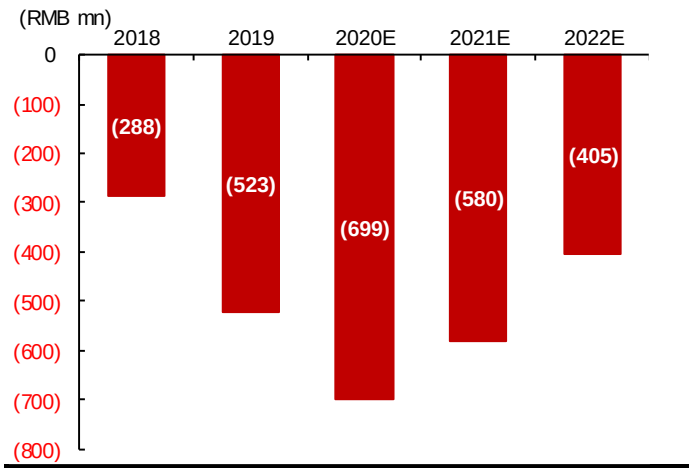
Genor recorded net losses of RMB288mn/ RMB522mn in FY18A/19A. We expect it to continue incur net losses of RMB699mn/RMB580mn/RMB405mn in FY20E/21E/22E and expect net profit to break even in 2024E.

Figure 84: P&L forecasts

(YE 31 Dec) RMB mn	2018	2019	2020E	2021E	2022E	2023E	2024E
Revenue	**7**	**13**	**0**	**23**	**643**	**882**	**1,895**
YoY	*N/A*	*89%*	*-100%*	*N/A*	*2650%*	*37%*	*115%*
Cost of sales	(5)	(10)	0	(9)	(129)	(168)	(341)
% of revenue	*-79%*	*-73%*	*N/A*	*-40%*	*-20%*	*-19%*	*-18%*
Gross profit	**1**	**3**	**0**	**14**	**514**	**714**	**1,553**
GPM	*21%*	*27%*	*N/A*	*60%*	*80%*	*81%*	*82%*
Other income	11	4	10	10	10	10	10
% of revenue	*163%*	*31%*	*N/A*	*43%*	*2%*	*1%*	*1%*
Administrative expenses	(22)	(89)	(200)	(90)	(129)	(132)	(227)
% of revenue	*-324%*	*-685%*	*N/A*	*-385%*	*-20%*	*-15%*	*-12%*
Research and development costs	(271)	(439)	(500)	(500)	(600)	(620)	(663)
% of revenue	*-3945%*	*-3365%*	*N/A*	*-2139%*	*-93%*	*-70%*	*-35%*
Selling expenses	0	0	(10)	(50)	(225)	(265)	(549)
% of revenue	*0%*	*0%*	*N/A*	*-214%*	*-35%*	*-30%*	*-29%*
Other (losses)/gains - net	(1)	0	0	0	0	0	0
% of revenue	*-21%*	*0%*	*N/A*	*0%*	*0%*	*0%*	*0%*
Profit from operations	**(283)**	**(521)**	**(700)**	**(616)**	**(429)**	**(293)**	**124**
% of revenue	*-4106%*	*-3992%*	*N/A*	*-2636%*	*-67%*	*-33%*	*7%*
Finance costs - net	(5)	(3)	1	36	24	11	3
% of revenue	*-79%*	*-24%*	*N/A*	*154%*	*4%*	*1%*	*0%*
Profit (loss) before tax	**(288)**	**(524)**	**(699)**	**(580)**	**(405)**	**(281)**	**126**
% of revenue	*-4186%*	*-4016%*	*N/A*	*-2482%*	*-63%*	*-32%*	*7%*
Income tax expense	0	1	0	0	0	0	(19)
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*-15%*
Profit (loss) for the year	**(288)**	**(523)**	**(699)**	**(580)**	**(405)**	**(281)**	**107**
Non-controlling interests	0	(1)	0	0	0	0	0
Profit (loss) attributable to shareholders	**(288)**	**(522)**	**(699)**	**(580)**	**(405)**	**(281)**	**107**
NPM	*-4186%*	*-4004%*	*N/A*	*-2482%*	*-63%*	*-32%*	*6%*

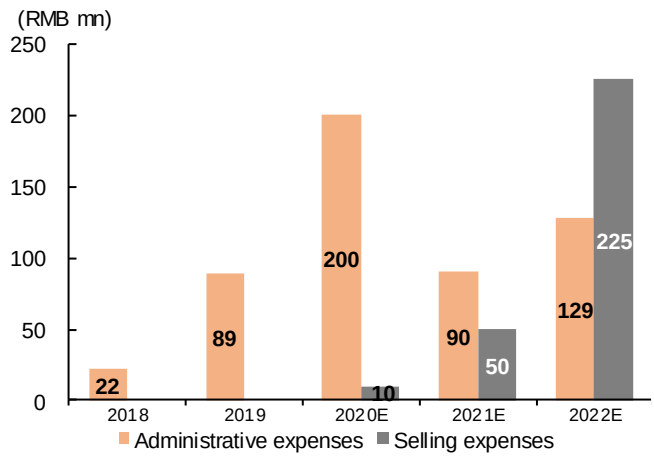
Source: Company data, CMBIS estimates

Figure 85: Net profit forecasts



Source: Company data, CMBIS estimates

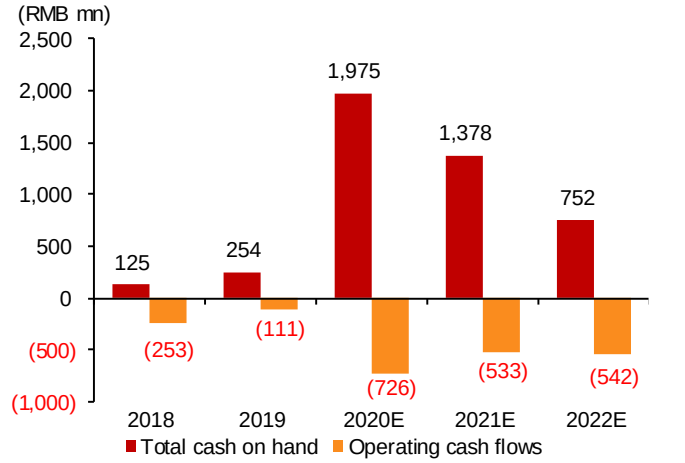
Figure 86: SG&A expenses forecasts



Source: Company data, CMBIS estimates

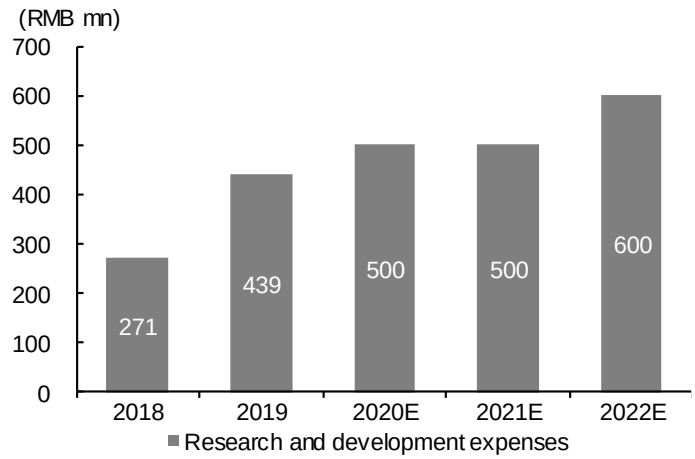
We forecast R&D cost to climb from RMB271mn/ RMB439mn in FY18A/19A to RMB500mn/RMB500mn/RMB600mn in FY20E/21E/22E, mainly due to initiation of new clinical trials and progress of existing clinical trials.

Figure 87: Cash on hand and operating cash flows



Source: Company data, CMBIS estimates

Figure 88: R&D expenses



Source: Company data, CMBIS estimates

Financial Statements

Income statement

YE 31 Dec (RMB mn)	FY18A	FY19A	FY20E	FY21E	FY22E
Revenue	**7**	**13**	**0**	**23**	**643**
GB491 (CDK4/6) - risk adjusted	*0*	*0*	*0*	*0*	*0*
GB226 (PD1) - risk adjusted	*0*	*0*	*0*	*23*	*46*
GB221 (HER2) - risk adjusted	*0*	*0*	*0*	*0*	*473*
GB242 (Infliximab) - risk adjusted	*0*	*0*	*0*	*0*	*124*
GB223 (RANKL) - risk adjusted	*0*	*0*	*0*	*0*	*0*
GB492 (STING) - risk adjusted	*0*	*0*	*0*	*0*	*0*
Cost of sales	(5)	(10)	0	(9)	(129)
Gross profit	**1**	**3**	**0**	**14**	**514**
Other income	11	4	10	10	10
Administrative expenses	(22)	(89)	(200)	(90)	(129)
R&D expenses	(271)	(439)	(500)	(500)	(600)
Selling & distribution expenses	0	0	(10)	(50)	(225)
Other (losses)/gains	(1)	0	0	0	0
Operating profit (loss)	**(283)**	**(521)**	**(700)**	**(616)**	**(429)**
Finance costs	(5)	(3)	1	36	24
Pre-tax profit (loss)	**(288)**	**(524)**	**(699)**	**(580)**	**(405)**
Income tax	0	1	0	0	0
Minority interests	0	(1)	0	0	0
Attributable net profit (loss)	**(288)**	**(522)**	**(699)**	**(580)**	**(405)**

Cash flow summary

YE 31 Dec (RMB mn)	FY18A	FY19A	FY20E	FY21E	FY22E
Profit before tax	**(288)**	**(524)**	**(699)**	**(580)**	**(405)**
Depreciation and	73	149	40	43	46
Change in working capital	(43)	261	(71)	0	(187)
Others	5	3	4	4	4
Net income tax paid	0	0	0	0	0
Net cash from operating	**(253)**	**(111)**	**(726)**	**(533)**	**(542)**
Purchase of PP&E	(28)	(21)	(50)	(50)	(70)
Purchase of land use right	(2)	(7)	(10)	(10)	(10)
Net cash used in business combination	0	(13)	0	0	0
Others	0	0	0	0	0
Net cash from investing	**(30)**	**(41)**	**(60)**	**(60)**	**(80)**
Proceeds from issuance of	997	863	2,511	0	0
Capital contribution from	392	0	0	0	0
Borrowings from related	69	0	0	0	0
Others	(1,111)	(584)	(4)	(4)	(4)
Net cash from financing	**347**	**279**	**2,507**	**(4)**	**(4)**
FX changes	0	1	0	0	0
Net change in cash	64	127	1,721	(597)	(626)
Cash at the beginning of the	61	125	254	1,975	1,378
Cash at the end	**125**	**254**	**1,975**	**1,378**	**752**

Balance sheet

YE 31 Dec (RMB mn)	FY18A	FY19A	FY20E	FY21E	FY22E
Non-current assets	**305**	**385**	**404**	**421**	**455**
PP&E	204	191	213	231	266
Right-of-use assets	37	33	33	33	33
Intangible assets	16	94	93	91	90
Other non-current assets	48	66	66	66	66
Current assets	**682**	**348**	**2,075**	**1,478**	**852**
Inventories	25	25	20	20	20
Trade receivables	1	0	10	10	10
Other receivables, deposits and	57	45	45	45	45
Amounts due from related parties	467	21	21	21	21
Cash and cash equivalents	125	254	1,975	1,378	752
Contract cost	8	4	4	4	4
Non-current liabilities	**64**	**147**	**147**	**147**	**147**
Borrowings	2	1	1	1	1
Lease liabilities	36	29	29	29	29
Others	27	117	117	117	117
Current liabilities	**100**	**360**	**294**	**294**	**107**
Trade payables	31	103	100	100	35
Contract liabilities	11	12	12	12	12
Other payables and accruals	46	213	150	150	28
Lease liabilities	9	12	12	12	12
Amounts due to related parties	0	16	16	16	16
Total net assets	**824**	**225**	**2,038**	**1,458**	**1,052**
Minority interest	0	6	6	6	6
Shareholders' equity	**824**	**219**	**2,031**	**1,451**	**1,046**

Key ratios

YE 31 Dec	FY18A	FY19A	FY20E	FY21E	FY22E
Sales mix (%)					
GB491 (CDK4/6) - risk adjusted	0	0	0	0	0
GB226 (PD1) - risk adjusted	0	0	0	100	7
GB221 (HER2) - risk adjusted	0	0	0	0	74
GB242 (Infliximab) - risk	0	0	0	0	19
GB223 (RANKL) - risk adjusted	0	0	0	0	0
GB492 (STING) - risk adjusted	0	0	0	0	0
Total	100	100	100	100	100
Profit & loss ratios (%)					
Gross margin	N/A	N/A	N/A	60	80
EBITDA margin	0	N/A	N/A	N/A	(60)
Pre-tax margin	N/A	N/A	N/A	N/A	(63)
Net margin	0	N/A	N/A	N/A	(63)
Effective tax rate	0	0	0	0	0
Balance sheet ratios					
Current ratio (x)	7	1	7	5	8
Trade receivables turnover	N/A	N/A	N/A	0	60
Trade payables turnover	N/A	N/A	N/A	0	100
Net debt to total equity ratio (%)	Net cash	Net cash	Net cash	Net cash	Net cash
Returns (%)					
ROE	(35)	(232)	(34)	(40)	(39)
ROA	(29)	(71)	(28)	(31)	(31)

Source: Company data, CMBIS estimates

Valuation

We expect Genor to commercialize three products, GB226, GB221 and GB242, in 2021E/2022E/2022E and its future cash flows will rely on the successful commercialization of pipeline drugs. We see DCF as appropriate in valuing the Company. We derive target price of HK$26.49 based on a 10-year DCF valuation (WACC: 11.1%, terminal growth rate: 2.0%).

Figure 89: Base case risk-adjusted DCF valuation (terminal growth rate: 2.0%)

DCF Valuation (in Rmb mn)	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
EBIT	(616)	(429)	(293)	124	1,013	1,657	1,951	2,104	2,264	2,465
Tax rate	0%	0%	0%	15%	15%	15%	15%	15%	15%	15%
EBIT*(1-tax rate)	(616)	(429)	(293)	105	861	1,409	1,658	1,788	1,924	2,095
+ D&A	43	46	51	56	60	60	60	60	61	61
- Change in working capital	0	(187)	(136)	(174)	(319)	(150)	(73)	(57)	(58)	(74)
- Capex	(60)	(80)	(80)	(80)	(60)	(60)	(60)	(60)	(60)	(60)
FCFF	**(633)**	**(650)**	**(457)**	**(93)**	**541**	**1,259**	**1,586**	**1,732**	**1,867**	**2,021**
Terminal value										**22,721**
FCF + Terminal value	(633)	(650)	(457)	(93)	541	1,259	1,586	1,732	1,867	24,742

Present value of enterprise	10,388
Net Cash	(1,288)
Minorities	6
Equity value (RMB mn)	11,669
Equity value (HK$ mn)	**13,009**
Equity value (US$ mn)	**1,666**
Corporate value per share (HK$)	**26.49**
Terminal growth rate	**2.0%**
WACC	**11.1%**
Cost of Equity	14.0%
Cost of Debt	5.0%
Equity Beta	1.1
Risk Free Rate	3.0%
Market Risk Premium	10.0%
Target Debt to Asset ratio	30.0%
Effective Corporate Tax Rate	15.0%

Source: CMBIS estimates

Figure 90: Valuation range based on sensitivity analysis

Corporate value per share (HK$)		Corporate value				
		10.1%	**10.6%**	**11.1%**	**11.6%**	**12.1%**
	3.0%	34.63	31.58	28.93	26.61	24.57
	2.5%	32.82	30.06	27.64	25.51	23.62
Terminal growth rate	**2.0%**	31.24	28.72	**26.49**	24.52	22.77
	1.5%	29.84	27.52	25.47	23.64	22.00
	1.0%	28.60	26.45	24.54	22.83	21.29

Source: Company data, CMBIS estimates

Investment Risks

Having incurred net losses in the past and will continue to incur losses for the foreseeable future

Investment in pharmaceutical drug development is highly speculative. It entails substantial upfront capital expenditures and significant risk that a drug candidate will fail to gain regulatory approval or become commercially viable. Genor incurred losses in each period since its inception. If Genor is unable to maintain adequate working capital, it may default on payment obligations and may not be able to meet capital expenditure requirements.

Failure in obtaining regulatory approval for drug candidates

The Company's operations to date have focused on organizing and staffing its operations, business planning, raising capital, establishing its intellectual property portfolio and conducting pre-clinical and clinical trials of its drug candidates. Genor has not yet demonstrated an ability to successfully manufacture, obtain marketing approvals for or commercialize its drug candidates. Genor has no products approved for commercial sale and have not generated any revenue from product sales. Consequently, any predictions about its future success or viability may not be as accurate as they could be if it had a longer operating history.

If Genor is unable to obtain the NMPA approval for its drug candidates to be eligible for an expedited registration pathway as innovative drug candidates, the time and cost the Company incur to obtain regulatory approvals may increase. The NMPA has mechanisms in place for expedited review and approval for drug candidates that are innovative drug applications, provided such drug or drug candidate has a new and clearly defined structure, pharmacological property and apparent clinical value and has not been marketed anywhere in the world. However, there is no assurance that an innovative drug designation will be granted by the NMPA for any of Genor's drug candidates.

Competition from peers with more competing and successful drugs

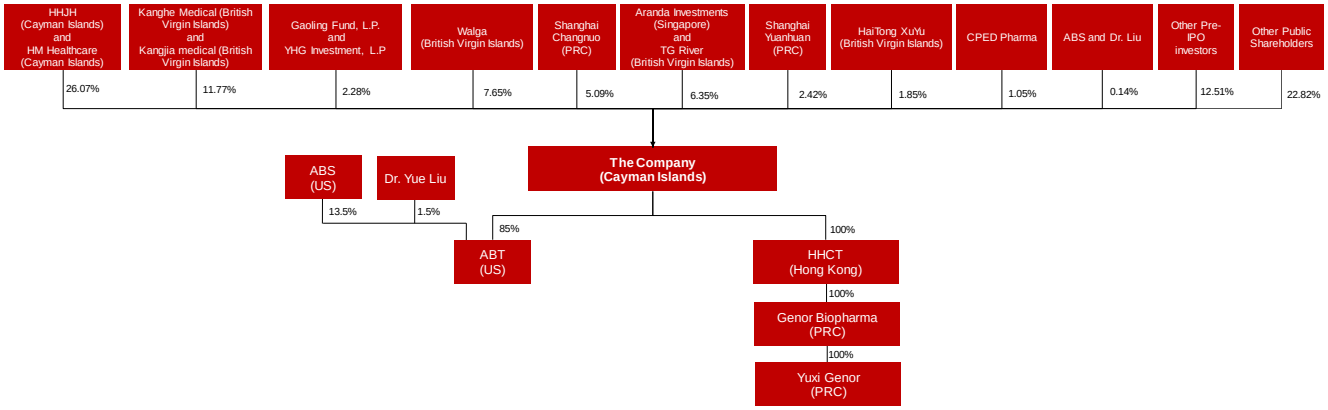
Genor faces intense competition and rapid technological change and the possibility that its competitors may develop therapies that are similar, more advanced, or more effective than Genor, which may adversely affect its financial condition and its ability to successfully commercialize its drug candidates. The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. Genor continues to face competition with respect to its current novel and biosimilar drug candidates, and will face competition with respect to any novel and biosimilar drug candidates that Genor may seek to develop or commercialize in the future.

Failure in protecting intellectual property rights

The absence of patent linkage, patent term extension and data and market exclusivity for NMPA-approved pharmaceutical products could increase the risk of early generic competition with Genor's products in China.

Appendix: Company Profile

Figure 91: Shareholder structure (after IPO allotment and issue of the over-allotment shares)



Source: Company data, CMBIS

Figure 92: Management profile

Name	Age	Date of Joining	Position	Roles and Responsibilities
Dr. ZHOU Joe Xin Hua (周新华博士)	67	14 Oct 2008	President and Chief Scientist	In charge of overall R&D strategy and execution, and business direction of the Company
Dr. GUO Feng (郭峰博士)	50	16 Apr 2020	CEO	In charge of overall management, business and strategy of the Company
Dr. HU Qiyong (胡琦勇博士)	46	2 Sep 2019	CFO and Chief Strategy Officer	Overall financial strategy and operations, financing, investor relations, overall strategic planning, business development and IT of the Company
Dr. KAN Steven Ziyi (阚子义博士)	58	1 Mar 2017	CTO	Manufacturing science and technology of drug products and quality control
Mr. CHEN Wende (陈文德先生)	57	7 Jul 2020	COO	Strategic planning and execution of the commercialization of Genor's drug candidates
Ms. LI Tung (李彤女士)	51	4 Aug 2020	CMO	Overall management of clincal trials and clinical development
Ms. CHENG Huiyang (程慧旸女士)	45	15 Nov 2010	VP, global strategy	Overall management of global commercial strategies
Mr. LIN Jun (林军)	35	1 Dec 2008	VP, quality analysis	CMC and quality analysis
Ms. CHEN Yao (陈瑶)	46	10 Jul 2019	VP, regulatory affairs	Overall management of drug registration affairs
Mr. DUAN Qingtang (段清堂)	38	8 Jul 2014	General Manager of Yuxi Genor	Overall supervision of Yuxi Genor manufacturing base

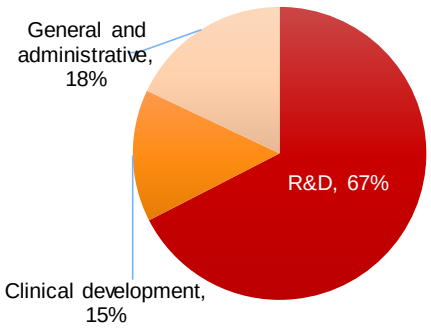
Source: Company data

Figure 93: Employee structure (as of 31 May 2020)

Function	# of staff	% of Total
Research and development	259	67%
Clinical development	56	15%
General and administrative	69	18%
Total	**384**	**100%**

Source: Company data

Figure 94: Employee number split (as of 31 May 2020)



Source: Company data

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