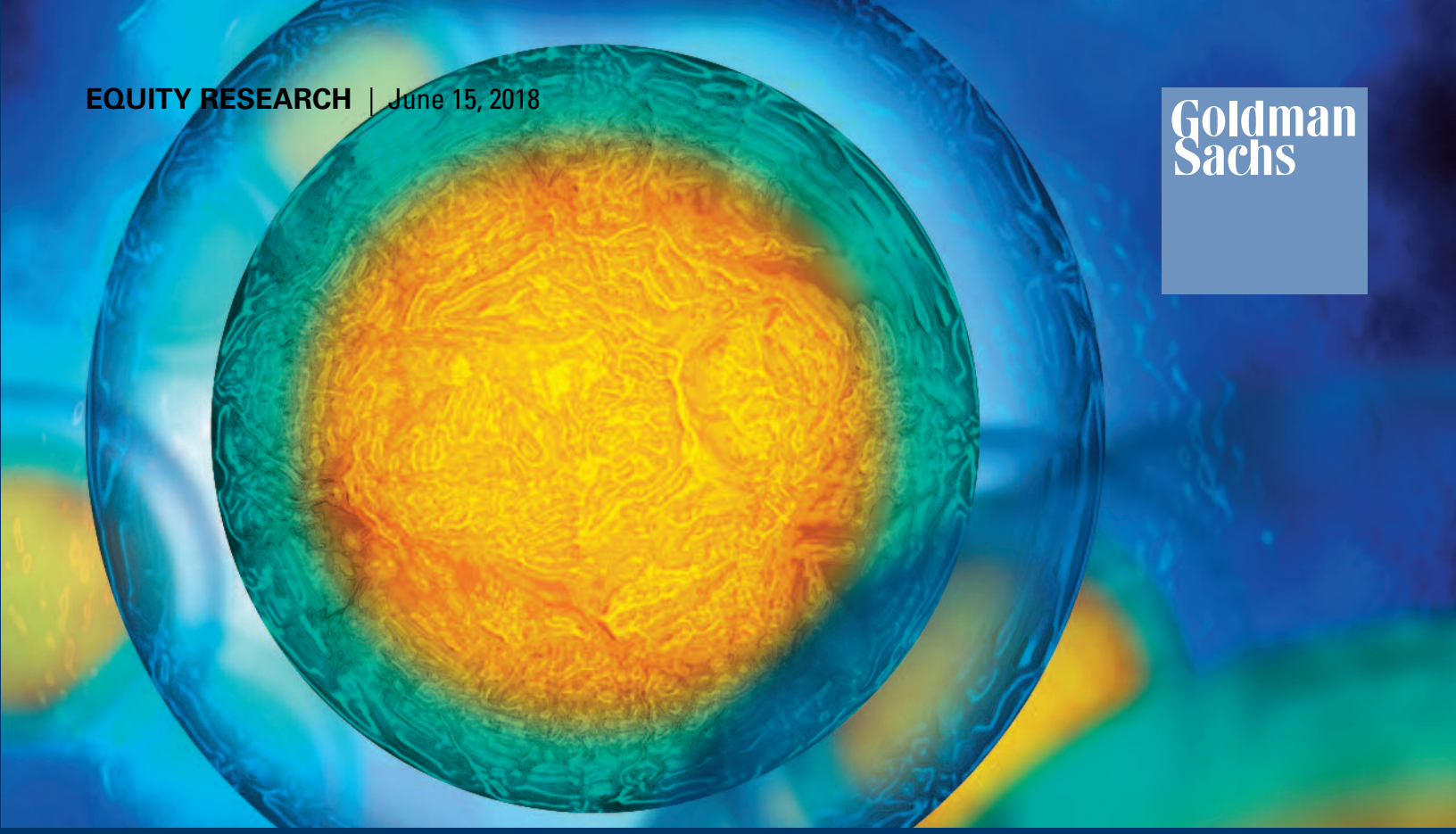
Goldman Sachs



China Biotech Primer

Guidebook for a new chapter of healthcare investment

China's biotech era has arrived – CFDA's transformative shift in favor of new drugs, significant capital in-flows, a highly specialized talent pool and a sizable Chinese pharma/biotech market in couple of the upcoming new biotech listings in the Hong Kong Stock Exchange are driving major new investment opportunities in the growing healthcare space. Investing in China's emerging biotech segment requires a hybrid of financial/ scientific expertise and in-depth understanding of China's healthcare system. To provide a roadmap to investors on the upcoming paradigm shift in the biotech industry, we publish the first edition of biotech primer, which features the following basic building blocks of the sector:

What's inside:

Richard Yeh
+852 2978-0526
richard.yeh@gs.com
Goldman Sachs (Asia) L.L.C.

Ziyi Chen
+86 21 2401-8928
ziyi.chen@ghsl.cn
Beijing Gao Hua Securities Company Limited

The Goldman Sachs Group, Inc.

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CHINA BIOTECH in numbers

What is the size of the market?

~Rmb35bn
Our estimate of China's medical biotech market, or biologics market, in 2017

c.5%
of Chinese hospital prescription chemical/biotech Rx drug sales

10.3%
2012-17 CAGR

15%-20%
CAGR expected over the next 3 years

Improving capital access – growing PE/VC investment

US$2.3bn
In 2017

<US$200mn
In 2013

Key drivers: accessibility and affordability

21
Number of monoclonal antibody (mAbs)/fusion proteins, i.e. the newer generation of biotech drugs approved by the CFDA in China by May 2018

vs <80
in the US

Risk management is critical

9.6%
Success rate for a candidate looking to go through phase I/II/III trials and obtain final regulatory approval

~70%
The highest failure rate (lowest pass rate) was at phase II, which is the "proof-of-concept" trial that tests the efficacy of the candidate, ~70% of the candidates fail to show statistically meaningful efficacy at their phase II trial.

Higher success rate for biologics

6%
Small-molecule drugs have the lowest success rate…

11%
…and the rate for biologics is almost twice as high

PM summary: All you need to know about China Biotech

- Diverging ROI to drive R&D shift from generics to novel therapies
  - Chinese innovators - improving R&D return with more efficient approval / reimbursement system
  - Chinese generic players - potential decline in ROI could drive consolidation

- What makes a biotech winner - R&D/commercial capability built on talent and capital

- MNCs in China: An evolving business model
  - China vs. global peers: Single-payer system with affordability as key hurdle
  - Fast follow-on R&D strategy: Adapt to pricing constraints in China
  - Growing global collaboration to accelerate global biotech asset convergence
  - Key drivers for biotech in China: Improving accessibility and affordability

- Risk management is critical when it comes to investing on biotech
  - Drug development is a probability game
  - Embedding risks of drug development into valuation

PM summary: All you need to know about China biotech

We envision that China's pharma/biotech landscape will reshape in the coming years. The risk-reward profile of pharma/biotech business and the drug R&D are likely to change given: 1) CFDA's seismic drives to build a more transparent and efficient drug approval system with global standards; 2) prescription mix shifts that are increasingly focusing on clinical benefits; and 3) the establishment of a more dynamic, pharmacoeconomic driven single-payer system. These changes will likely shift industry strategic focus from generics to novel drugs, driving consolidation in generic industry and emergence of innovative biotech companies, potentially providing significant economic returns on investment.

The history of the U.S. biotech industry suggested that despite R&D is a risky and costly business, financial returns from R&D have more than offset risks and costs. We expect the industry will undergo considerable changes on their operational model with: 1) increase in R&D costs; and 2) lower approval rate for new drug applications, i.e. higher R&D risks; 3) decrease in internal rate of return (IRR) on drug development. However, at company level, we expect growing divergence on R&D return, with leading companies that are capable of incorporating strong IP, global R&D standards and higher R&D productivity/entry barriers will lead to better returns on investment (ROI).

In our view, the Chinese healthcare sector is at the inflection point of shifting towards more structural transformation as the market is shifting away from generic products and public services that dominate the market, towards a higher quality product and services focused on and driven by R&D and innovation, new business models and advanced technologies. In a system where the industry structure is reshaping and healthcare value chain is shifting, we expect the profit pool will shift towards products and services that offer premium clinical benefits and pharmacoeconomic value, while MNCs and domestic biotech leaders focusing on optimized capital allocation and value creation by means of pipeline, in/out-licensing, M&A and global expansion will become the structural winners over the long term. In an increasingly competitive environment, we see two types of domestic companies to differentiate themselves from the crowd: 1) innovators with strong pipeline; 2) large scale cost players. We also see MNCs will shift away from brand generics and will focus more on innovative product portfolios.

We expect the development of the biotechnology industry a game changer that will potentially catalyze the innovation ranging from contract research, drug discovery to drug manufacturing in the Chinese market. While a significant number of the Chinese biotech companies are developing me too/me better products to mitigate the R&D risks, driving cancer and other therapeutic categories into more crowded space, we expect a gradual evolution of the R&D strategies into first-in-class in the future. Companies focusing on manufacturing quality, market access and direct to patient and digital channels will more likely differentiate themselves from the competition. In light of new industry dynamics and growing talent pool, we envision the likelihood more globally focused Chinese pharma/biotech players in the years to come.

We expect the ongoing healthcare reform will further address government's goal of balancing a healthcare system with a provision of affordable and equitable access and higher-end demand from a patient base that is more affluent. We remain concerned about the pricing and reimbursement pressure imposed by the single payer system that may limit the R&D return of the biotech drugs. We expect more rational design of the pricing mechanism under the new reimbursement infrastructure and more opening of the commercial medical insurance market to address these pricing and reimbursement concerns. We expect government policies can compensate rising hurdles for reimbursement on generic and innovative drugs, making the healthcare system more accessible and the biotech industry more sustainable.

The biotech primer explores the basic building blocks for understanding the biotech sector:

- **An overview of biotech market and biotech basics in China:** From characteristics of biologics, particularly monoclonal antibodies, to the R&D process in China, biologics manufacturing and commercialization, including market access and reimbursement.
- **A comprehensive manual on assessing preclinical/clinical trials:** How to understand the drug discovery and development process and how to read the data from preclinical/clinical studies of new therapies, focusing on oncology drugs.
- **Dissection of key disease categories:** Seven major cancer types in China with a dedicated section for cancer immunotherapies (I/O), autoimmune disorders, diabetes, age-related macular degeneration (AMD), central nervous system diseases, and hepatitis C. In each section, we cover disease demographics, the treatment paradigm in China and a detailed analysis of the key pipeline candidates on the horizon.
- **An appendix on pipeline, valuation and glossary**: The appendix of this primer includes: 1) a comprehensive pipeline by therapeutic areas/drug targets and by listed companies in China; 2) a valuation matrix for biotech companies; and 3) a glossary to help readers navigate through the technical terms in this report.

The authors would like to thank Shuyuan Gong and Jian Gong for their contributions to this report

Diverging ROI to drive R&D shift from generics to novel therapies

Chinese innovators - improving R&D return with more efficient approval / reimbursement system

The innovation in pharma/biotech in China has historically been hindered by a slow drug approval process, inadequate reimbursement coverage to maximize commercial value, and manufacturing barriers that did not incentivize the start-ups/research institutions needed to invest in drug discovery.

The CFDA reform since 2H15 and new NRDL are addressing the issue:

1) a more efficient and transparent drug approval procedure for novel therapies, particularly the potential shorter time for granting approval for clinical trials and the establishment of an accelerated review system in China (e.g., priority review, conditional approval); and

2) expansion of the National Reimbursement Drug List (NRDL) in 2017 to provide reimbursement coverage for higher-priced advanced therapies (e.g., monoclonal antibodies), and the government targets to review the list every two years to provide more timely reimbursement coverage for newly launched drugs. 3) China's joining of the International Council for Harmonisation (ICH) – a global regulatory agency established in 1990 by the US, EU and Japanese governments to standardize an efficient drug development process – will make it possible for data from clinical trials that are conducted outside of China to be cross-recognized domestically (in the past, the CFDA did not recognize such data).

We believe China's joining of the ICH will significantly reduce the cost of clinical development and expedite the market entry timelines for MNCs and domestic products. We expect the move will also drive CFDA adoption of global clinical development standards and result in China becoming one of the first global markets for innovative drugs. The move should also help domestic companies compete globally on clinical trials and products.

Chinese generic players - potential decline in ROI could drive consolidation

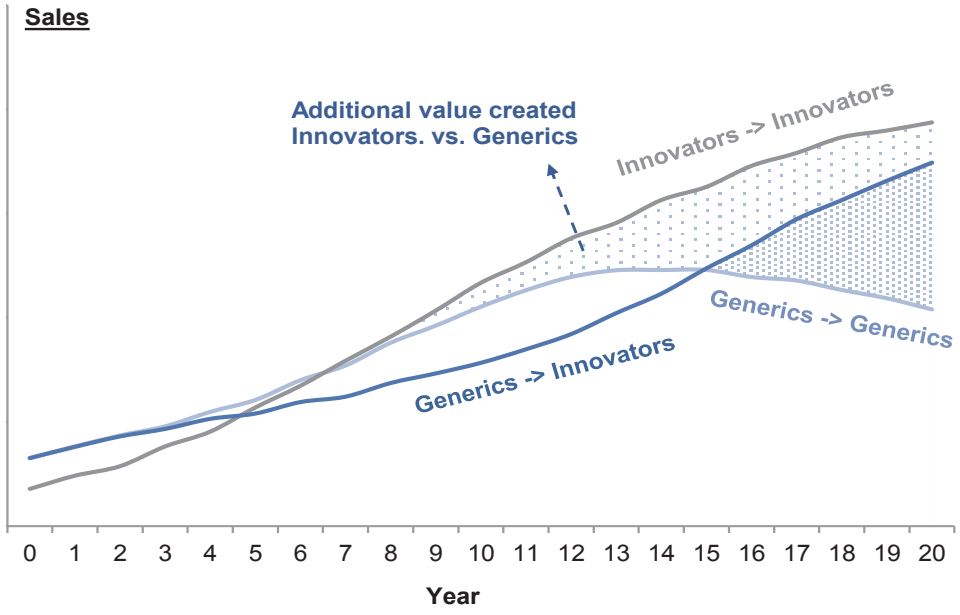
We expect declining investment return for generics players, given: 1) substantially higher R&D costs of developing formulations and the mandatory bioequivalence studies (cost of over Rmb10-20mn per drug, with a pass rate of 40%-50%, vs. costs as low as Rmb3 mn-Rmb4 mn previously); and 2) the norm of price erosion.

The overall generics market is likely to consolidate over the coming years, driving out smaller/substandard players. Only generic leaders with: 1) the balance sheet strength needed to afford the increasing R&D cost for generics; 2) diversified product portfolios to mitigate the risk of price erosion on individual drugs; and 3) established commercial infrastructure to compete with MNCs in channels to maintain or gain market share, are likely to eventually survive the business with thinner margins.

To illustrate the value of investing in R&D, we performed several detailed R&D analyses and conducted a study to simulate the effects of pharma/biotech companies investing (or not investing) in innovation via R&D. We did this by creating a hypothetical company

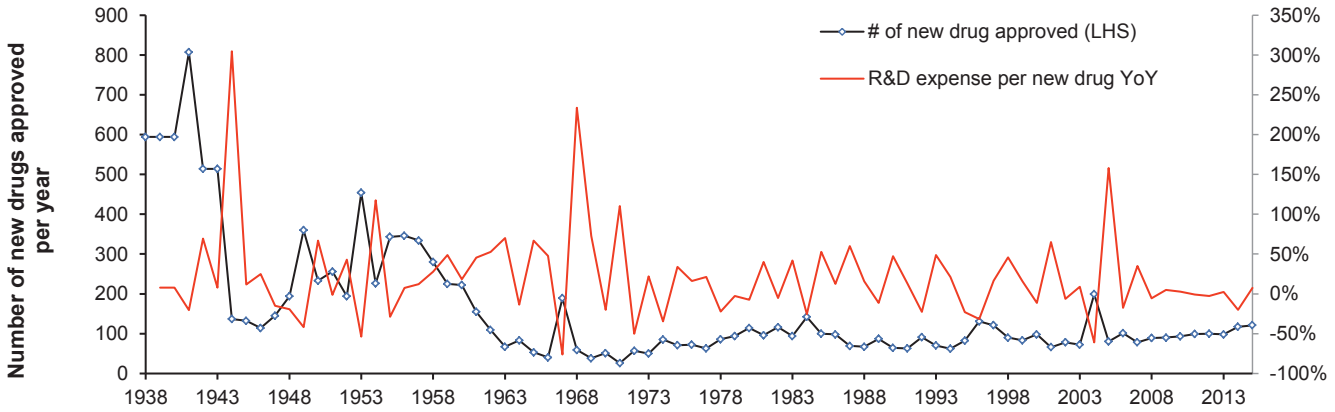
built on historical data from over 100 drugs marketed in China (generics and novel drugs), and we tested this hypothetical company across three scenarios: 1) purely focusing on generics; 2) focusing on innovative drugs; and 3) transitioning from a generic player to an innovator. Our simulation study suggests **innovation is key to defining the future return for the pharma players**.

Exhibit 1: The value of innovation
Simulation of revenue projection for a hypothetical company: innovator, generic company and transformer



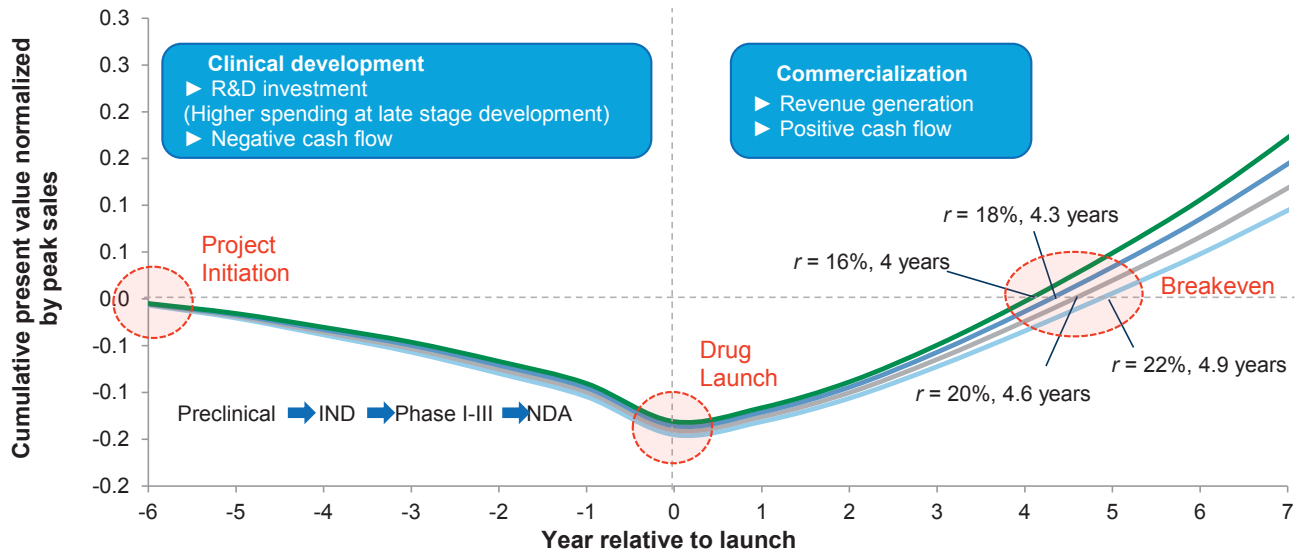
Source: PDB database, Goldman Sachs Global Investment Research

Exhibit 2: Number of new drugs approved by the FDA and R&D expenses per new drug y/y



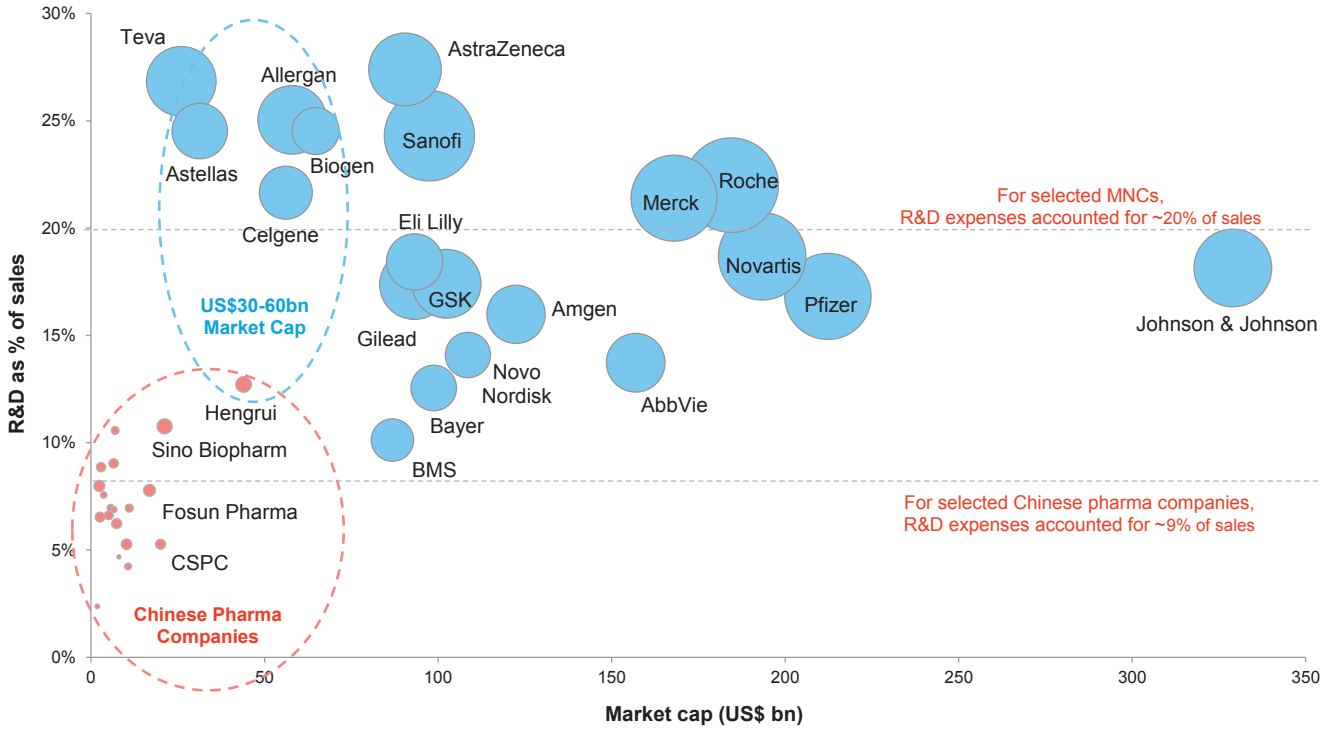
Source: FDA, Goldman Sachs Global Investment Research

Exhibit 3: Expected breakeven timeline for novel drugs in China with risk-adjusted probability discount (r is the discount rate)



Source: Goldman Sachs Global Investment Research

Exhibit 4: Chinese pharma companies chasing MNCs on market cap, but still behind on R&D expenses
Market cap, R&D as % of sales, and R&D expenses (bubble size) of major MNCs and Chinese pharma companies



Source: bloomberg, PharmExec

What makes a biotech winner - R&D/commercial capability built on talent and capital

We believe the success of a biotech company is built on four major pillars:

- **Pipeline of drug candidates** - assessed by depth and breadth of the drug discovery platform and pipeline (i.e., how thorough a specific area and how many modalities/therapeutic areas have been covered), originality (new mechanisms of action, new targets, new formulation technology, biosimilar, or chemical generics), market potential (i.e., total addressable market or patient base) and competitive landscape.
- **Clinical development capability** - assessed by the clinical team's size and experience/track record in the specific therapeutic area or drug target. Clinical development could be the bottleneck for most of the R&D-stage companies in China. Though clinical CROs, e.g. Tigermed, could facilitate the process and help connect the drug developer to rare clinical development resources in China (i.e., principal investigators and qualified clinical trial sites), a biotech company's understanding of clinical development is irreplaceable and crucial to the success rate of the project.
- **Manufacturing capability** - lower hurdle for chemical drugs but a substantially higher hurdle for biologics. There are few biotech companies or even CMOs (contract manufacturing organizations) in China with the experience of manufacturing large-molecule therapeutic proteins (e.g., monoclonal antibodies) locally in commercial batches, thus posing potential risks in quality assurance.
- **Commercial infrastructure -** marketing a novel drug in China involves a complicated market access process, including passing provincial drug tenders, listing in individual hospitals' formulary (mainstream channel), connecting to specialty retail channels (e.g. Direct-to-Patient/DTP pharmacies) for patient penetration at the initial stage of product launch before obtaining access to hospital channels, listing in provincial/national reimbursement list and extensive patient/physician education, all of which need to be managed by an established sales force and commercial team. The commercial infrastructure could be assessed by the size and structure of the team and the experience of key sales/marketing management.

The build-up of the capability in drug discovery, clinical development, manufacturing and commercialization relies on the access to talent pool and capital:

- **Established talent pool:** Biotech talent pool is ideally a mix of global insights/track record and local market practice. For the emerging biotech segment in China, backflow of talents trained at big pharma/biotech companies in the EU and the US for 10-20 years, particularly top executives/scientists, is the key enabler.
- **Improving access to capital:** 1) HKEx listing rule changes for pre-revenue biotech companies, the CSRC's new fast-track approval for listing high-tech "unicorns"; 2) growing PE/VC investment in biotech (US$2.3 bn in 2017 vs. <US$200 mn in 2013).

MNCs in China: An evolving business model

Branded generics (off-patent originator drugs) represent a core revenue/profit contributor for multinational pharma companies (MNCs) in China, due to: 1) the notable pricing premium over domestic generics, which can be priced at 30%-60% of the price of MNCs' products, as a result of the government's favorable pricing policy for MNCs in the past two decades (e.g., separate tier in drug tenders to minimize price competition); 2) brand recognition among physicians/patients due to superior quality; and 3) slow progress in introducing most advanced therapies into China, given the lengthy and complicated approval process, including specific clinical trials on Chinese patients.

However, we believe MNCs are likely to see two major changes that could alter their operations in China, the world's second-largest market:

- **Strategic focus shifts to patented drugs:** With the government's initiative to upgrade the quality of Chinese generic drugs paving the way for a narrowing of the price gap between MNC's off-patent drugs and cheaper domestic alternatives, the return from those assets is likely to decline. However, what's more important is that the CFDA's opening-up to accept overseas clinical trial data for local registration of imported drugs, together with the initial establishment of fast-track pathways for therapies aimed at unmet medical needs, could result in patented novel drugs becoming the new focus of MNC operations in China, driving a strategy realignment among MNCs, e.g. off-loading non-core China assets to local partners to focus more on their core novel therapy portfolios (e.g., AstraZeneca sold China rights of Plendil to CMS, GLP-1 portfolio to 3SBio and Seroquel/Seroquel XR to Luye Pharma).
- **Talent attrition a potential challenge:** In contrast to the ongoing strategy shift for more established MNCs, biotech start-ups in China with improved access to capital are offering potentially more attractive career opportunities for sales and R&D talent trained at MNCs, including more flexibility in operation, more responsibilities in bigger roles, career development upside and compensation, which could be highly competitive with stock option/restricted shares incentive schemes. We have observed the trend of seasoned talent transitioning from prestigious MNCs to domestic biotech leaders in the past year, from junior-level sales people to middle management and senior executives.

China vs. global peers: Single-payer system with affordability as key hurdle

China's healthcare system is built on a single-payer structure, i.e. a government-run medical insurance fund that covers over 90% of the Chinese population as the key payer in the system, while commercial health insurance remains insignificant. Though the government has initiated several trials in past years aimed at opening up the medical insurance system to commercial insurers, progress has been gradual.

Exhibit 5: China vs. US and Asian peers: healthcare system and biotech/pharma growth path

	China	United States	Japan	South Korea	India
Health indicators					
NHE as % of GDP	6.2%	16.8%	10.9%	7.4%	3.9%
Per capita health spending (US$)	425.6	9535.9	3732.6	2012.7	63.3
OOP as % NHE	32.4%	11.1%	13.1%	36.8%	65.1%
Population (million)	1,390	326	127	51	1,343
Population aged 65+ year (%)	10.12%	15.03%	26.56%	9.65%	5.81%
**: NHE - National Health Expenditure; OPP - out-of-pocket spending*					
Payer system					
Payer system	Single-payer (three major insurance schemes potentially to merge)	Pluralistic system, multiple-payer	Employees' health insurance + National Health insurance	Single-payer (National Health Insurance Service since 2004)	Single-payer
Government's involvement	High	Low	Medium	Medium	High
Financing	Employer / employee (payroll contribution, general tax), voluntary contribution from non-employees	General taxes, premiums	Premium shared by employer / employee, general tax	Premium shared by employer / employee, general tax	Premium shared by employer / employee, general tax
Major reimbursement model	Mixed with various pilot models - global budgeting, preliminary DRGs, fee-for-servce / drug, capitation	Various - DRGs, negotiated fee-for-service, per diem, capitation	Per diem payments	Per diem payments	Per diem payments
Biotech / Pharma growth paths					
Geographic focus					
- Current	Domestic market	Domestic + overseas	Domestic + overseas	Overseas	Overseas
- Next phase	Domestic + overseas	Domestic + overseas	Overseas	Overseas	Overseas
Modality focus					
- Current	Generics	Novel therapies	Novel therapies	Biosimilars	Generics
- Next phase	Mixed innovation - me-better (or biobetter) & best-in-class therapeutics, biosimilars	Novel therapies	Novel therapies, biosimilars (guideline issued in 2009)	Biosimilars	Specialty drugs

Source: WHO, United Nations, Goldman Sachs Global Investment Research

Compared with the US and other Asian markets (Japan, South Korea and India), two major elements define the key hurdles for biotech products' commercialization in China's pharma/biotech market:

- **Public hospitals as dominant channel**: Over 90% of patient flow is captured by public hospitals, which is the major channel for dispensing prescription drugs in China. More importantly, drugs used to be the key sales/profit contributor to hospitals and the source for rebates to physicians in China, given the artificially lower service fees and physicians' compensation, but the recent hospital reform policies, e.g. "zero drug mark-up" and "control on drug sales to hospital revenue ratio" (<30%, vs. used to be over 50%), have led to a decline in supportive medicines or therapies without clear clinical benefits.
- **Medical insurance funding defines growth**: The growth of drug consumption at hospitals was largely capped by the growth of medical insurance funds' annual budgets, which is a function of fund inflows from contributors (i.e. employers/employees' payroll, general tax and unemployed residents' individual contribution).
- **Upcoming power consolidation as milestone**: With the setup of a new Bureau of Health Insurance, which could potentially consolidate the supervision responsibility of three medical insurance schemes to form a uniform national healthcare insurance system, the single payer's bargaining power is likely to be strengthened and could play a key role in addressing the affordability of medical products/services in China.

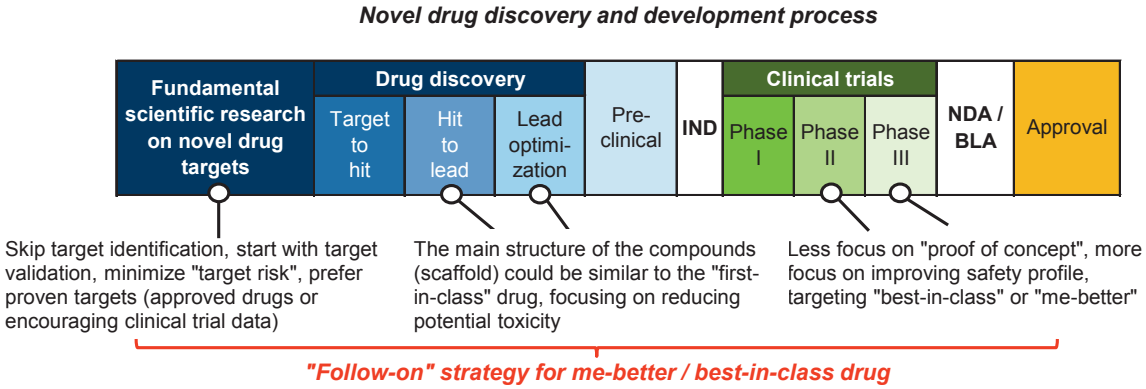
As the result of a single-payer system with constraints on expanding the medical insurance fund size and the slow opening-up to commercial insurance, the Chinese government is putting stringent controls on medical costs. Over the next two to three years, the ramp-up of new drugs/therapies that offer clinical benefits to patients will be at the expense of lower-quality/unnecessary medicines, driving prescription mix shift. However, over the longer term, we see the establishment of a more diversified payer system as inevitable to facilitate the emergence of an affordable and accessible biotech market.

Fast follow-on R&D strategy: Adapt to pricing constraints in China

Considering: 1) the pricing constraints in China given the affordability hurdle; and 2) the lack of experience in drug discovery and clinical development in China for most biotech start-ups, managing development risks and costs is critical in securing a reasonable return on R&D investment in China, leading to the wide adoption of a fast follow-on R&D strategy among pharma/biotech companies.

In a fast follow-on strategy, companies minimize the efforts on the most risky step in drug discovery, i.e. identifying a novel drug target, and only screen for druggable molecules against targets that have been proven by global leaders. The drugs developed using this strategy could be "me-too" drugs (i.e., drugs acting against the same target as first-in-class drugs, with a similar efficacy/safety profile), "me-better" drugs (superior efficacy/safety), or potentially "best-in-class (BIC)" drugs.

Exhibit 6: Fast follow-on drug R&D strategy in China

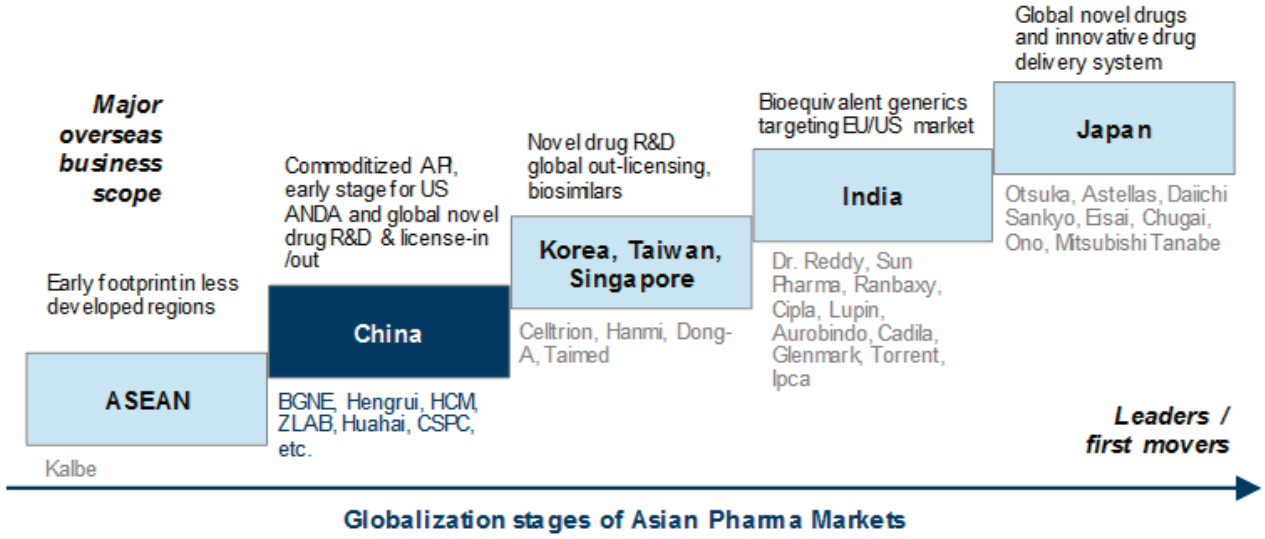


Source: Goldman Sachs Global Investment Research

Growing global collaboration to accelerate global biotech asset convergence

Chinese pharma/biotech players in general are still in the early stages of expanding into overseas markets, with exports of pharmaceutical products mainly consisting of commoditized APIs and generics. Nevertheless, leading pharma companies in the market (e.g. Hengrui, CSPC) and biotech start-ups (e.g., BeiGene) with global insights have incorporated overseas expansion as an essential part of the next-decade business development strategy, and they are following various paths to increasing their global footprints. The increasing number of deals in cross-border M&A, license-in/out and co-development between Chinese biotech players and overseas partners is leading to the convergence of global biotech assets. For investors looking to gain exposure to China's emerging biotech sector, assessing companies requires knowledge about the global competitive landscape and drug development trends, and not just an understanding of the China market in isolation.

Exhibit 7: Chinese pharma/biotech at early stage of globalization
China vs. Asian peers in globalization stages



Source: Goldman Sachs Global Investment Research

We consider a global strategy as increasingly important for Chinese biotech players, as the strategy, if well planned and executed, could create significant value for their biotech franchise:

- **Maximize the commercial value of novel drugs developed:** Given the affordability hurdle in the home market that may cap the overall return on new drugs developed and slow the sales ramp-up trajectory, generating additional revenue stream in overseas markets could potentially boost returns, though a feasible commercial model (e.g., self-built sales force, sales/marketing partnership, license out or leveraging local CSO) must be selected with caution to match the operating capability of the biotech company.
- **Access to the high-quality global assets**: We see business development (BD) capability as critical for Chinese biotech companies in supplementing in-house R&D, which could be a multiple-year process, to build in-depth pipeline, and increasing exposure to the global biotech market could bring new opportunities in acquiring high-quality biotech assets.
- **Gain insight into frontiers in science**: As part of the global strategy, some leaders in China are setting up venture capital funds to invest in advanced fundamental research or early target identification in the biotech space to gain the most up-to-date insights into the latest trends in drug development.

Exhibit 8: Select in-/out-licensing deals on novel drug candidates

Date	Company	Candidates	MoA	Rights	Partners	Upfront	Milestones	Royalties
Out-licensing								
Mar, 2007	Chipscreen	Chidamide (HBI-8000)	HDACI	ex-China	HUYA	Not disclosed	Not disclosed	Not disclosed
Dec, 2011	HCM	HMPL-504	c-MET	ex-China	AstraZeneca	US$20mn	US$120mn	Double-digit
May, 2013	BeiGene	Lifirafenib (BGB-283)*	RAF	ex-China	Merck	Not disclosed	US$233mn	Double-digit
Oct, 2013	HCM	Fruquintinib (HMPL-013)	VEGFR	Global	Eli Lilly	US$86.5mn		Mid-teen
Nov, 2013	BeiGene	Pamiparib (BGB-290)	PARP	ex-China	Merck	Not disclosed	US$232mn	Not disclosed
Mar, 2015	Innovent	CD20 mAb, PD-1	CD20 PD1	ex-China	Eli Lilly	(1) US$56mn (2) cMET right in China	US$400mn	Not disclosed
Sept, 2015	Hengrui	SHR-1210*	PD-1	ex-Greater China	Incyte	US$25mn	US$770mn	Not disclosed
Oct, 2015	Innovent	3 Bispecific mAbs	-	ex-China	Eli Lilly	Not disclosed	US$1bn+	Not disclosed
Dec, 2015	Akesobio	AK-107	I/O	Global	Merck	Not disclosed	US$200mn	Not disclosed
Jan, 2016	Sino Biopharm	TLR7 agonist	TLR7	ex-China	JnJ	US$253mn		Not disclosed
Mar, 2016	Fudan University	IDO inhibitor	IDO	ex-Greater China	HUYA	Not disclosed	US$65mn	Not disclosed
July, 2017	BeiGene	Tislelizumab (BGB-A317)	PD-1	ex-Asia+Japan, solid tumor	Celgene	(1) US$413mn: US$263mn license fee + US$150mn equity investment (2) Celgene's China operation + exclusive license to Abraxane, Revlimid, and Vidaza	US$980mn	Not disclosed
Aug, 2017	Gloria / Wuxi Biologics	GLS-010	PD-1	North America, EU, Japan	Arcus	US$18.5mn	US$797.5mn	Not disclosed
Dec, 2017	Genscript	LCAR-B38M	CART	Global	JnJ	US$350mn	Not disclosed	Genscript / JnJ split at 50/50 ex-Greater China; 70/30 in Greater China
Jan, 2018	Hengrui	SHR-0302	JAK1	US/EU/Japan, skin diseases	Acrutis	US$2mn	US$220.5mn	Not disclosed
Jan, 2018	Hengrui	SHR-1459 & SHR-1266	BTK	ex-Asia	TG Therapeutics	US$1mn	US$346.2mn	10%-12%
In-lisensing								
Sept, 2013	CANbridge	ATI-1123	-	China, North Asia	Azaya Therapeutics	Not disclosed	Not disclosed	Not disclosed
Mar, 2015	Zai Lab	ZL-2301 (Brivanib)	VEGFR / FGFR	China, HK, Macau	BMS	Not disclosed	Not disclosed	Not disclosed
July, 2015	Zai Lab	ZL-2302	ALK	Global	Sanofi	Not disclosed	Not disclosed	Not disclosed
July, 2015	CANbridge	APG101	CD95	China, HK, Macau	Apogenix	Not disclosed	Not disclosed	Double-digit
Sept, 2015	Zai Lab	ZL-1101	OX40	Global	UCB	Not disclosed	Not disclosed	Not disclosed
Nov, 2015	Zai Lab	HM61713	EGFR	China	Hanmi	Not disclosed	Not disclosed	Not disclosed
Mar, 2016	CANbridge	AV-203	HER3	China, North Asia	AVEO	US$1mn	US$133mn	Not disclosed
Sept, 2016	Zai Lab	ZL-2306 (Niraparib)	PARP	China, HK, Macau	Tesaro	US$10.9mn	Not disclosed	Not disclosed
Oct, 2016	Zai Lab	ZL-3101 (Fugan)	Eczema	Global	GSK	Not disclosed	Not disclosed	Not disclosed
Apr, 2017	Zai Lab	ZL-2401 (Omadacycline)	-	China, HK, Macau	Paratek	US$7.5mn	Not disclosed	Not disclosed
Dec, 2017	Zai Lab	FPA144 (Bemarituzumab)	FGFR2b	China, HK, Macau	Five Prime Therapeutics	US$5mn	US$39mn	High-teens to low twenties
Feb, 2018	CANbridge	Neratinib	HER3	Greater China	Puma	Not disclosed	Not disclosed	Not disclosed
Apr, 2018	Zai Lab	ETX2514SUL	β-lactamases	Asia Pacific	Entasis Therapeutics	US$5mn	US$98.6mn	Not disclosed
June, 2018	Cstone	Avapritinib; BLU-554; BLU-667	KIT, PDGFRα; FGFR4; RET	Greater China	Blueprint	US$40mn	US$346mn	Mid-teens to low twenties

Greater China: Mainland China, Hong Kong, Macau and Taiwan
**: Hengrui-Incyte deal has been terminated; BeiGene-Merck agreement on BGB-283 has been revised: Merck holds minor rights to BGB-283*

Source: Company data

Exhibit 9: Summary of select drugs in late-stage clinical trials in China

	Candidates	Dose form	Brand	Status	MoA	Indication	Company
	Oncology						
	Dacomitinib	Tablets	-	NDA	irreversible EGFR TKI	NSCLC	Pfizer
	Enzalutamide	Capsules	Xtandi	NDA	AR (antiantrogen)	mCRPC	Astellas
	Lanreotide	Injection	Somatuline Depot	NDA	Somatostatin analog	GEP-NETs	Ipsen
	Utidelone (UTD1)	Injection	-	NDA	Epothilone analog	2L mBC	Beijing Biostart Tech
	Alectinib	Capsules	Alecensa	NDA	ALK, RET	ALK+ NSCLC	Roche/Chugai
	Para-Toluenesulfonamide (PTS)	Injection	-	NDA	-	Primary central airway NSCLC	Chasesun Pharma
	Eribulin	Injection	Halaven	NDA	Halichondrin class - mitotic inhibitor	mBC	Eisai
	Bendamustine	Injection	Treanda / Levact	NDA	Nitrogen mustard	CLL, MM, NHL	TEVA
B	Camrelizumab	Injection	-	NDA	PD-1	cHL	Hengrui
B	IBI308	Injection	-	NDA	PD-1	cHL	Innovent
B	JS001	Injection	-	NDA	PD-1	Melanoma	Junshi Bio
B	Nivolumab	Injection	Opdivo	NDA	PD-1	NSCLC	BMS
B	Pembrolizumab	Injection	Keytruda	NDA	PD-1	Melanoma	Merck/MSD
B	Pertuzumab	Injection	Perjeta	NDA	HER2	HER2+ breast cancer	Roche
B	Rituximab (Rituxan biosimilar)	Injection	-	NDA	CD20	NHL	Henlius
B	Rasburicase	Injection	Eliteck	NDA	Urate-oxidase enzyme	Tumor lysis syndrome (TLS)	Sanofi
	Diabetes						
B	Insulin degludec / aspart	Injection	Ryzodeg	NDA	Insulin analog	Type 2 diabetes	Novo Nordisk
B	Insulin aspart	Injection	-	NDA	Insulin analog	Type 2 diabetes	United Labs
B	Insulin aspart 30 premix	Injection	-	NDA	Insulin analog	Type 2 diabetes	United Labs
B	Insulin glargine	Injection	-	NDA	Insulin analog	Type 2 diabetes	Tonghua Dongbao
B	Insulin aspart 30 premix	Injection	-	NDA	Insulin analog	Type 2 diabetes	Gan & Lee
	CNS						
	Bupropion HCl	ER tablets	Wellbutrin XL	NDA	SLC6A2	Depression	GSK
	Atomoxetine	Oral solution	Strattera	NDA	5-HT,SLC6A2	Attention deficit hyperactivity disorder	Eli Lilly
	Respiratory						
	Tiotropium Bromide/Olodaterol	Inhalation	Stiolto Respimat	NDA	Anticholinergic brochodilator / ultra-LABA	COPD	Boehringer Ingelheim
	Fluticasone / Vilanterol	Inhalation	Breo Ellipta	NDA	Corticosteroid / ultra-LABA	COPD, asthma	GSK
	Cardiovascular						
B	Evolocumab	Injection	Repatha	NDA	PCSK9	Dyslipidemia	Amgen
B	rhM-tPA	Injection	Yi Zhen Tong	NDA	tissue plasminogen activator (tPA)	Stroke	TPB Pharma
	Autoimmune						
	Benvitimod	Cream	-	NDA	AhR angonist	Psriosis	Grandhope / Beijing Wenfeng
B	Certolizumab pegol	Injection	Cimzia	NDA	anti-TNF-α	Rheumatoid arthritis	UCB Pharma
	Bone and muscle						
	Eldecalcitol	Soft capsules	Edirol	NDA	Vitamin D3 derivative	Osteoporosis	Chugai
B	Teriparatide (Foteo biosimilar)	Injection	-	NDA	Parathyroid hormone	Osteoporosis	Suzhou Genemen
	Others						
	Roxadustat	Capsules	-	NDA	HIF prolyl-hydroxylase inhibitor (HIF-PHI)	Renal anemia	Fibrogen
	Edoxaban	Tablets	Savaysa / Lixiana	NDA	Factor X	Venous thromboembolisms	Daiichi Sankyo
	Sofosbuvir / Ledipasvir	Tablets	Harvoni	NDA	NS5B / NS5A	Hepatitis C (genotype 1, 4, 5, 6)	Gilead
	Posaconazole	Enteric tablet	Noxafil	NDA	Triazole class	Invasive fungal infection	Merck/MSD
	Ceftaroline fosamil	Injection	Teflaro / Zinforo	NDA	5th-genetration cephalosporin	Skin infection	AstraZeneca
	Nemonoxacin	Injection	Taigexyn	NDA	Non-fluorinated quinolone	Community acquired pneumonia	Zhejiang Medicine / Taigen
	Remimazolam	Injection	-	NDA	GABA(A) receptor agonist	Pain management	Hengrui

EGFR: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; NCSLC: non small cell lung cancer; mCRPC: metastaic castration-resistant prostate cancer
GEP-NETs: gastro-entero-pancreatic neuroendocrine tumors; mBC: metastatic breast cancer; CLL: chronic lymphocytic leukemia; MM: multiple myeloma
NHL: non-Hodgkin's lymphoma; cHL: classic Hodgkin's lymphoma; COPD: chronic obstructive pulmonary disease; P-CABs: Potassium-competitive acid blocker
B Biologics

Source: Insight database

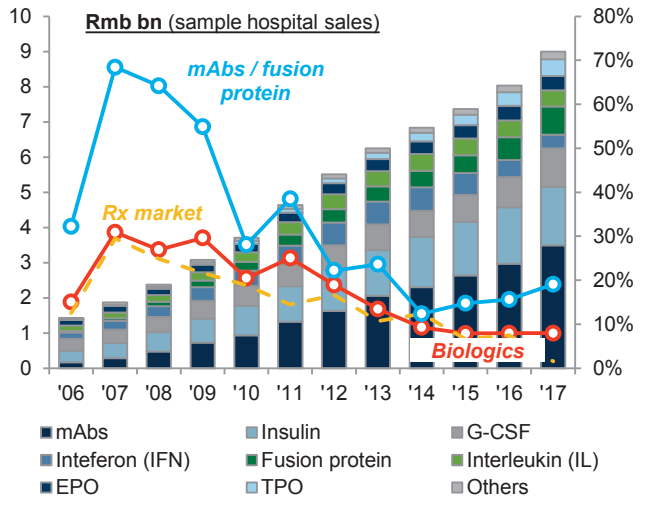
Key drivers for biotech in China: Improving accessibility and affordability

We estimate China's medical biotech market, or biologics market, was worth ~Rmb30-40 bn in 2017, accounting for ~5% of Chinese hospital prescription chemical/biotech drug sales (biologics contributed over 25% of global pharma revenue in 2017).

We expect the emergence of biotech drugs in China to be driven by improvements on two major fronts:

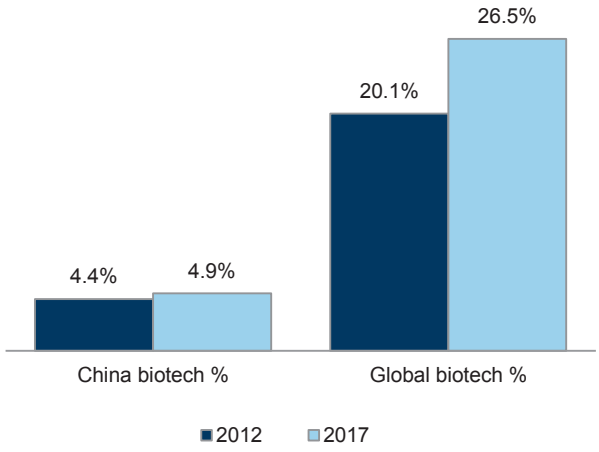
- **Accessibility:** By May 2018, only 21 monoclonal antibody (mAbs)/fusion proteins, i.e. the newer generation of biotech drugs, had been approved by the CFDA in China (vs. more than 80 in the US). In fact, it used to take 5-7 years for a new therapy approved in the US to obtain access to the Chinese market. We believe the issue of accessibility is being addressed by the CFDA's initiatives to: 1) further open up the market to new global therapies (e.g., recognizing overseas clinical trial data vs. previously mandating China-specific trials); and 2) prioritize and accelerate the approval of new therapies.
- **Affordability.** Without reimbursement, the affordability issue is the key hurdle to driving higher penetration of biotech drugs in the eligible patient base. We expect the affordability of higher-priced biotech therapies in China to improve this year, due to:
  - **Reimbursement coverage for new drugs:** In 2017, a total of 9 mAbs and fusion proteins were included in the NRDL for the first time. More importantly, the government guided that the NRDL will be revised every two years (vs. 5-7 years previously), potentially resulting in more timely reimbursement coverage for upcoming new therapies.
  - **Prescription mix shift based on clinical outcomes:** Overall medical insurance fund growth is under stringent control, but the government's initiatives aimed at cutting spending on drugs that lack solid evidence of clinical benefits (e.g., traditional Chinese medicine (TCM) injections) could make room for medical insurance spending on novel therapies.
  - **Growing adoption of pharmacoeconomics:** Government agencies running the medical insurance system in China have begun to recognize the value of pharmacoeconomics in assessing the cost-benefits of new therapies.
  - **Upcoming product cycle of biosimilars:** Biosimilars developed by Chinese companies are potentially cheaper alternatives to originator biologics manufactured by MNCs. The biosimilar pathway was established in March 2015, and the first biosimilar (likely Fosun Henlius' biosimilar Rituxan given that it was the first NDA-filed biosimilar) could obtain CFDA approval in late 2018, followed by more in 2019/2020 (over 150 biosimilar candidates are at different stages of clinical development).
  - **Increasing income level:** The average disposable income of residents was Rmb25,974 in 2017 (or US$4,120), up 57% from 2012.

Exhibit 10: Chinese biologics market growth, 2006-2017
Sample hospital sales data of Chinese biologics



Source: PDB database

Exhibit 11: Biotech accounts for only 5% of the Chinese pharma market
Biotech as a % of total pharma market: China vs. global



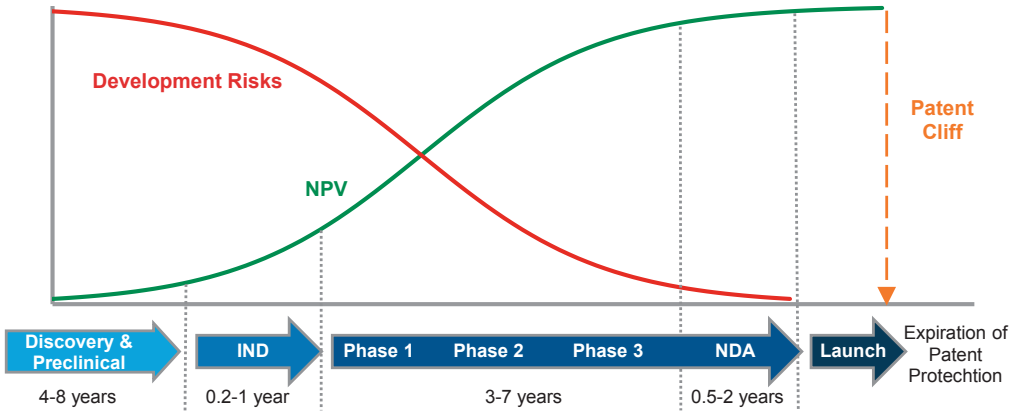
Source: PDB database, EvaluatePharma

Risk management is critical when it comes to investing on biotech

Drug development is a probability game

Drug development has a high rate of failure. While a "normalized" success rate for drug development is not available in China, we believe the success rate for novel therapies in the US is indicative for assessing the risk for drug R&D in China in the coming decade, since China joined the ICH in 2017 and has been catching up with US/EU standards in clinical trials and drug approval.

Exhibit 12: Development risks vs. NPV profile of a drug throughout product life cycle

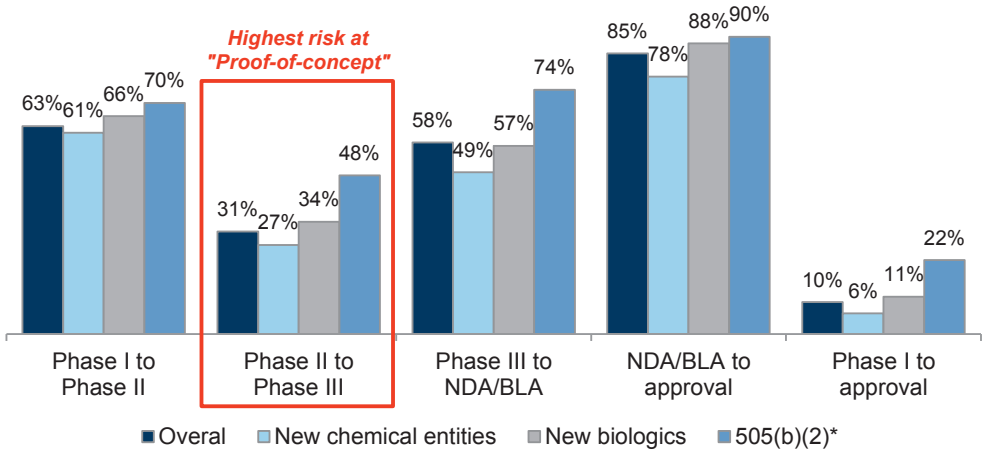


Source: Goldman Sachs Global Investment Research

In general, the later the development stage, the higher the success rate for a drug candidate. The Biotechnology Innovation Organization's success rate data for 2006-2015 suggests the following:

- **Overall <10% success rate:** The success rate for a candidate looking to go through phase I/II/III trials and obtain final regulatory approval was 9.6%.
- **Highest risk at "proof-of-concept":** The highest failure rate (lowest pass rate) was at phase II, which is the "proof-of-concept" trial that tests the efficacy of the candidate, as ~70% of the candidates failed to show statistically meaningful efficacy at their phase II trial.

Exhibit 13: Less than 10% success rate for pre-clinical candidates
Clinical development success rate based on FDA 2006-2015 data



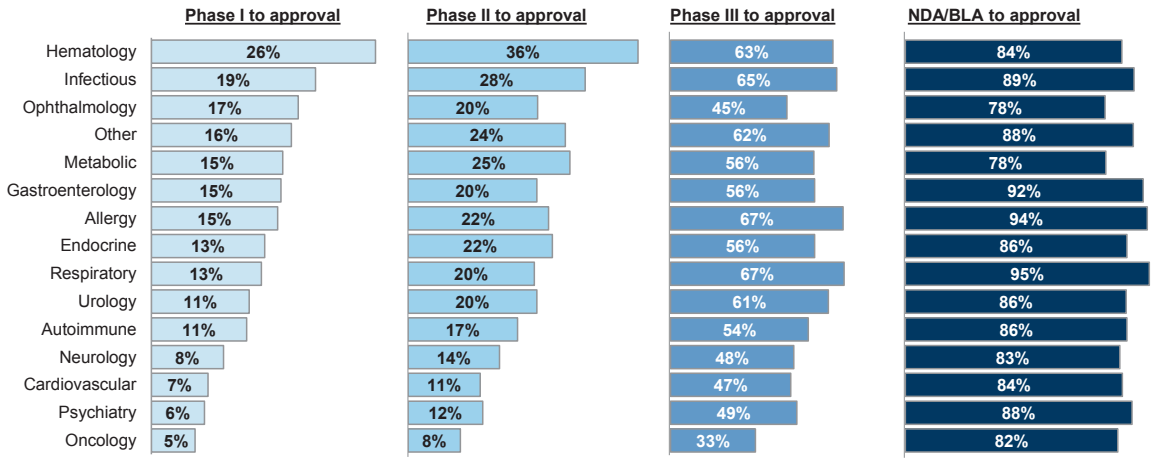
**505(b)(2) is the US FDA pathway for FDA approved molecules in new formulations*

Source: Clinical Development Success Rates 2006-2015 (BIO)

- **Potential higher success rate for biologics:** Comparing new molecular entity (NME, mostly small-molecule drugs in this study), biologics and drugs with innovative formulations that went through FDA's 505(b)(2) pathway, the success rate for small-molecule drugs is the lowest (6% from phase I to approval), but better than for biologics (11%).
- **Toughest for developing oncology drugs:** The success rate also varies notably among different therapeutic categories, and the success rate for developing a hematology drug (e.g., hemophilia) could be five times higher than developing an oncology drug (only 5.1%).

It is worth noting that the number of new drug applications (NDAs) turned down by the CFDA hit a record high in 2017, partially due to the quick rejection of historically accumulated applications that could not meet the new standards. We believe a success rate more in line with the rate in the US is likely to be the new norm for drug development in China.

Exhibit 14: Lowest success rate in oncology drug development
Success rate of candidates at different phases of clinical development: by therapeutic category

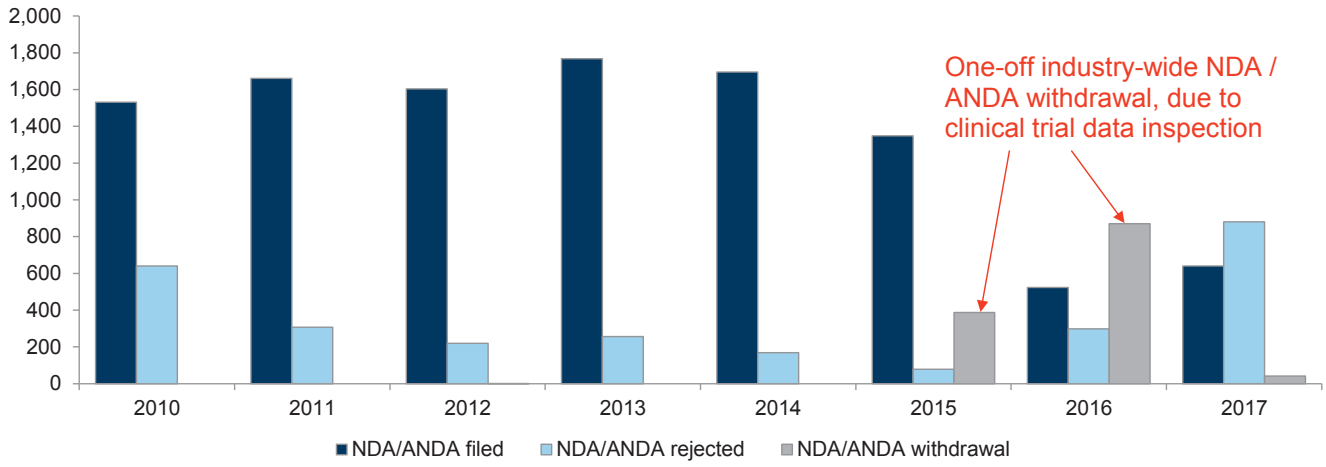


Source: Clinical Development Success Rates 2006-2015 (BIO)

Embedding risks of drug development into valuation

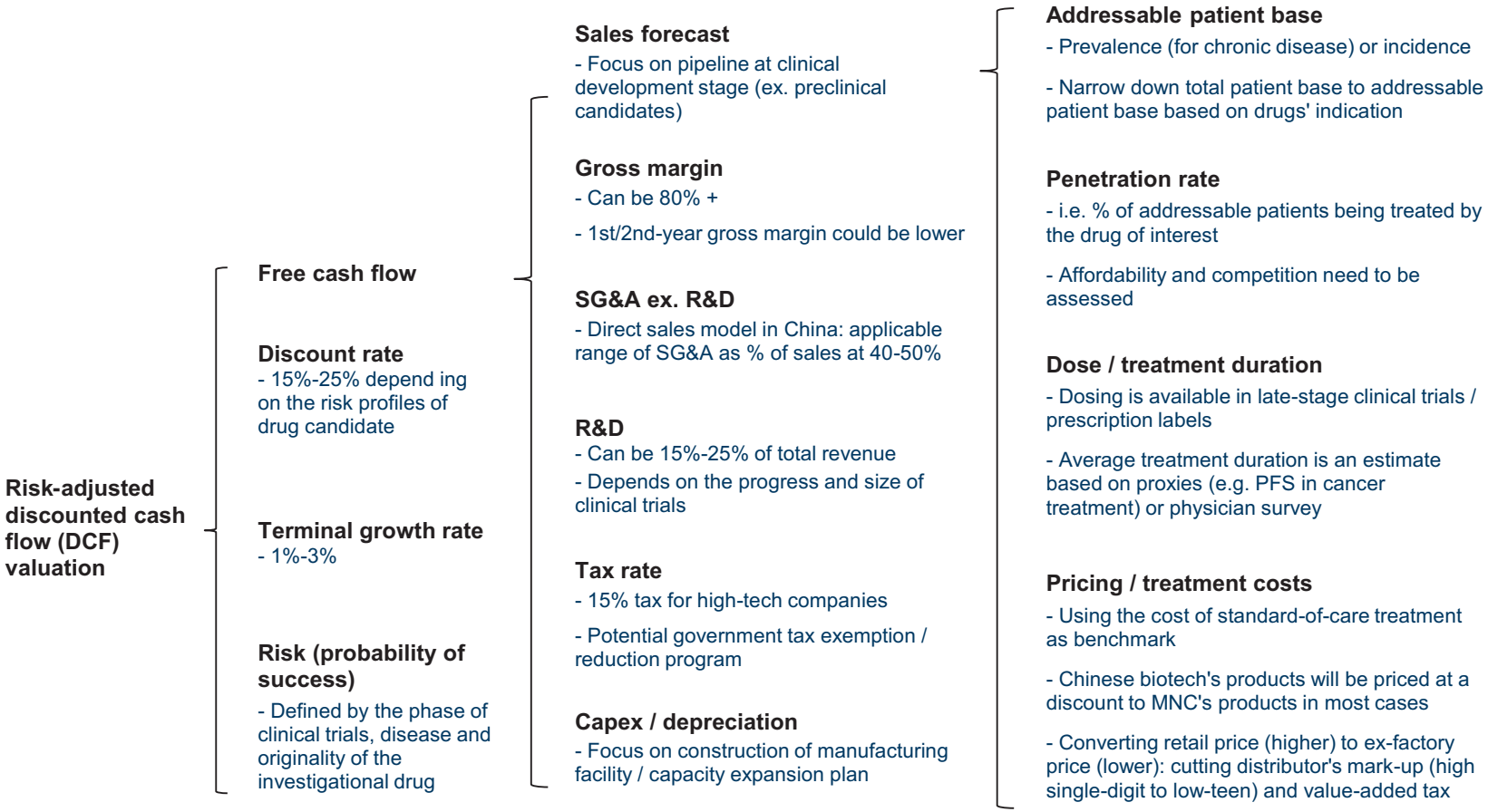
Risk-adjusted DCF is one of the most widely used methodologies to value biotech companies, particularly for companies at the pre-revenue/loss-making stage as they cannot be valued by applying earnings-/revenue-based market comparable multiples (e.g., P/E, PEG, P/S). While sharing the basis of traditional DCF (i.e., discounting the value of future free cash flows back to the present), risk-adjusted DCF incorporates: 1) the sales forecast of the products still in the pipeline; 2) the estimated time for product launch and 3) the probability of the drug candidates in pipeline being approved (i.e., the risk factor to be reflected in valuation).

Exhibit 15: Higher drug approval standards in China have led to more NDA turndowns
NDA/ANDA filings, turndowns and withdrawals in China: 2010-2017



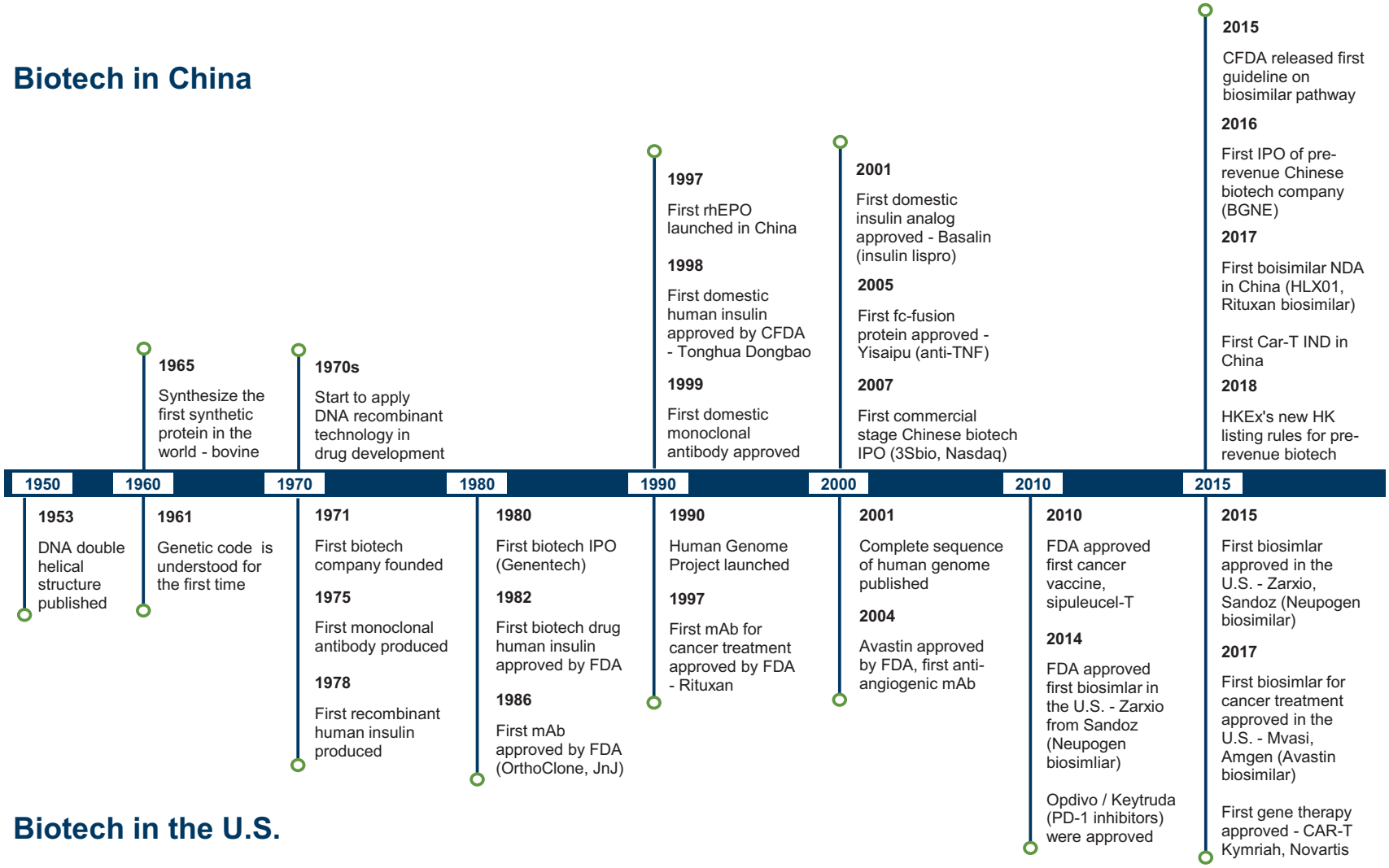
Source: Insight database

Exhibit 16: Risk-adjusted DCF valuation methodology



Source: Goldman Sachs Global Investment Research

Exhibit 17: A brief history of biotech in the China and the US



Source: Goldman Sachs Global Investment Research

Biotech in China: From science to commercialization

- Overview of China's biotech market
  - An emerging biotech market in China
  - Healthcare value chain to shift toward higher-tech biologics
  - Top 20 biotech drugs in China vs. global: Antibodies likely to emerge
  - We expect a new product cycle for biotech to begin in 2018
  - Humira/Avastin the most in-demand targets for Chinese biosimilars
  - Establishing a regulatory framework on biosimilars in China
  - MNCs actively target Chinese market for next-generation biologics

- Overview of biotech basics
  - Biologics vs. chemical drugs: Larger and more complex molecules
  - Major types of biologics - from older generation to newer therapies
  - Monoclonal antibodies - the focus of biotech investment
  - Manufacturing process is intricate and complex
  - New MAH policy a positive to both biologics CMOs and biotech start-ups

Biotech in China: from science to commercialization

Biotechnology, or biotech for short, is the technology based on the understanding of cellular and biomolecular processes to develop therapeutic products for disease treatment. Biotechnology has also been widely adopted in agriculture (e.g., improving the yield of crops), animal health (e.g., animal vaccines) and industry processing/environmental protection (e.g., industrial waste treatment). In this report, we will primarily focus on biotech applied for human health, or medical biotech.

Overview of China's biotech market

The history of the application of biotech in disease management and prevention is relatively short. The first biotech company was founded in the early 1970s in the US, the first monoclonal antibody was produced in 1975, and the first biotech IPO (Genentech) took place in 1980. China's biotech industry began in the mid-1980s, and the introduction of the new-generation biotech therapeutics began in the late 1990s/early 2000s. 3SBio's listing on NASDAQ in 2007 marked the first IPO of a pure China biotech play, and BeiGene was the first IPO of a Chinese pre-revenue biotech company (see Exhibit 18)

Exhibit 18: Milestone events in China's biotech history

Year	Events
1965	Scientists in China synthesized the first synthetic protein in the world (crystalline bovine insulin)
1997	First domestic recombinant human erythropoietin (rhEPO) launched
1998	First domestic recombinant human insulin launched (Tonghua Dongbao)
1999	First monoclonal antibody launched in China (Muromonab)
2001	First domestic insulin analog approved (Basalin from Gan & Lee)
2005	First Fc-protein launched (Yisaipu from 3SBio)
2007	First China-based commercial stage biotech IPO (3SBio listing on NASDAQ)
2015	CFDA released first guideline on biosimilar pathway
2016	First CRISPR/Cas9 gene-editing clinical study (Sichuan University)
2016	First Chinese pre-revenue biotech's overseas IPO (BeiGene listed on NASDAQ)
2017	First Chinese biosimilar NDA (HLX01 from Fosun Pharma)
2017	First Chinese CAR-T IND (by Nanjing Legend)
2018	HKEx's new listing rule for pre-revenue biotech

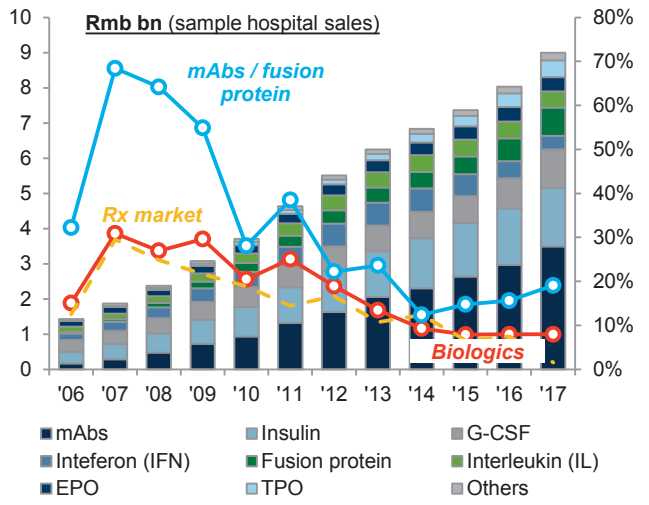
Source: Goldman Sachs Global Investment Research

An emerging biotech market in China

The market size of the Chinese biotech industry was Rmb35bn in 2017, which grew at ~10% y/y and accounted for ~6.5% of Chinese hospital prescription chemical/biotech drug sales, with about one-third of the biologics sales generated from monoclonal antibodies and over 20% from insulin products. Compared with the global benchmark, i.e. biologics contributed over 25% of global pharma revenue in 2017, we see notable potential upside for the biotech market in China if the accessibility and affordability

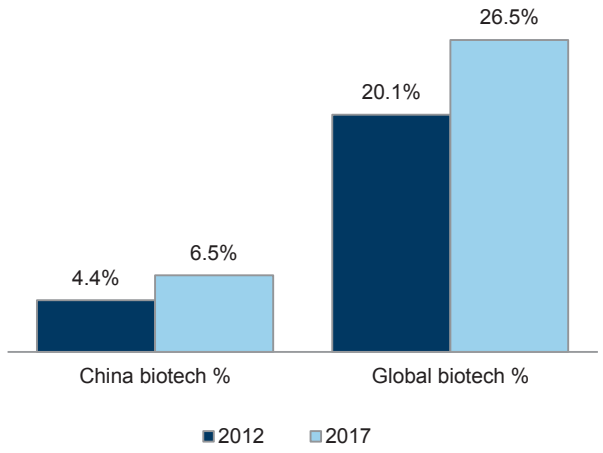
issues can be addressed by accelerated drug approval and improving reimbursement coverage.

Exhibit 19: Chinese biologics market growth, 2006-2017
Sample hospital sales data of Chinese biologics



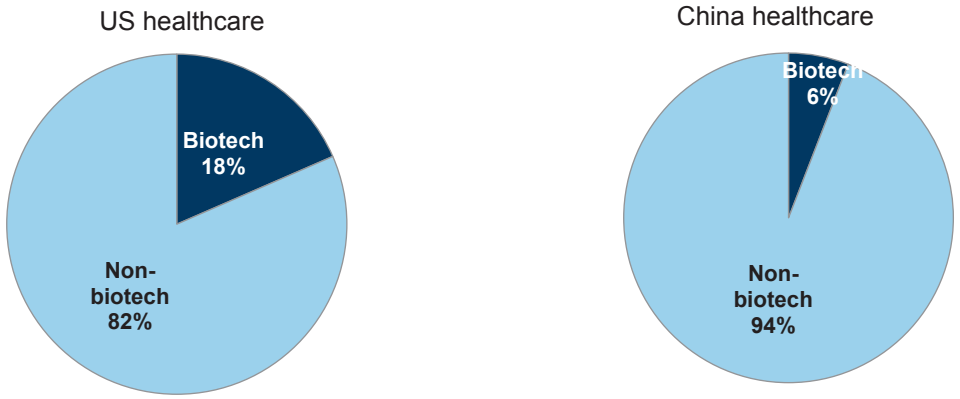
Source: PDB database

Exhibit 20: Biotech accounts for only 5% of the Chinese pharma market
Biotech as a % of the total pharma market: China vs. global



Source: PDB database, EvaluatePharma

Exhibit 21: Biotech accounts for only 6% of healthcare market cap in China vs. 18% in the US
Market cap breakdown by biotech and non-biotech in the US and China

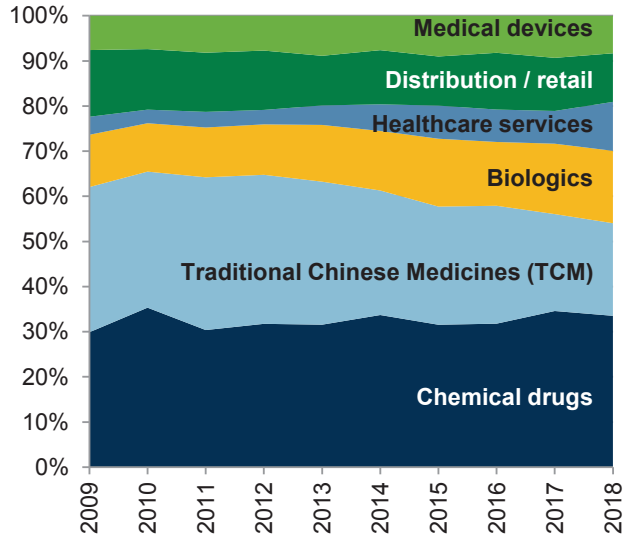


Source: Bloomberg

Healthcare value chain to shift toward higher-tech biologics

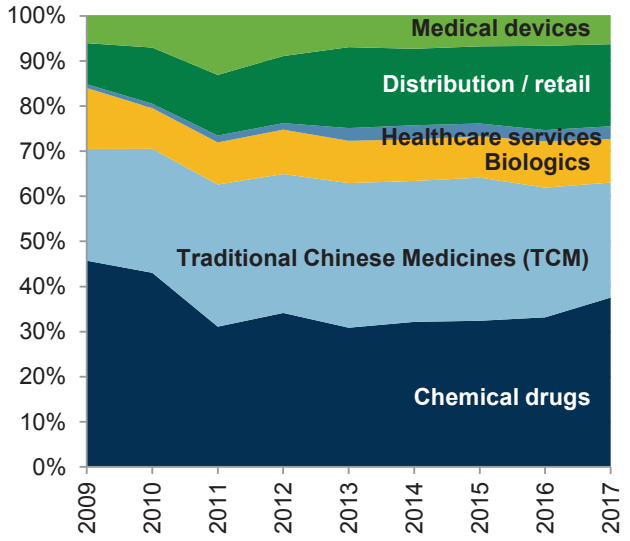
The value chain and capital market's focus are both shifting to higher-tech segments, including biologics and the CRO/CMO business. Our analysis of 331 A-share/HK-listed Chinese healthcare stocks suggests that the biologics segment contributed 16% of total A/H healthcare market cap, vs. 10% a decade ago – though most of the profit came from older-generation products (e.g., interferon, EPO).

Exhibit 22: Market share breakdown of 331 A/H China healthcare companies



Source: Bloomberg

Exhibit 23: Profit breakdown of 331 A/H China healthcare companies



Source: Bloomberg

Top 20 biotech drugs in China vs. global: Antibodies likely to emerge

The best-selling biotech drugs are a mix of new-generation monoclonal antibodies (6 out of the top 20), insulin products (5) and less sophisticated biologics, e.g. EPO and growth hormone, while the global top 20 biotech drug list was dominated by antibodies and insulin analogs (only Neulasta is an exception). Moreover, sales of mAbs (monoclonal antibody) remain relatively small in China, e.g. Herceptin sales were Rmb2 bn-Rmb3 bn in China in 2016 (GS estimates, sample hospital sales of Rmb737 mn), only accounted for 5%-6% of its global sales. With improving reimbursement for advanced therapies since 2017, we expect the opportunities for more mAbs (including fusion proteins, such as Yisaipu) and insulin analog to emerge.

Exhibit 24: Top 20 biotech drugs in China
Based on sample hospital sales

#	Brand		Molecules	Company	PDB '16 sales (Rmb mn)	Indication
1	Rituxan	美罗华	Rituximab	Genentech / Roche	943	NHL/CLL, RA
2	Herceptin	赫赛汀	Trastuzumab	Genentech / Roche	737	Breast / gastric cancer
3	Lantus	来得时	Insulin glargine	Sanofi	599	Diabetes
4	Gonal-F	果纳芬	Human FSH	Merck	532	Infertility
5	NovoMix	诺和锐	Insulin aspart premixed	Novo Nordisk	453	Diabetes
6	Avastin	安维汀	Bevacizumab	Genentech / Roche	438	CRC, NSCLC
7	TPIAO	特比澳	rh thrombopoietin (TPO)	3Sbio	423	ITP, CIT
8	Ruibai	瑞白	rh G-CSF	Qilu	395	Neutropenia
9	EPIAO	益比奥	rh erythropoietin (EPO)	3Sbio	335	Anemia
10	Lucentis	诺适得	Ranibizumab	Novartis	293	AMD
11	Novolin	诺和灵	Human insulin	Novo Nordisk	293	Diabetes
12	Yisaipu	益赛普	Etanercept	3Sbio	287	RA, AS, psoriasis
13	Lishenbao	丽申宝	Urofollitrophin	Livzon	240	Infertility
14	Humalog	优泌乐	Insulin lispro	Eli Lilly	235	Diabetes
15	Endu	恩度	rh endostatin	Simcere	234	NSCLC
16	Pegasys	派罗欣	Peginterferon alfa-2a	Roche	218	Hepatitis B, C
17	NovoRapid	诺和锐	Insulin aspart	Novo Nordisk	212	Diabetes
18	Jintropin	赛增	rh growth hormone	GenSci	206	Children slow growth
19	Basalin	长秀霖	Insulin glargine	Gan & Lee	178	Diabetes
20	Taixinsheng	泰欣生	Nimotuzumab	Biotech	164	Cancers

Monoclonal antibodies and fusion proteins
ITP: immune thrombocytopenia; CIT: chemo-induced thrombocytopenia; G-CSF: Granulocyte-colony stimulating factor
FSH: follicle-stimulating hormone; NHL: Non-Hodgkin's Lymphoma; CLL: Chronic Lymphocytic Leukemia;
AMD: Age-related macular degeneration; RA: rheumatoid arthritis; AS: ankylosing spondylitis;
CRC: colorectal cancer; NSCLC: non small cell lung cancer

Source: PDB database

Exhibit 25: Top 20 biotech drugs globally

#	Brand	Molecules	Company	'16 global sales (US$ mn)	Indication
1	Humira	Adalimumab	AbbVie	16,078	Autoimmune diseases
2	Rituxan	Rituximab	Genentech / Roche	7,407	NHL/CLL, RA
3	Remicade	Infliximab	Johnson & Johnson	6,966	Autoimmune diseases
4	Avastin	Bevacizumab	Genentech / Roche	6,883	CRC, NSCLC, RCC, glioblastoma, etc.
5	Herceptin	Trastuzumab	Genentech / Roche	6,882	Breast cancer, gastric cancer
6	Lantus	Insulin glargine	Sanofi	6,323	Diabetes
7	Enbrel	Etanercept	Amgen	5,965	RA, PA, AS
8	Eylea / Zaltrap	Aflibercept	Sanofi / Bayer	5,210	wAMD, colorectal cancer
9	Neulasta	Pegfilgrastim	Amgen	4,648	Neutropenia
10	NovoLog	Insulin aspart	Novo Nordisk	4,520	Diabetes
11	Opdivo	Nivolumab	BMS / Ono	3,774	Cancers
12	Lucentis	Ranibizumab	Novartis	3,262	AMD
13	Stelara	Ustekinumab	Johnson & Johnson	3,232	Crohn's disease, PP, PA
14	Prolia/Xgeva	Denosumab	Amgen	3,164	Osteoporosis, bone metastase
15	Soliris	Eculizumab	Alexion	2,843	PNH, aHUS, anti-AchR+ gMG
16	Humalog	Insulin lispro	Eli Lilly	2,769	Diabetes
17	Levemir FlexTouch	Insulin detemir	Novo Nordisk	2,538	Diabetes
18	Simponi	Golimumab	JnJ / Merck	2,511	RS, PA, AS
19	Xolair	Omalizumab	Genentech / Novartis	2,356	Allergic Asthma
20	Orencia	Abatacept	BMS	2,265	RA, PA

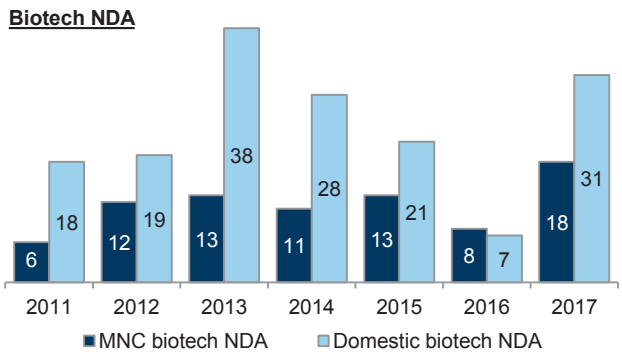
Monoclonal antibodies and fusion proteins
PNH: paroxysmal nocturnal hemoglobinuria; aHUS:atypical hemolytic uremic syndrome;
RCC: renal cell carcinoma; gMG: generalized myasthenia gravis

Source: Company data

We expect a new product cycle for biotech to begin in 2018

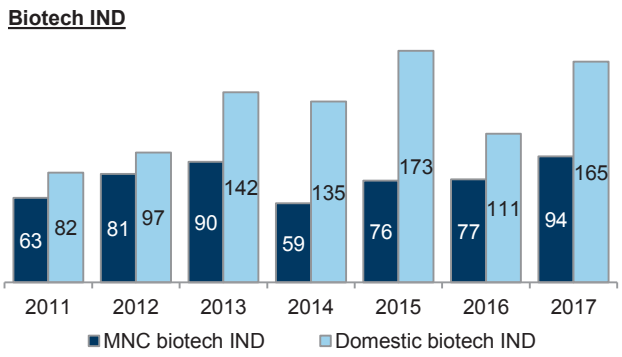
The biotech industry is driven by a growing pipeline, and we see the potential for a new product cycle of biotech to start in 2018/2019, given the accelerated NDAs from both domestic and multinational players in 2017 (a total of 49 vs. 15 in 2016 and 34 in 2015). Moreover, the number of IND applications was above 100 per annum from domestic players in the past five years, reflecting the commitment to R&D of biologics from domestic biotech/pharma companies.

Exhibit 26: Biotech NDAs accelerated in 2017
Number of biotech NDAs from 2011 to 2017: MNC vs. domestic



Source: Insight database (CDE data)

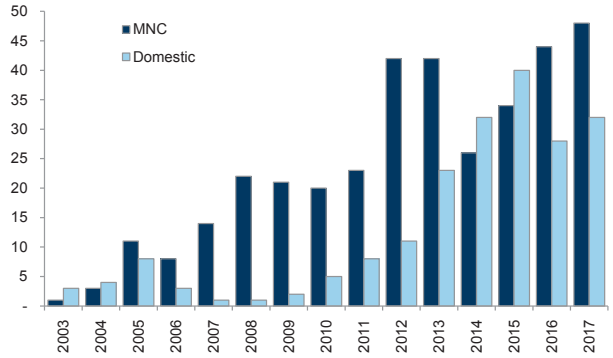
Exhibit 27: Biotech applications for clinical trials increased in 2017
Number of biotech IND from 2011 to 2017: MNC vs. domestic



Source: Insight database (CDE data)

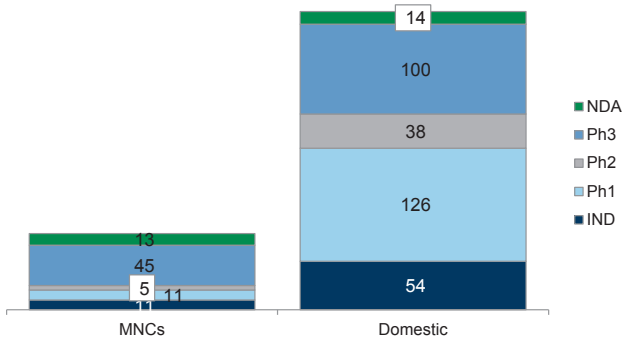
Exhibit 28: Domestic biologics IND filings increased notably since 2013

Number of IND filings for biologics/biosimilars, 2003-2017



Source: Insight database

Exhibit 29: Breakdown of biologics/biosimilar pipeline by R&D progress as of May 2018



Source: Insight database

Humira/Avastin the most in-demand targets for Chinese biosimilars

In the biosimilar space, our analysis of all the applications with the CFDA for clinical trials/production permits suggest three key developments as of May 2018:

- Over 60 domestic players are developing biosimilar versions of 13 mAbs/fc-fusion proteins, including 8 CFDA-approved originator biologics and five that are under clinical trials in China.
- Among all the biosimilar targets (i.e. originator mAbs): 1) seven mAbs each have more than five biosimilar versions in the pipeline; 2) Humira (adalimumab) and Avastin (bevacizumab) are potentially the most crowded mAbs for biosimilar developers, with 25 and 23 domestic players as potential competitors, followed by Rituxan (rituximab) and Herceptin (trastuzumab).
- Fosun Pharma's subsidiary Henlius and Innovent are potential frontrunners in the biosimilar space with four candidates at the late stage of development, i.e. at the phase 3 trial or NDA (new drug application)/BLA (biologics licenses application) stage.

Exhibit 30: Humira, Avastin and Rituxan the most in-demand targets for Chinese domestic biosimilar developers
Mapping of domestic biosimilar pipeline of seven key monoclonal antibodies (mAbs) and fc-fusion proteins

mAbs/Fc-protein	Adalimumab	Bevacizumab	Rituximab	Trastuzumab	Cetuximab
Targets	TNFα	VEGF-A	CD20	HER2/neu	EGFR
Originator					
Brand	Humira	Avastin	Rituxan	Herceptin	Erbitux
Indications	RA / PA / Ps / AS / CD / UC	mCRC / NSCLC	B-cell NHL	HER2+ breast / gastric cancer	wt-KRAS CRC
Source	Human	Humanized	Chimeric	Humanized	Chimeric
Developer	AbbVie	Roche	Roche	Roche	Merck
US Approval	2002	2004	1997	1998	2004
2017 global sales	US$18,427m	US$6,795m	US$9,065m	US$7,126m	US$1,595m
CFDA approval	2010	2010	2000	2002	2005
2017 China sales*	Rmb18m	Rmb573m	Rmb1,075m	Rmb887m	Rmb224m
**: sample hospital data*					
Domestic Biosimilars					
# of candidates	**26**	**26**	**14**	**13**	**12**
IND	- GenorBio (嘉和) - Maitaiyabo (迈泰亚博生物) - Sinomab-Pharm (迈博太科) - Longrui (龙瑞) - Shanghai Harmony Pharma (上海谐生医药) - Alphamab (康宁杰瑞) - Hua'Aotai (华奥泰) - SL Pharma (双鹭) - Anhui weiwei dab (安徽未名达木生物) - Wuhan Institute of Biological Products (武汉生物制品研究所) - Shandong Danhong (山东丹红制药)	- Zhifei Luzhu (绿竹生物) - Longrui (龙瑞) - Hua'Aotai (华奥泰) - Henlius/Fosun Pharma (indication expansion) - Dragonboat (宝船) - Guilin Sanjin (桂林三金) - JHL (喜康)	- JHL (喜康)	- Shanghai Biologics Research Institute	
CTA passed (i.e. approved for clinical trials)	- Qilu Pharma - Eastern Biotech (东方百泰) - Sinobiopharm - North Pharma Group (华北制药) - DZM Bio (东竺明生物) - Zhifei Luzhu (绿竹生物)	- Mabworks (天广实) - FDZJ (复旦张江) - Aosaikang (奥赛康) - Eastern Biotech (东方百泰) - Kanda tech (康岱生物) - 3SBio - Teruisi (浙江特瑞思)	- Mainluck (万乐) - Teruisi (浙江特瑞思) - Shanghai Biologics Research Institute	- Mainluck (万乐) - Shanghai Pharma - Alphamab (康宁杰瑞)	- Harbin Pharma - Henlius/Fosun Pharma - Humanwell - Hubei Institute of Biotech Pharma Industry - Wuhan ChemLigand Biopharma (珂美立德) - Qilu Pharma
Clinical trials – Ph 1	- 3SBio - Tonghua Dongbao - Hualan	- Simcere (先声) - T-mab Bio (泰康生物) - Qilu Pharma - Stainwei Bio (思坦维) - Hualan - Sinobiopharm - Sinocelltech (神州细胞)	- Sinocelltech (神州细胞) - Yoko Bio (南京优科) - Livzon - Lunan New-Era Pharma (鲁南新时代) - Sinobiopharm - Hualan	- Qilu Pharma - Anke Bio (安科生物) - Livzon - Hualan - Sino Biopharm	- Zhangjiang Biotech (张江生物) - Guilin Sanjin (桂林三金) - AmpoBio (安普泽) - 3SBio - Longrui (龙瑞)
Clinical trials – Ph 2	- Livzon		- Hisun (海正) - Henlius/ Fosun Pharma (indication expansion)		
Clinical trials – Ph 3	- Innovent (信达) - Bio-Thera (百奥泰) - Hisun (海正) - Union Biopharm (众合) - Henlius/Fosun Pharma	- Innovent (信达) - Henlius/Fosun Pharma - Bo'an (博安生物) - Hengrui - GenorBio (嘉和生物) - Bio-Thera (百奥泰)	- Innovent (信达)	- Henlius/Fosun Pharma - Hisun (海正) - GenorBio (嘉和生物)	- Kelun
NDA/BLA			- Henlius/ Fosun Pharma	- 3SBio (plans to refile NDA)	
Approved					

Disease abbreviations (indications):
RA: rheutmatoid arthritis; PA: psoriasis arthritis; Ps; psoriasis; AS: ankylosing spondylitis; CD: Crohn's disease; UC: ulcerative colitis; mCRC: metastatic colorectal cancer; NSCLC: non-small cell lung cancer; NHL: non-Hodgekin's lymphoma

Source: Insight database, Company data, PDB database

Establishing a regulatory framework on biosimilars in China

China lacked a regulatory framework for biosimilars before February 2015, when the CFDA released the first guidelines on a biosimilar pathway, eliminating phase 2 proof-of-concept trials for biosimilars while requesting mandatory head-to-head comparison against originator drugs (previously, biosimilars had followed a new drug approval pathway, i.e. full Phase 1-3 trials but without head-to-head comparison against originator biologics). The new pathway is still at the testing stage, with more details to be constantly tested and revised alongside biosimilar development in China. Fosun Pharma/Henlius's rituximab is the furthest along in development and will likely be the first biosimilar product to go through the new pathway assuming the approval goes smoothly.

Exhibit 31: Comparison of biosimilar regulatory framework in China, US and EU

	China	US	EU
Legal framework	only a trial version guideline for biosimilar to theraputic recomniant protein based products (ex. Pegylated and ADCs)	BPCI Act (2009), Patient Protection and Affordable Care Act (2010), 7 FDA guidance (2012-2015)	Comparability of medicinal products containing biotechnology-derived proteins as drug substance: non-clinical and clinical issues; Comparability of medicinal products containing biotechnology-derived proteins as active substance - Quality issues
Time	2015, February	2010, March	2003, December
Regulatory body	CFDA	FDA	EMA
Pathway	Biosimilar	351(k), PHS Act	Similar Biological Medicinal Products (SBMP)
Definition / comparison with reference product	1) Therapeutic 2) Similar in terms of quality, safety and potency 3) Same amino acid sequence 4) Special treatment for PEGylated product, ADC products etc.	1) Therapeutic 2) No clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency	1) Biological medicine 2) No meaningful differences from the reference medicine in terms of quality, safety or efficacy
Reference product	1) CFDA approved in China (for clinical comparison); 2) Production site consistency for reference products used in different stages of R&D	FDA-approved: single biological product, licensed under section 351(a) of the PHS Act (not more than 1)	EU-licensed reference product (for all pivotal studies)
Exclusivity	No exclusivity for first approved biosimilar product	1) 12 years for reference product (Biosimilar applicant can file 4 years after) 2) 1 year for first approved interchangeable biosimilar product	1) 8 (data exclusivity) + 2 (market exclusivity) + 1 (new indication) years for innovator biologic 2) No exclusivity for the first approved interchangeable product
Inter-changeability	Not mentioned	1) Interchangeable: "biological product [that] may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product" 2) Biosimilars can choose to be not interchangeable	To be decided by member countries
Principles for development and evaluation	1) Comparable basis; 2) Stepwise evidence development; 3) Equivalence basis; 4) Biosimilarity basis	1) A stepwise approach, 2) Totality-of-the-evidence approach, 3) General scientific principles	1) A stepwise approach, 2) Totality-of-the-evidence approach

Source: CFDA, FDA, EMA

MNCs actively target Chinese market for next-generation biologics

With the Chinese government further opening the domestic pharma market to overseas players with better recognition of overseas clinical trial data and potential priority review for novel drugs targeting major diseases (e.g., cancers), MNCs are stepping up the pace of introduction of most advanced therapies, particularly biologics into China. Our analysis suggests that as of May 2018:

- 76% of globally marketed biologics were making progress in China: Out of the 72 mAbs and fusion proteins approved globally, 14 have been approved in China (or 19% of total globally available ones, 12 approved in 2000-2013) and 41 have filed IND/NDA or are under clinical trials.
- Oncology/autoimmune diseases as a key focus: Among the 41 upcoming novel biologics, oncology is the key focus with 19 (46%) candidates in the pipeline, among which six are immunotherapies, followed by autoimmune diseases (12 candidates), while AMD/COPD/asthma present niche market opportunities.
- PD1/PDL1 as the single most competitive targets: 2 PD-1 inhibitors, Opdivo/Keytruda; 3 PD-L1 inhibitors, Tecentriq/Imfinzi/Bavencio; and one CTLA-4 inhibitor Yervoy.
- Potentially 15-20 novel biologics expected over the next five years: For 20 candidates at NDA or phase 3 trials, we could see product launches over the next 3-5 years assuming development proceeds smoothly.

Exhibit 32: Clinical development progress of the US approved biologics products in China - part 1

#	Brand	Molecule	Developer	Target	'16 Sales (US$ mn)	US Appl year	CFDA	# of biosimilars
							IND Ph 1 Ph 2 Ph 3 NDA Appvl	
Oncology								
1	Rituxan	Rituximab	Roche	CD20	7,482	1997	2000	14
2	Herceptin	Trastuzumab	Roche	HER2/neu	6,884	1998	2002	13
3	Erbitux	Cetuximab	Merck	EGFR	1,555	2004	2005	12
4	TheraCIM	Nimotuzumab	Biocon, PT Kalbe etc.	EGFR	NA	2006	2008	5
5	Avastin	Bevacizumab	Roche	VEGF-A	6,885	2004	2010	26
6	Opdivo	Nivolumab	BMS / Ono	PD-1	4,735	2014		-
7	Keytruda	Pembrolizumab	Merck	PD-1	1,402	2014		-
8	Perjeta	Pertuzumab	Roche	HER2	1,874	2012		3
9	Tecentriq	Atezolizumab	Roche	PD-L1	159	2016	NSCLC	-
10	Imfinzi	Durvalumab	AZ (MedImmune)	PD-L1	NA	2017	NSCLC	-
11	Bavencio	Avelumab	Merck / Pfizer	PD-L1	NA	2017	NSCLC	-
12	Darzalex	Daratumumab	JnJ (Janssen)	CD38	572	2015	MM	-
13	Blincyto	Blinatumomab	Amgen	CD19 / CD3	115	2014	r/r ALL	-
14	Vectibix	Panitumumab	Amgen / Betta	EGFR	785	2006	Colorectal cance	4
15	Prolia/Xgeva	Denosumab	Amgen	RANKL	3,459	2010	Osteoporosis	6
16	Kadcyla	Ado-trastuzumab emtansine	Genentech / Roche	HER2 (ADC)	843	2013	Breast cancer	-
17	Cyramza	Ramucirumab	Eli Lilly / ImClone	VEGFR2	614	2014	Gastric cancer	
18	Yervoy	Ipilimumab	BMS	CTLA-4	1,053	2011	SCLC	-
19	Gazyva	Obinutuzumab	Roche	CD20	199	2013	DLBCL	-
20	Arzerra	Ofatumumab	GSK / Genmab	CD20	46	2009	DLBCL	-
21	Besponsa	Inotuzumab ozogamicin	Pfizer / UCB	CD22 (ADC)	NA	2017	ALL	-
22	Adcetris	Brentuximab vedotin	Seattle Genetics	CD30 (ADC)	544	2011		-
23	Portrazza	Necitumumab	Eli Lilly	EGFR	15	2015		-
24	Zevalin	Ibritumomab tiuxetan	Spectrum	CD20 (ADC)	11	2002		-
25	Poteligeo	Mogamulizumab	Kyowa Hakko Kirin	CCR4	18	2012	No application	-
26	Bexxar	Tositumomab	Novartis	CD20	8	2003	No application	-
27	Mylotarg	Gemtuzumab ozogamicin	Pfizer	CD33 (ADC)	NA	2000	No application	-
28	Unituxin	Dinutuximab	United Therapeutics	GD2	63	2015	No application	-
29	Lartruvo	Olaratumab	Eli Lilly	PDGFRα	12	2016	No application	-
30	Empliciti	Elotuzumab	BMS	SLAMF7	150	2015	No application	-

Source: Insight database

Exhibit 33: Clinical development progress of the US approved biologics products in China - part 2

#	Brand	Molecule	Developer	Target	'16 Sales (US$ mn)	US Appl year	CFDA	# of biosimilars
							IND Ph 1 Ph 2 Ph 3 NDA Appvl	
Autoimmune diseases								
1	Zinbryta	Daclizumab	Biogen / AbbVie	IL-2R	17	1997	2000	-
2	Remicade	Infliximab	JnJ (Janssen)	TNFα	8,070	1998	2006	4
3	Enbrel	Etanercept	Pfizer	TNFα	5,965	1998	2010	7
4	Humira	Adalimumab	AbbVie	TNFα	16,515	2002	2010	26
5	Actemra	Tocilizumab	Roche (Chugai)	IL-6R	1,713	2010	2013	-
6	Stelara	Ustekinumab	JnJ (Janssen)	IL-12 / IL-23	3,232	2009	2017	-
7	Simponi	Golimumab	JnJ (Janssen)	TNFα	2,511	2009	2017	-
8	Cimzia	Certolizumab pegol	UCB	TNFα	1,446	2008		-
9	Orencia	Abatacept	BMS	CD80/CD86	625	2005	Lupus nephritis	-
10	Benlysta	Belimumab	GSK	BAFF(Blys)	414	2011	Lupus nephritis	3
11	Ilaris	Canakinumab	Novartis	IL-1β	283	2009	Gout	-
12	Cosentyx	Secukinumab	Novartis	IL-17a	1,128	2015	AS	-
13	Taltz	Ixekizumab	Eli Lilly	IL-17a	113	2016	Ps	-
14	Sylvant	Siltuximab	JnJ (Janssen)	IL-6	11	2014		-
15	Lemtrada	Alemtuzumab	Sanofi	CD52	470	2001		-
16	Ocrevus	Ocrelizumab	Roche	CD20	NA	2017		-
17	Alzumab	Itolizumab	Biocon, CIMAB, Probiotec	CD6	NA	2013		-
18	Kevzara	Sarilumab	Regeneron / Sanofi	IL-6R	NA	2017		-
19	Siliq	Brodalumab	Valeant / Amgen / AZ	IL-17RA	NA	2017	No application	-
20	Tremfya	Guselkumab	MorphoSys / JnJ	IL-23 p19	NA	2017	No application	-
21	Tysabri	Natalizumab	Biogen	α4β1 & α4β7	1,964	2004	No application	-
COPD / Asthma								
1	Xolair	Omalizumab	Novartis	IgE Fc region	2,356	2003	2017	-
2	Fasenra	Benralizumab	AZ (MedImmune)	IL-5R (CD125)	NA	2017	Asthma	-
3	Dupixent	Dupilumab	Regeneron / Sanofi	IL-4Rα	NA	2017		-
4	Nucala	Mepolizumab	GSK	IL-5	138	2015		-
5	Cinqair	Reslizumab	Merck / Teva / UCB	IL-5	5	2016	No application	-

Source: Insight database

Exhibit 34: Clinical development progress of the US approved biologics products in China - part 3

#	Brand	Molecule	Developer	Target	'16 Sales (US$ mn)	US Appl year	CFDA	# of biosimilars
							IND Ph 1 Ph 2 Ph 3 NDA Appvl	
Other therapeutic areas								
1	Simulect	Basiliximab	Novartis	CD25	114	1998	2002	-
2	Lucentis	Ranibizumab	Novartis	VEGF-A	3,262	2006	2011	1
3	Eylea / Zaltrap	Aflibercept	Sanofi / Bayer	VEGF-A/B	5,195	2011	2018	-
4	Repatha	Evolocumab	Amgen / Astellas	PCSK9	151	2015		-
5	Praxbind	Idarucizumab	Boheringer Ingelheim	Dabigatran	18	2015	Dabigatran etex	-
6	Praluent	Alirocumab	Sanofi	PCSK9	116	2015	Acute coronary	-
7	Hemlibra	Emicizumab	Chugai / Roche	CF IXa and X	NA	2017	Hemophilia A	-
8	Soliris	Eculizumab	Alexion	Protein C5	2,843	2007		-
9	Reopro	Abciximab	Eli Lilly	GPIIb/IIIa & αVβ3 integrin	87	1993	No application	-
10	ABthrax	Raxibacumab	GSK	BAPA	1	2012	No application	-
11	Anthim	Obiltoxaximab	Elusys Therapeutics	BAPA	NA	2016	No application	-
12	Zinplava	Bezlotoxumab	Merck / BMS / UM	Tcd B	NA	2016	No application	-
13	Rabishield	Rmab	SII / UM	Rabie virus G-protein	NA	2016	No application	-
14	Orthoclone OKT3	Muromonab-CD3	JnJ	CD3	46	1986	No application	-
15	Synagis	Palivizumab	AZ / AbbVie	RSV gpF	1,055	1998	Application rejected	-

Immuno-Oncology (I/O) therapies

Abbreviations

ACD: Atherosclerotic cardiovascular disease
ALCL: anaplastic large cell lymphoma
ALL: acute lymphoblastic leukemia
AMD: age-related macular degeneration
AML: Acute myeloid leukemia
AS: ankylosing spondylitis
(m)CRC: (metastatic) colorectal cancer
MM: multiple myeloma
NC: Nasopharyngeal cancer
NHL: non-hdgkin lymphoma
NSCLC: non-small cell lung cancer
PA: psoriatic arthritis
PC: Pancreatic cancer
PNH: paroxysmal nocturnal hemoglobinuria
Ps: psoriasis
RA: rheutomaid arthritis
(r)MS: recurrent multiple sclerosis
SCCHN: squamous cell carcinoma of the head and neck
SLE: systemic lupus erythematosus
UC: ulcerative colitis

Source: Insight database

Overview of biotech basics

Biologics vs. chemical drugs: Larger and more complex molecules

A biologic – also known as a biological product, a biopharmaceutical, or a biotech drug/medicine – is different from small single-molecule medicines, larger in terms of molecule (e.g., monoclonal antibodies, or mAbs, at molecular weight of ~150K Dalton vs. a few hundred for chemical drugs) and are much more complex in structure. Biologics are produced in living cells, e.g., Chinese Hamster Ovary (CHO) cells are used in most of the mAbs available in the market, and the manufacturing process is: 1) time-consuming (CHO about 6-9 months for cell line manufacture and release); and 2) intricate and complex.

Given their complex manufacturing process, biosimilars can only be a highly similar version of the originator biologics (same amino acid sequence, but the modification and 3D structure are not identical), while chemical generics can be identical copies of the reference drugs.

Exhibit 35: Biologics are different from chemical drugs in terms of development and manufacturing
Chemical drugs vs. biologics; chemical generics vs. biosimilars

	Chemical drugs	Biologics
Molecule	Small molecules	Large and complex molecules, e.g. proteins / peptides
Size (molecular weight)	Lower molecular weight (e.g. Aspirin 180 Da; Lipitor 559 Da)	Higher molecular weight, could be as heavy as 150kDa
Immunogenicity	Mostly non-immunogenic	Immunogenic
Administration route	Multiple routes: oral, injectable and others	Mostly injectable
Thermostability	Relatively stable	Sensitive
Manufacturing	Chemically synthesized (made by following a chemical formula); less sensitive to minor changes in manufacturing process and environment; identical copy can be made	Grown in living cells (e.g. mammalian cell, *E.coli*, yeast, etc.); slight changes in manufacturing process could lead to notable change to product quality; impossible to produce identical copy (only "similar")
	Chemical generics	**Biosimilar**
Interchangeable	Chemical generics are identical; in most cases, interchangeable with originator drug in clinical application	Biosimilar are not identical to the reference products, only highly similar; in most cases, not interchangeable in clinical setting unless approved by regulators
Development time	~2-3 years	5+ years or even longer, depending on the complexity of the targeted biologics
Development cost	~US$2-5mn	Could be over US$50mn or more

Source: Goldman Sachs Global Investment Research

Major types of biologics - from older generation to newer therapies

Major types of biologics in the market include: monoclonal antibodies (mAbs), fc-fusion proteins, insulin products (animal insulin, human insulin and insulin analogous), granulocyte colony stimulating factor (GCSF, including PEG-G-CSF), interferons (IFN), interleukins (IL), erythropoietin (EPO), thrombopoietin (TPO), human growth factors (hGF), and several cytokines.

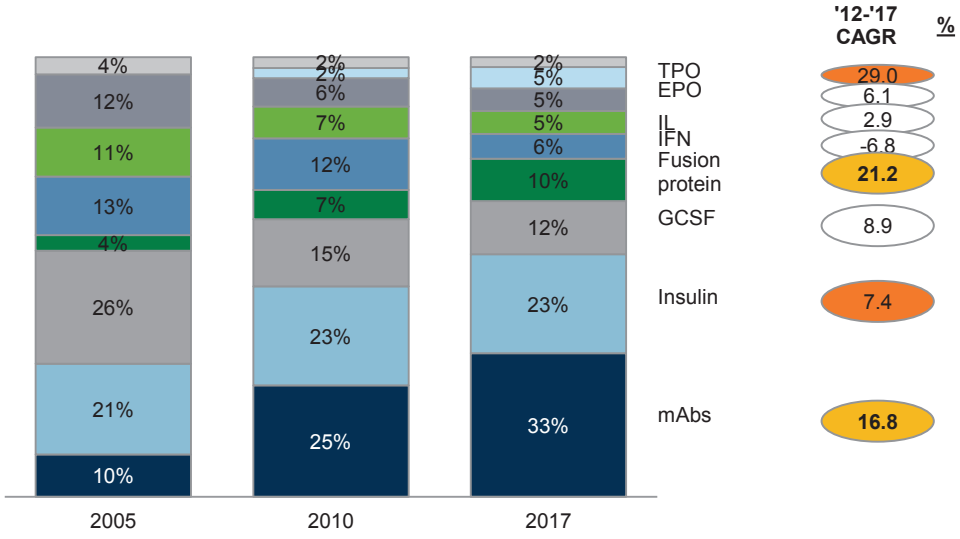
Exhibit 36: Key types of therapeutic biologics in China

Biologics	Abbr.	Key products in China	What is it?
Monoclonal antibody	mAb	Herceptin (Roche)	Antibodies produced by identical immune cells, which are clones of a single ancestor cell. Antibodies can bind to specific part (i.e. epitopes) of the antigens (proteins in most cases) to regulate the cell activities.
Fusion protein	-	Yisaipu (3SBio), Conbercept (Kanghong)	Therapeutic proteins made by joining two or more genes that coded for separate proteins. Also referred as chimeric proteins
Recombinant human Insulin & insulin analog	-	Novolog (Novo Nordisk), Lantus (Sanofi)	Peptide produced by recombinant DNA technology in treating diabetes. Three generations: 1st-gen animal insulin, 2nd-gen recombinant human insulin, and 3rd-gen insulin analog
Granulocyte colony-stimulating factor	G-CSF	Jinyouli (CSPC)	A cytokine that stimulates the production of white blood cell, used in treating cancer chemotherapy induced low white blood cell count. There are short-acting version and long-acting ones (PEG-G-CSF)
Interferon	IFN	Pegasys (Roche)	A family of proteins that modulate the responses of the immune system to viruses, bacteria and other foreign substances. Clinical applications include treating hepatitis B/C and cancers
Interleukin	IL	Ju He Li (IL-11 from Qilu Pharma)	A cytokine involved in cell signaling of the immune and hemopoietic systems. There are two major ILs available in China: 1) IL-2, used in cancer treatment and immune system disorders; 2) IL-11, used as booster of platelet production in cancer patients received chemotherapies
Erythropoietin	EPO	EPIAO (3SBio)	A cytokine made by the kidney to stimulate red blood cell production. Recombinant EPO is used in dialysis patients and post-chemo patients as blood red cell booster
Thrombopoietin	TPO	TPIAO (3SBio)	A cytokine regulate production of platelets, used as booster of platelet production in cancer patients received chemotherapies and ITP patients

Source: Goldman Sachs Global Investment Research

mAbs and fc-fusion proteins, two major new-generation biologics, have gained significant share in the past 10 years in the Chinese biologics market – their collective share was up from 14% in 2005 to 43% in the first nine months of 2017, based on sample hospital data.

Exhibit 37: China biologics product mix shifts to mAbs and fusion proteins
Market share of key biologics categories



Source: PDB database, Goldman Sachs Global Investment Research

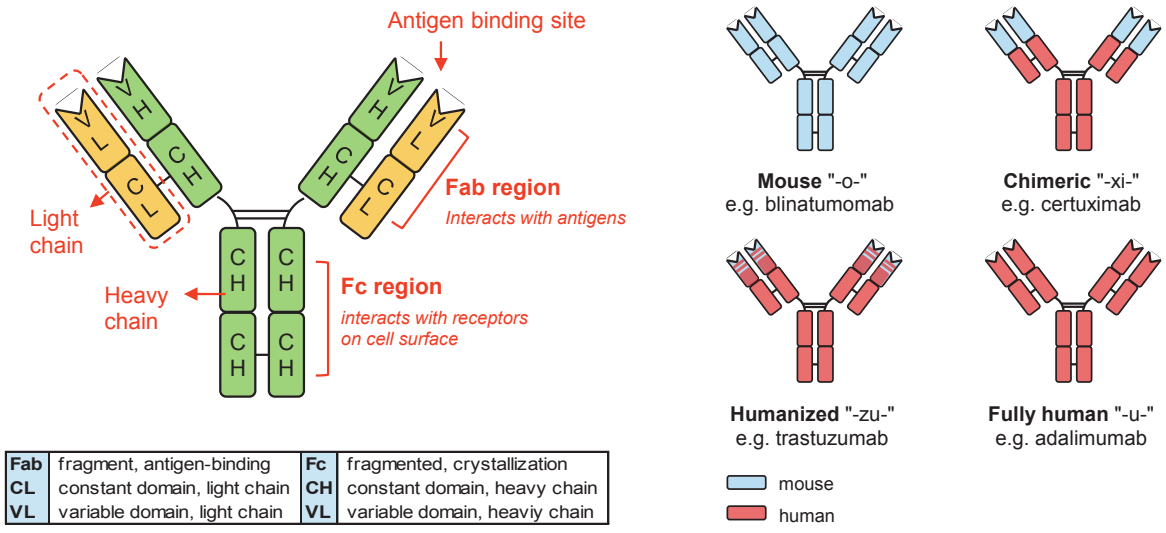
Monoclonal antibodies - the focus of biotech investment

Antibodies are special proteins produced by B lymphocytes, a type of white blood cell that plays a key role in the immune system, to counteract foreign substances (i.e.,

antigens). In the early 1970s, technologies were developed to grow clones (i.e., identical copies) of B lymphocytes to produce large numbers of the same antibody. An antibody from a single clone of cells is termed a monoclonal antibody (mAb).

- **Antibody structure:** Each antibody is a Y-shaped protein made up of two regions: 1) the variable region (short arms of the Y) recognizes antigens, while the constant region (the long arm) affects the way the antibody summons other immune components to respond. See Exhibit 38 for illustration.
- **From mouse source to fully human:** The first mAb licensed (muromomab-CD3, approved in 1986) was derived from mouse lymphocytes. One major issue of mouse antibodies is that they are recognized by patients' immune systems as foreign substances, thus potentially triggering the production of anti-mouse antibodies, which will neutralize the benefit of the mouse antibodies or even lead to severe side-effects. To improve the immunogenicity profile, non-human sequences were minimized to create chimeric (1/3 mouse, 2/3 human), humanized (90% human) and fully human antibodies.

Exhibit 38: Antibody structure and the different monoclonal antibody technology

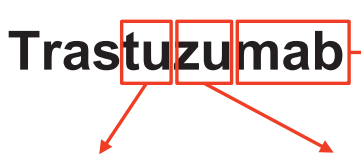


Fab	fragment, antigen-binding	**Fc**	fragmented, crystallization
CL	constant domain, light chain	**CH**	constant domain, heavy chain
VL	variable domain, light chain	**VL**	variable domain, heaviy chain

Source: Goldman Sachs Global Investment Research

It is worth highlighting that the names (international nonproprietary names, INN) of mAbs include two important details of the mAbs: 1) source, whether the mAb is derived from mice or is chimeric, humanized or fully human mAbs, e.g. the "-xi-" infix in "rituximab" implies this is a chimeric mAb and trastuzumab is a humanized one with the infix "-"zu-"; and 2) diseases or targets of the mAbs, e.g. the "-tu-" infix in "rituximab" and "trastuzumab" indicates the two mAbs are targeting tumors (see Exhibit 39 for details).

Exhibit 39: Illustration of monoclonal antibody nomenclature scheme



Suffix **"-mab"** for all mAbs, antibody fragments and radiolabeled antibodies

Target / disease class infix (substem A)

Infixes	Definitions	Examples (target/diseases)
-tu- / -t-*	tumors	rituximab (lymphoma)
-li- / -l-	immunomodulator	nivolumab (immuno-oncology)
-ci- / -c-	cardiovascular	evolucumab (colestrol control)
-ba- / -b-	bacterial	edobacomab (sepsis)
-ki- / -k-	interleukins	ixekizumab (target IL-17A)
-so- / -s-	bone	denosumab (osteoporosis)
-ne- / -n-	neurons	aducanumab (Alzheimer's disease)
-gr(o)-	skeletal muscle	Landogrozumab (muscle wasting)
-vi- / -v-	viruses, antiviral	palivizumab (influenza A)
-fu- / -f-	antifungal	-

*: tumor specific infixes used to be used (e.g. -mel- for melanoma), but was discontinued since most anti-cancer mAbs are investigated for more than 1 type of tumor

Source infix (substem B)

Infixes	Sources	Examples
-o-	mouse	blinatumomab
-xi-	chimeric	cetuximab
-zu-	Humanized	trastuzumab
-u-	Fully human	adalimumab
-xizu-	humanzied + chimeric chains	Otelixizumab

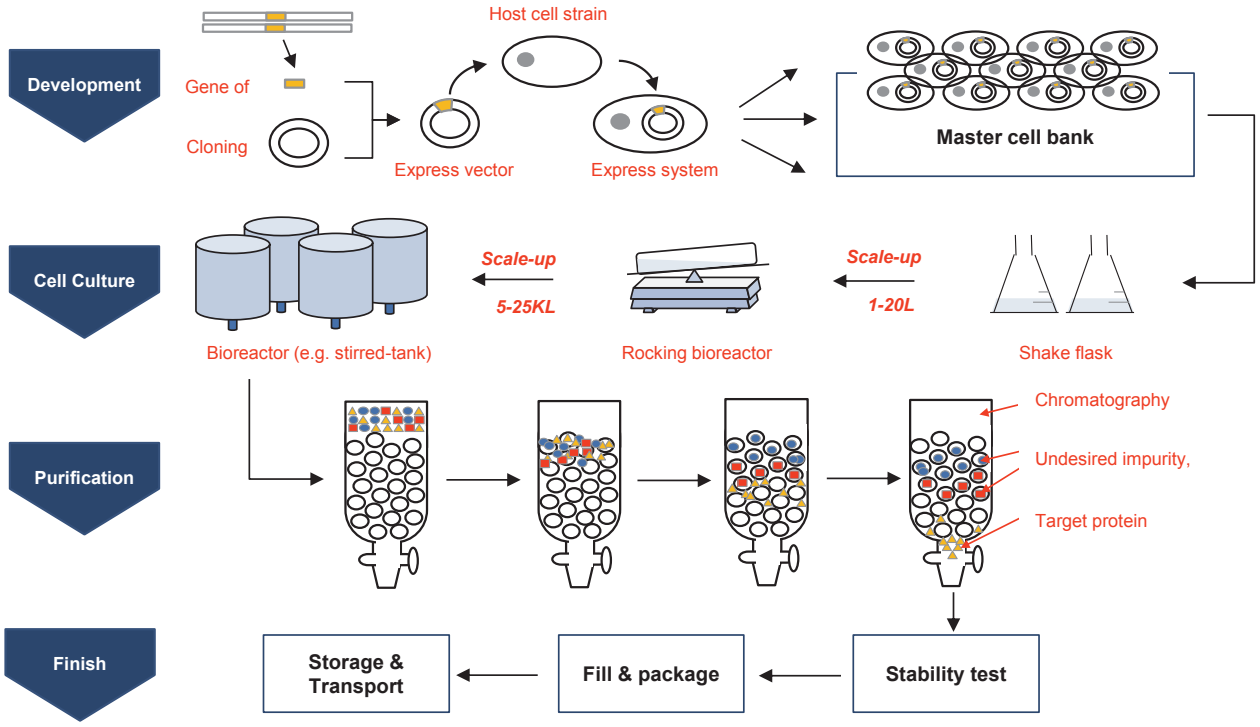
*: a few more seldom used source infixes: -axo- (rat/mouse chimer), -e- (hamster), -a- (rat) and -i- (primate)

Source: United States Accepted Names Council (USAN)

Manufacturing process is intricate and complex

Different from the manufacturing process for chemical drugs, which is based on chemical synthesis with a highly controllable process and quality, the manufacturing of biologics is based on the protein expression of living cells (i.e., the express system), which is highly sensitive to the environment, including factors like temperature.

Exhibit 40: Illustration of manufacturing process for monoclonal antibodies (mAbs)



Source: Goldman Sachs Global Investment Research

The detailed manufacturing process is proprietary to each manufacturer for each product, and various technologies involved in each of the steps have been developed to enhance the yield and maintain acceptable quality. However, they share similar basic steps:

- **Development:** Gene clone, i.e. insert a specific gene of interest, which contains the genetic code for the protein to be produced, into a host cell strain to make an express system, and grow the cells into a master cell bank.
- **Upstream process:** Grow the cells from a small scale (e.g., starting with a shake flask in labs) to industrial-level bioreactors. The progress is referred to as "scale-up", which is one of the key bottlenecks for biologics manufacturers, as the multi-parameter quality control in a significantly larger scale becomes highly complex.
- **Downstream process:** After the cell culture is harvested, the mixture fluid, which contains the antibodies of interest and side products (e.g., undesired impurities, virus, medium), will go through the purification process to concentrate the target protein.
- **Finishing steps:** Turning the concentrated target protein into a product, including stability test, filling (e.g., in a prefilled syringe) and packaging, as well as storage and transport, which in most cases involves cold-chain logistics technologies.

Exhibit 41: Key glossary of biomanufacturing

Term	Definition
Batch / Lot	A specific quantity of material produced in a process that is homogeneous
Bioreactor	A device (a big stirred-tank type is the typical bioreactor) to grow cells in cell culture
Cell bank	Cells grown from those maintained in a master cell bank with well characterized stability and uniformity
Characterization method	An analytical test method used to evaluate a specific quality attribute of the target protein
Culture initiation	At the beginning of each batch, a vial of cells is transported to an prep room and the culture is initiated by thawing the vial
Downstream	Refer to the purification process in biomanufacturing, typically 2-3 chromatographic steps
Expression system	Protein expression, i.e. after DNA being translated into a polypeptide chain and folds into a functional 3D structure
Feed stream	Cells and culture media being fed into the bioreactor continuously
Fermentation	The culture of mammalian, yeast, or microbial cells for protein drug production
GCP/GLP/GMP	Good Clinical / Laboratory / Manufacturing Practice, i.e. a set of guidelines published to set the standards for conducting clinical trials, laboratory studies and manufacturing
Generation number	The population-doubling level of the cell bank
Glycoproteins	Proteins with sugar residues attached
Glycosylation	The progress of attaching the sugar residues to proteins, the process is important in making the protein functional
Polishing	The elimination of trace contaminants and impurities, final steps in purification
Purity assay	a quantitative analytical procedure used to determine the purity of the active product ingredient, a "purity method" mostly refers to a "qualitative" procedure
Quality Assurance (QA)	Systematic monitoring and evaluation of the manufacturing process to assure that the products are of the required quality to be commercial products
Quality Control (QC)	All tastings performed during the biomanufacturing process to verify that appropriate standards of quality are attained
Single-use bioreactor	Bioreactor with a disposable (plastic) bag to grow cells, vs. a more permanent stainless steel vessel
Sterile	The complete absence of living microorganisms
Titer	The concentration of a solution determined by titration

Source: Goldman Sachs Global Investment Research

New MAH policy a positive to both biologics CMOs and biotech start-ups

Before June 2016, the manufacturer of a specific drug had to be the corresponding drug certificate holder, leading to industry-wide overcapacity, difficulties in expanding contract manufacturing organizations (CMO) business (previously most orders from overseas clients), and challenges for biotech start-ups and research institutions in commercializing innovative products.

As part of the full set of reforms to drive pharma innovation, the State Council released the new marketing authorization holder (MAH) policy on June 6, 2018, noting that the trial run of the new regulation will be conducted in 10 pilot provinces until November 4, 2018, i.e. a ~30-month trial run. Under the new regulation, drug approvals could be granted to drug manufacturers and non-manufacturer entities, including research institutions, R&D-driven start-ups without manufacturing capability and even individuals; while the CRO/CMO partners could be responsible for manufacturing at the clinical trial stage and the commercial stage.

An overview of pharma/ biotech R&D in China: Key for pipeline evaluation

- What is a drug target? - the starting point for drug discovery
- Drug discovery in China: mostly focusing on “follow-on” strategy
- Preclinical studies: preliminary test of drug activities and toxicities
- Clinical development: Key bottleneck for new drug development
- Phase I trials - safety profile, dose finding and PK/PD
- Phase-II trials: Proof of concept (POC) studies
- Phase-III trials: confirmation in larger scale
- Phase 0 & IV trials - Exploratory studies and post-marketing surveillance
- Unconventional biomarker driven trial as a new option
- Access to clinical trial design and clinical data
- Regulator’s role in drug development - gatekeeping at IND/NDA

An overview of pharma/biotech R&D: Key for pipeline evaluation

The value of a pre-revenue biotech company is largely defined by its pipeline, which can be analyzed using data obtained during the drug R&D process, including the characteristics of the molecules, preclinical data from animal experiments and, most importantly, the in-human data from clinical trials.

The drug development process typically starts with the selection of a target disease, followed by: 1) the drug discovery process, which includes identification/validation of the target based on the understanding of the disease biology and screening for "druggable" molecules; 2) preclincial studies to test the candidates in vitro (i.e., outside of a living organism) and in experimental animals; 3) in-human clinical trials, which are usually done in three phases (phases I, II, III); and 4) regulatory review of the data collected from all the studies being conducted on the candidates. The whole process will normally also include the development of a manufacturing process for smaller-batch production for clinical trials and future commercial batch production.

Exhibit 42: Overview of drug R&D process in China

Stage	Key focus / purpose	Time / scope
Drug discovery	Identify potential compounds against specific biological targets; modify compounds to reduce toxicities and enhance potency	2-5 years
Preclinical studies	Extensive laboratory and animal testing to determine the biological activity and safety of compounds	2-3 years
Investigational new drug (IND) application	Application filed with CFDA, covering results from preclinical results and protocols for clinical trials. An approval for clincal trials wil be granted to applicants once IND passed CFDA's review	Target 60 days for review (vs. prev. 12+ months)
Phase I clinical trials	Establish safe dosage, gather information on absorption, distribution, metabolism, excretion (AMDE) and toxicity of the compounds	0.5-1 year, 10-100 enrollees, could be healthy volunteers
Phase II clinical trials	"Proof-of-concept": test the preliminary efficacy of the compounds in specific group of patients	1-2 years, 100+ patients
Phase III clinical trials	Comfirm the side effects and efficacy in large population	2-4 years, 300+ patients
New drug application (NDA)	Extensive documentation of drug structure, preclinical and clinical data, formulation, manufacturing details, and proposed indications. Drug approval will be granted if the NDA passed CFDA's review and onsite inspection on manufacturing and clinical data	0.5-2 years for review (vs. prev. unpredictable timeline)

Source: CFDA, Goldman Sachs Global Investment Research

In this section, we will discuss the process of drug R&D, from discovery to clinical trials, highlighting the key components/metrics to focus on when evaluating the preclinical and clinical data. We use the development of anti-cancer drugs as an example, as oncology is one of the key areas that biotech companies are focusing on and represents about 30% of ongoing clinical trials registered at the Center for Drug Evaluation (CDE), under the CFDA.

What is a drug target? - the genesis point for drug discovery

The current drug discovery strategy is more target-based (or mechanism based), particularly in developing oncology drugs, focusing on identifying therapeutic molecules that can cure/delay the progress of a disease by modulating one or more specific targets, which are biological molecules (or "biomolecules") that play critical roles in particular metabolic/signal pathways that are important to a disease condition.

In most cases, drug targets are proteins, so nucleic acids are playing an increasingly important role as drug targets in drug discovery. According to a study[1] conducted by a group of scientists in the UK and the US in 2016:

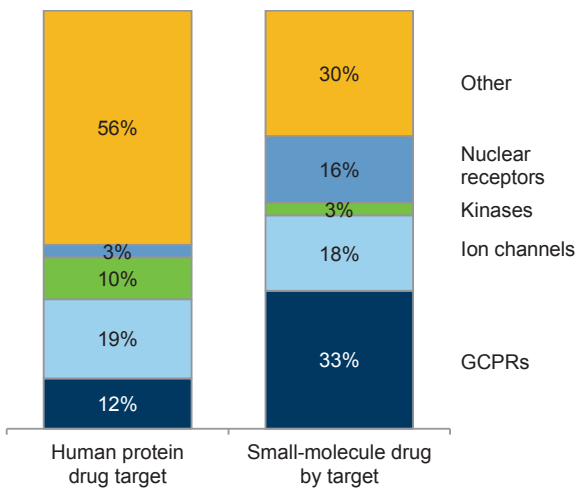
- At end-2016, there were 893 human/pathogen-derived targets based on 1,578 FDA-approved drugs (vs. 324 in 2006, based on an earlier study also conducted by the same group of scientists), 749 targeted by small molecule drugs and 179 by biologics (there are targets for both small molecule drugs and biologics).
- About 44% of targets belong to four families of targets: 1) G protein coupled receptors (GPCRs), a group of transmembrane receptors that are important to the detection of molecules outside of a cell and activate the signal transduction pathway within the cell, 12%; 2) ion channels, 19%; 3) kinase, 10%; and 4) nuclear receptors, 3%. About 70% of small-molecule drugs act against the four families of targets.

Exhibit 43: Major classes of drug targets

Target class	Mode of action	Examples
Enzymes	Inhibitors	TKIs (e.g. apatinib), DPP-4i
	Activators	Glucokinase activators (GKA)
Receptors	Agonists	GLP-1 AR (e.g. Byetta)
	Antagonists / blockers	Calcium channel blockers (CCB, e.g. amlodipine)
Ion channels	Inhibitors	lidocaine, quinidine
	Openers	Toxins (sodium channel openers), minoxidil (potassium channel opener)
Transport proteins	Inhibitors	SGLT-2 inhibitors (anti-diabetic)
Transcription factors	inhibitors	SOX-18 inhibitors (under dev.)
	Activators	E2F activators (under dev.)
Nucleic acids	Alkylation	Temozolomide (old-gen anti-cancer drugs)
	Complexation	Platins (e.g. cisplatin, carbonplatin)
	Intercalation	Doxorubicin, cyclophosphamide

Source: Goldman Sachs Global Investment Research

Exhibit 44: GCPR/ion channels/kinases as key drug targets



Source: A comprehensive map of molecular drug targets (Nat Rev Drug Discov. 2017 Jan; 16(1):19-34)

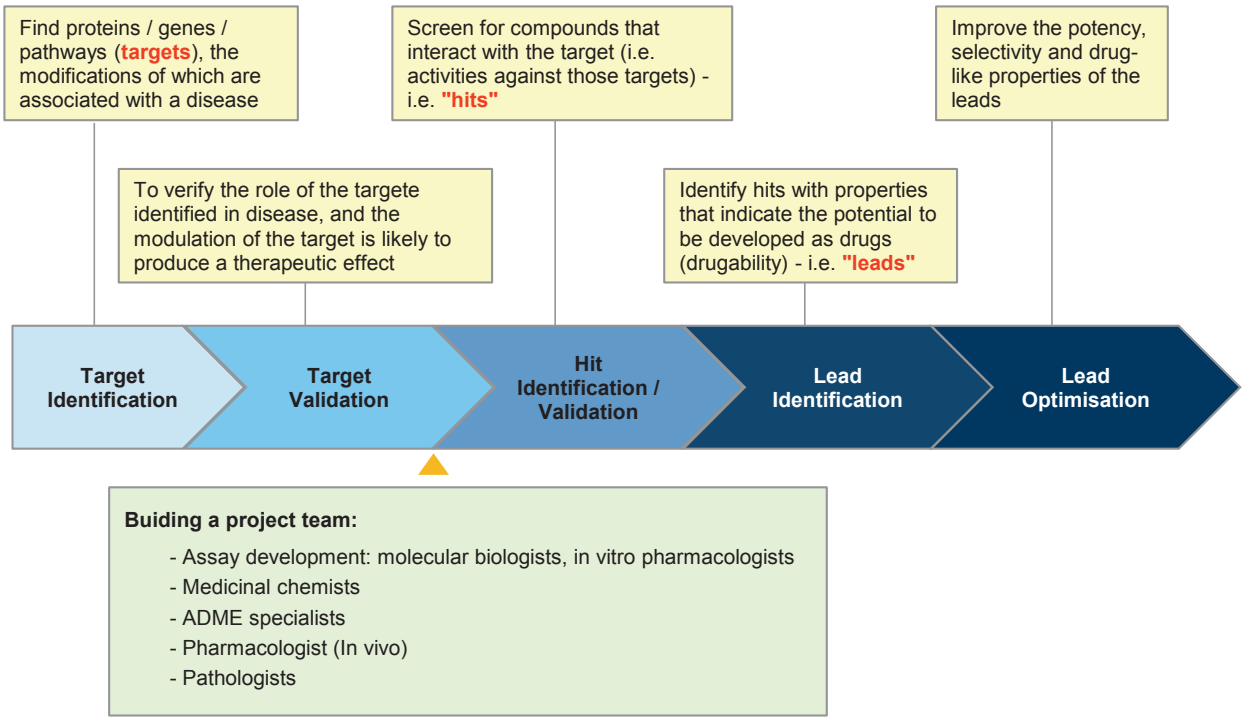
It is worth noting that human disease is highly complicated, and many targets are involved in disease progress. Therefore, activities against one or few specific targets might not be able to cure or even control diseases. However, some targets might be more important than others in terms of the pathogenesis of the disease, and thus should be selected for drug discovery.

[1] A comprehensive map of molecular drug targets, published on January 2017, Nature Review Drug Discovery

Drug discovery in China: Mostly focusing on "follow-on" strategy

After the disease of interest is determined, the drug discovery process is kicked off, starting with target identification/validation, followed by a screening process to find the optimal druggable molecule, which is further modified to improve its potency and selectivity to be a candidate for pre-clinical studies.

Exhibit 45: Basic drug discovery process



Source: Goldman Sachs Global Investment Research

Target identification:

A drug target is a molecule, a protein in most cases, that plays a critical role in a particular metabolic/signal pathway that is important to a disease condition. In cancer biology, the protein (target) could be involved in the formation of a cancer (oncogenesis or carcinogenesis), tumor proliferation or cancer metastasis (the spread of cancer cells to other parts of the body from their original location). It is worth noting that human disease is highly complicated, and many targets are involved in disease progress, thus focusing on one or few specific targets might not be able to cure or even control the diseases. However, some targets might be more important than others in the pathogenesis of the disease, and thus could be selected for drug discovery. Target identification requires basic research into the disease biology, mostly done in academic laboratories.

Target validation (TV)

Target validation is a crucial step, as it is a major commitment to start the project of developing a drug against a specific drug target after this step. The high failure rate at clinical trials could be attributable to the molecule under investigation, but in most cases, the target is what caused the failure (it is either ineffective or unsafe). A series of

bioassay (i.e., a system/method for assessment of a biological substance, i.e. "target" identified in drug discovery) will be developed to characterize the properties of the identified target. An ideal target for developing oncology drugs may have the following characteristics: 1) proven function in the formation of cancers; 2) highly selective; 3) structure is well understood; 4) suitable for high-throughput screening (i.e., drug development efficiency); 5) availability of biomarkers to monitor efficacies, and potentially more.

Hit identification (Hit ID)

Once the target has been validated, compound libraries (i.e., a collection of compounds) are used in screening to find the initial batch of molecules that can bind to the target and modify its function, i.e. hits. Different screening technologies have been developed, e.g. high throughput screening (HTS), virtual screening, and fragment screening.

Hit to lead (H2L)

For the hits identified from the screening, a series of tests are conducted for confirmation (e.g., reproducibility) evaluation of their druggability, e.g. dose response curve (IC_{50} / EC_{50}), functional cellular assay to test in vitro efficacy, and biophysical testing (how effective the hit binds to the target). Intellectual property experts also check the database to see if patents can be filed for the hit structures. Following the confirmation process, the structure-activity relationship (SAR) will be studies for a few best-performing molecules and their analogues selected from compound libraries.

Lead optimization (LO)

The understanding of the structure-activity relationship (SAR) will be utilized in this phase to improve the potency, minimize the off-target activities and other drug-related properties. Animal models will also be used in this phase to screen for the best candidates, i.e. leads.

Preclinical studies: Drug activities and toxicities

Before drug candidates can be tested in the human body (i.e., clinical trials or clinical development), preclinical studies (or preclinical development), including both *in vitro* tests ("in the glass", tests in test tubes) and *in vivo* tests ("within the living", animal experiments), need to be conducted to test the agents' pharmacodynamics (PD)/pharmacokinetics (PK) as well as its absorption, distribution, metabolism, and excretion (ADME) and toxicity.

Based on the data collected from preclinical studies, researchers aim to:

- Confirm the mechanisms of action, i.e. further test the hypothesis.
- Provide preliminary safety and efficacy data.
- Characterize the dose-effect relationship, and thereby make better estimates of the initial dose ranges for in-human trials.

The preclinical data presentation could vary, but we would like to highlight a few shared components in the read-out of preclinical studies, using Sino Biopharm's investigational anti-cancer drug anlotinib as an example (the full set of preclinical data of which was published in the February 2018 issue of Cancer Science).

Exhibit 46: IC50 indicates the target selectivity
Anlotinib case study: In vitro kinase inhibition profile

Market drug with similar MoA as benchmark

Kinase	IC_{50} (nmol/L, mean ± SD) Anlotinib	Sunitinib
VEGFR2	0.2 ± 0.1	4.0 ± 2.9
c-Kit	14.8 ± 2.5	11.0 ± 1.5
PDGFRβ	115.0 ± 62.0	7.7 ± 2.2
VEGFR1	26.9 ± 7.7	71.5 ± 12.8
VEGFR3	0.7 ± 0.1	15.7 ± 2.1
c-Met	>2000	>2000
c-Src	>2000	>2000
HER2	>2000	>2000
EGFR	>2000	>2000

A panel of tyrosin kinases (i.e. potential targets) measured

Lower IC50 means higher selectivity - Anlotinib is more potent than sunitinib in inhibiting VEGFR1/2/3

Little inhibitory activity

Potency of anlotinib against recombinant tyrosine kinases in vitro, expressed as IC50. Values are presented as mean ± SD (n = 3).

EGFR, epidermal growth factor receptor; PDGFRβ, platelet-derived growth factor receptor b; VEGFR1/2/3, vascular endothelial growth factor receptor-1/2/3

As a multi-target TKI, anlotinib shows stronger inhibitiory activity against VEGFR2/3 vs. others VEGFR1, PDGFR, c-Kit

Source: Cancer Sci. 2018;109:1207–1219., Goldman Sachs Global Investment Research

IC_{50} - In vitro selectivity

Inhibition is the most common mode of action for anti-cancer drugs, and selectivity is important for a drug to be more "targeted", which theoretically may reduce the risk of "off-target" toxicity. To measure the selectivity and potency of the drug in inhibiting the target(s), IC_{50} (half maximal inhibitory concentration) is introduced. IC_{50} means how much of an investigational drug is needed (in terms of concentration) for 50% inhibition

of the target (the smaller the number, the higher the potency/selectivity). For example, Anlotinib's IC_{50} profile shows the drug can inhibit VEGFR 1/2/3, PDGFRß and c-Kit, but it is more potent in inhibiting VEGFR2/3 than other targets.

Human tumor xenografts – in vivo efficacy

Xenografts are a group of human tumor cell lines inoculated into the experimental animal, which are mice in most cases of oncology research. The xenografts models are an important tool in evaluating the anti-cancer agents' activities in living organisms, which could potentially be indicative in forecasting the agent's activity in humans.

Exhibit 47: In vivo test with human tumor xenograft models

Anlotinib case study: In vivo efficacy against a panel of human tumor xenografts

Tumor xenograft	Tumor origin	Compound	Dose (mg/kg)	% TGI	% Regression
SW620	Colon	Anlotinib	0.75	50**	-
		Anlotinib	1.5	62**	-
		Anlotinib	3	83**	-
		Sunitinib	50	78**	-
U-87MG	Glioma	Anlotinib	1.5	43**	-
		Anlotinib	3	55**	-
		Anlotinib	6	88**	-
		Sunitinib	50	44*	-
Caki-1	Kidney	Anlotinib	0.75	48	-
		Anlotinib	1.5	27	-
		Anlotinib	3	80**	-
		Sunitinib	50	78**	-
SK-OV-3	Ovarian	Anlotinib	1.5	86**	-
		Anlotinib	3	97**	17
		Anlotinib	6	95**	17
		Sunitinib	50	88**	-
Calu-3	Lung	Anlotinib	1.5	57**	-
		Anlotinib	3	91**	17
		Anlotinib	6	95**	50
		Sunitinib	50	92**	-

Human cancer cell lines innoculated into mice, with different expression level of VEGR / VEGFR2

Anlotinib at 3mg/kg already showed anti-cancer acitivites, inhibiting tumor growth by 80-97% in colon, kidney, ovarian and lung cancer

All those four were later picked as indications in phase I/II/III trials

In those two xenograft models, tumors' size became smaller when treated by 3mg/kg or 6mg/kg anlotinib

Tumor-bearing mice received vehicle (n = 12), anlotinib or sunitinib (n = 6) p.o. daily at the indicated doses, with the exception of anlotinib at 6 mg/kg in SK-OV-3 and Calu-3 xenografts, which was orally given daily for 9 d only. Tumor growth inhibition (TGI) was calculated from the start of treatment by comparing changes in tumor volume for vehicle and treatment groups. "-" means no regression.
*P < .05, **P < .01 compared with control groups.

Source: Cancer Sci. 2018;109:1207–1219., Goldman Sachs Global Investment Research

Clinical development: Key bottleneck for new drug development

Fewer than 10% of the preclinical candidates are eventually proven to be effective and tolerable in humans, implying that the positive results obtained from preclinical studies do not necessarily translate into therapeutic effect in humans.

Exhibit 48: Overview of clinical trials in China

Stages		Key focus	Size	Time	Success	Cost*
Clinical trials	Phase I	Establish safe dosage, gather information on absorption, distribution, metabolism, excretion (AMDE) and toxicity of the compounds	10-100	0.5-1 year	~60%	$100-150m
	Phase II	"Proof-of-concept": test the preliminary efficacy of the compounds in specific group of patients	100+	1-2 years	~30%	$150-200m
	Phase III	Check for side effects and efficacy in large population	300+	2-4 years	~60%	$200m-300m
NDA Review		Clinical data review - strong evidence of efficacy / safety, comparing with standard-of-care if available		0.5-2 years	~85%	<$50m
Phase IV trials		Post-marketing safety surveillance (voluntarily or required by regulators)	2000+	multi-years		

*: US data, lack of sufficient China specific data

Source: BIO (Biotechnology Innovation Organization), Nature Rev Drug Discovery, CFDA

The protocol, or clinical trial design, will cover a few key aspects:

Number of participants (enrollees)

The sample size of the clinical trials will be calculated by statisticians to meet the minimal requirements for data analysis. Underestimation of the sample size could make the trial unable to detect a clinical significance, while significant overestimation can also lead to trouble: 1) longer-than-needed time consumed; 2) potential ethical issues; and 3) some clinically irrelevant but statistically significant differences being detected, making the data analysis more complicated.

Inclusion and exclusion criteria

The specific patient population to be included into the trial. Broader population implies a larger addressable market if the investigational drug works, but may also increase the risk of failure. More stringent inclusion/exclusion criteria will lead to more time spent on patient enrollment.

The criteria, in trials on oncology drugs, usually cover:

- Age, e.g. 18-75 years old.
- Stage of disease, e.g. locally advanced/metastatic for cancers or stage III/IV.
- Histological/gene type, e.g. adenocarcinoma type of lung cancer (histological), or HER2+ type in breast cancer (genotype).

- Prior treatment, which defines the line of treatment the drug candidate is for, i.e. if target patients failed one prior treatment, the drug candidate is for second-line.
- Other medications and medical conditions.
- Performance status (PS), Eastern Cooperative Oncology Group (ECOG) scale is widely used, measuring patients' physical status on a scale of 0-4; the higher the score, the poorer the performance status, with a score of 4 meaning the patient is completely bedridden. Most trials require ECOG 0-1, and ECOG 2 is also common but normally accounts for a relatively small portion of the total sample size.

Ways to limit the bias

Allocation (how participants are assigned to different groups), masking (either blinded or open label) and adding control arms (such as a placebo, i.e. an inert substance that looks like the drug candidate, e.g. sugar pills, or positive control, i.e. a standard-of-care treatment) are all used to minimize the bias in clinical research. Randomized, double-blind, multicenter studies are considered the "gold-standard" design for evaluating the effectiveness and side-effects of new therapies, as randomized allocation minimizes differences between groups, while double blind masking reduces the bias in treatment as well as data reporting.

Exhibit 49: Basics of study design in clinical trials

Details	Major types	Definition	Application
Study design			
Entrollment (sample size)		# of patients / healthy volunteers (in phase I) included in the study	In most cases: 20-100 in phase I, 100+ in phase 2, 300+ in phase 3. Fewer for orphan drugs or breakthrough therapies
Allocation	Randomized	A type of allocation strategy in which participants are assigned to the arms of a clinical trial by chance.	Applied for most trials with more than one arms
Masking	Double blind	The investigator and participants do not know which participants have been assigned which treatment (could be the drug to be tested, placebo or standard-of-care therapy) to prevent bias in treatment and reporting	Randomized, double blind study is "gold standard" in phase III, and may also apply in phase II, while phase I is mostly open label studies
	Open label	Both investigators and enrollees know which treatment has been given	
Arms (group)	Experimental	Participants receive the investigational drug	Dosing strategy and treatment cycles are also laid out in this section of study records
	Control	Participants receive standard treatment or placebo if there is no effective standard treatment	

Source: Goldman Sachs Global Investment Research

Dosing strategy

Define how the investigational drug will be given to patients, including:

- **Dosage**: In cancer treatment, could be a fixed dose in milligrams or doses depending on body weight (e.g., in the form of mg/kg) or body surface area (BSA, in the form of mg per square meter, mg/sqm).
- **Frequency**: For oral formulations (e.g. tablets/capsules/pills), once daily is the ideal frequency in terms of patient compliance (i.e., how well the patient will follow the physician's instruction on taking the medicines), while three times a day is also common (i.e., by meal time); in chemotherapies with medicines in injectable formulation, a 3-week (21-day) or 4-week (28 day) cycle is most common.
- **Administration route**: The oral route is preferred given the convenience, lower non-drug treatment costs (e.g., bed charge, fee for injection services) and lower

exposure to injection-related side-effects. However, some advanced cancer therapies, e.g. monoclonal antibodies, can only be administrated via injection. For drugs given via intravenous injection, the bioavailability is 100% (i.e., 100% of the drug will enter the blood circulation and have an active effect), which decreases for other routes.

Exhibit 50: Most common prescription abbreviations in dosing strategy description

Abbreviations	Meanings	Drug / therapy examples
Route of administration		
p.o.	by mouth or orally	Those in oral form, e.g. tablets / capsules
ID	intradermal (within the skin)	Lidocaine (a local anesthesia medicine)
SC / SubQ / SQ / s.c.	subcutaneous (under the skin)	Enbrel (anti-TNF), insulin
IM / i.m.	intramuscular (deeper than. SC)	Invega (paliperidone), Abilify (aripiprazole)
IV / i.v.	intravenous	Most anti-cancer drug in injectable form
How often		
b.i.d. / b.d.	twice daily	Byetta (exenatide), premix insulin
t.i.d. / t.d.s. / t.d.	three times a day	Commana (icotinib tablets)
t.i.w	three times a week	Pegasys (interferon)
q.i.d	four times a day	Some antibiotics
o.d. / q.d. / QD	every day / once daily	Victoza (liraglutide), ATAN (apatinib), anlotinib
q.w. / QWK	every week	Bydureon (exenatide microspheres)
q3w / q4w	every 3 weeks or 4 weeks	Typical chemotherapies (3-4 weeks as 1 cycle)

Source: Goldman Sachs Global Investment Research

Endpoint selection

To understand the efficacy/safety profile of the investigational drug, a set of data/parameters (i.e., clinical endpoints) will be assessed for the candidates only or with comparison to a control group, which could be placebo or standard-of-care therapy. Those parameters should be clinically relevant, objective, reproducible and easy to measure. Endpoints are specific for different diseases. In cancer trials, typical endpoints include measurements of toxicity, response rate and survival.

The selection of primary endpoints can affect the resources (time and budget) required for a trial, the quality of the evidence from the trial and the regulatory approval. In cancer drug development, overall survival (OS) is considered the most reliable endpoint, but a surrogate marker might be applied given that it might require extraordinarily large and long studies to obtain overall survival data. In Exhibit 51 we provide the pros and cons of endpoints widely used in supporting past approvals in oncology, as well as the preferred study design for those endpoints as a reference.

Exhibit 51: Widely accepted clinical trial endpoints

Category	Endpoints		Definitions
Survival	**OS**	Overall Survival	Time from randomization to deaths from any cause
Endpoints based on tumor assessment	**PFS**	Progression-Free Survival	The time from randomization until objective tumor progression or death
	DFS	Disease Free Survival	Time the patient survives without any detectable cancer
	TTP	Time to Progression	The time from randomization until objective tumor progression, TTP does not include deaths (vs. deaths included in PFS)
	TTF	Time-to-Treatment Failure	Time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.
	ORR	Objective Response Rate	ORR = CR + PR
	CR	Complete Response	All detectable cancer is gone after treatment. There can still be cancer left (i.e. not cured), but not detectable
	PR	Partial Response	A decrease in the amount of cancer of at least 50%, but less than 100%
	DCR	Disease Control Rate	DCR = CR + PR + SD
	SD	Stable Disease	Tumors have remained about the same size with no new ones appearing.
	PD	Progressive Disease	Tumors are growing or new tumors are appearing.
Pharmacokinetic (PK)	**Cmax**	Maximum plasma concentration	The point of maximum concentration of drug in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration
	Tmax	Time to Cmax	The time for drug to reach peak concentration in plasma, used in estimate the rate of absorption of the drug. Onset time / onset of action are dependent upon Tmax
	t1/2	Terminal half life / biological half life	The time required for the plasma concentration of a drug to decease 50% in the final stage of its elimination
	AUC	Area under the curve	Represents the total integrated area under the plasma level-time profile and expresses the total amount of drug that comes into the systemic circulation after its administration, used in evaluating the bioavailability of a drug
Toxicity	**MTD**	Maximum Tolerated Dose	The highest dose of a drug, drug combination, or other treatment that most people can safely withstand.
	DLT	Dose Limiting Toxicity	Side effects that are severe enough to prevent giving more of the treatment
	AE	Adverse Events	Side effects, on the scale of 1-5. Grade 1/2 as mild / moderate AE; Grade 3+ as severe, Grade 5 as AE-related death

Source: FDA, Goldman Sachs Global Investment Research

Phase I trials - safety profile, dose finding and PK/PD

Phase I (sometimes written as phase 1) oncology trials are usually small single-arm studies, enrolling only 10-30 patients with specific cancers (for less toxic drugs targeting other diseases, e.g., diabetes, the participants could be healthy volunteers). The clinical endpoints of a phase I trial are typically tolerability – e.g., adverse event, dose limiting toxicity (DLT) and maximum tolerable dose (MTD) or PK (e.g., C_{max}/T_{max}, $t_{1/2}$, and area under the curve (AUC).

Characterize safety profile

What are the side-effects and how severe are they? In clinical trials, "adverse event (AE)" is used to refer to an unintended sign, symptom or disease associated with the use of the investigational therapy.

- **Grading system:** The US National Cancer Institute (NCI) of the National Institutes of Health (NIH) publishes standardized definitions for AEs, which is the common terminology criteria for adverse events (CTCAE); the most updated one is version 5.0 published in November 2017. The grading system for AEs has been widely adopted in clinical trials conducted worldwide, including in China. Grade 1 or 2 are AEs considered as mild/moderate side-effects (e.g., the hemangioma developed in patients that have received Hengrui's PD-1 antibody) , while Grade 3+ AEs are considered to be severe.

Exhibit 52: Grades of adverse events - CTCAE v5.0

Grade	Clinical descriptions of severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL*.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse effects

*: ADL - Activities of Daily Living: 1) instrumental ADL - preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc; 2) Self care ADL - bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Source: US National Cancer Institute

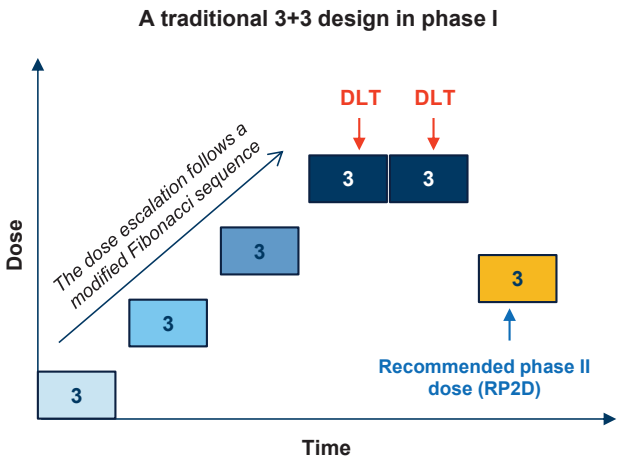
- **Serious AEs (SAEs):** In clinical trial data presentation, serious AEs (presented as the number of cases and the percentage of total participants) are usually singled out. However, the number of serious AEs is not necessarily equal to the number of Grade 3/4 AEs (i.e., severe AEs). This difference is due to the fact that the term "severe" is used purely to show the intensity or severity of a side-effect, which might be of relatively minor medical significance (e.g., a Grade 3 headache), i.e. severe but not serious, while serious AEs refer to severe AEs that pose a threat to a patients' life or ability to function.

Recommended dose for phase 2 (RP2D)

In most cases, the higher the dose, the stronger the efficacy, but higher doses also entail higher risk of side-effects, thus a recommended dosage would be the highest dosage with the side-effects still manageable (i.e., tolerable). The dose-finding process is conducted via a dose escalation study. While more and more different dose escalation methods have been developed for more efficient rational dose finding, the traditional 3+3 design remains most common in phase I oncology trials (e.g., the phase I trial of Sino Biopharm's anlotinib):

- Step 1: The initial cohort (i.e., a group of patients with a shared dosing strategy) of three patients is given a starting dose, which is considered to be safe based on extrapolation from preclinical animal experiments measuring toxicity.
- Step 2: The subsequent cohorts are treated using increasing dose levels. The dose escalation follows a modified Fibonacci sequence (though it can be less strict in real practice).
- Step 3: If one of the three patients experiences a dose limiting toxicity (DLT), which is typically defined before the start of the trial, three more patients will be added to the cohort to receive the same dose of test drug. The process will continue until at least two patients among a cohort of 3/6 patients experience DLT, and the dose right below the toxic dose level will be the recommended dose for the phase II trial.

Exhibit 53: Illustration of traditional 3+3 phase I design with anlotinib case



Anlotinib Phase I design

Dose Cohort		
Four consecutive weeks	5mg/day	4 pts
	10mg/day	4 pts
2-week on / 1-week off	10mg/day	3 pts
	12mg/day	21 pts
	16mg/day	3 pts

DLT (dose limiting toxicities)
Grade 4 blood toxicity Grade 3 neutropenia with fever ≥38.5 °C Grade 3+ non-hematologic toxicity

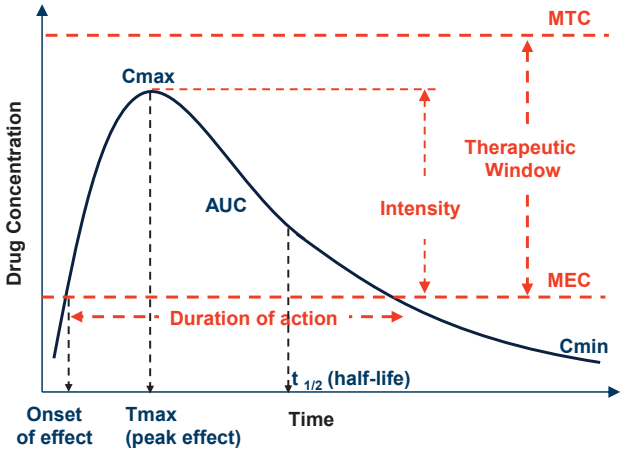
MTD (maximum tolerable dose)
The highest dose level for which the incidence of first-cycle DLT was <33 %

Source: Company data, Goldman Sachs Global Investment Research

Pharmacokinetics (PK)/pharmacodynamics (PD) studies

PK explains what the body does to a drug (summarized as ADME, i.e. absorption, distribution, metabolism and excretion) and PD refers to what the drug does to the human body. The PK profile is usually reflected in a set of parameters, among which C_{max} / T_{max}, $t_{1/2}$, and AUC are most commonly mentioned, which are key data used to guide the trial design of phase II/III trials.

Exhibit 54: Illustration of pharmacokinetics (PK) parameters in phase I trial



PK parameters		Interpretation
AUC	Area under the curve	Total drug exposure over time, proxy of bioavailability
Cmax	Maximum concentration	Important for dose selection
Cmin	Minimum concentration	(viewed relative to MEC / MTC)
Tmax	Time to reach Cmax	Most appropriate time to perform safety assessment
$t_{1/2}$	time for Cmax to drop by half, i.e. half life	Used in defining 1) how often a drug has to be dosed, i.e. dosage interval; and 2) washout period between treatments in crossover studies
MTC	Minimum toxic concentration	Minimum concentration in which toxicity usually occurs
MEC	Minimum effective concentration	Drug concentration level need to be maintained above MEC level to avoid resistance

Source: US FDA, Goldman Sachs Global Investment Research

Preliminary efficacy

While efficacy is not the primary focus of phase I trials, some preliminary efficacy data, such as objective response rate (ORR, including partial response and complete response), might be analyzed to provide early insights into the potential efficacy of the investigational drug in the human body.

Phase-II trials: Proof of concept (POC) studies

Phase II trials are key screening tools used to assess the efficacy (i.e., clinical outcome) of the investigational drug (proof-of-concept, POC) and gain further toxicity information, before entering more costly phase III trials. With the increasing cost of R&D in China, phase II trials will be critical in managing the overall return of the drug development projects for Chinese biotech companies.

Moreover, since the CFDA has set up a conditional approval pathway for breakthrough novel therapies, phase II trials alone could act as a potential registrational trial. For example, Hengrui filed an NDA for pyrotinib, a novel anti-HER2 targeted therapy for breast cancer, based on a phase II trial; and the NDAs of three domestic PD-1 antibodies – i.e. Hengrui's SHR1210, Innovent's IBI-08 and Junshi Bio's JS001 – were also filed with small-scale pivotal phase II data. In a biosimilar pathway established in 2015 in China, phase II trials could be exempted, if the bioequivalence is proven in the phase I study.

Phase II trial design

We outline three typical phase II trial designs below: 1) pyrotinib (Hengrui), which is an example of a Chinese player conducting phase II trials on a combination therapy with standard-of-care treatment as positive control; 2) anlotinib (Sino Biopharm), an example of a Chinese player's phase II of a single-agent therapy with placebo as control; and 3) crizotinib (Pfizer), an example of an MNC's single-arm open label phase II in China on a single agent therapy. While the design of phase II trials can vary by allocation, masking and intervention, due to different focuses, they share similarity in:

Exhibit 55: Comparison of three phase II trial designs

	Pyrotinib	Anlotinib	Crizotinib
MoA	anti-HER2	VEGFR2/3	ALK
Sponser	Hengrui	Sino Biopharm	Pfizer
Phase	Phase I/II	Phase IIb	Phase II
Regimen	Pyrotinib + capecitabine	Single-agent	Single-agent
Indication	HER2+ mBC, 2L	NSLCLC, 3L	ROS1+ NSCLC
Multi-center?	Single site	14 sites	41 sites (22 in China)
Allocation	Randomized	Randomized	Unrandomized
Control group	Lapatinib + capacitabine	Placebo	-
Masking	Open-label	Double-blinded	Open-label
Intervention	Parallel	Parallel	Single-arm
Dose	400mg, q.d. (pyrotinib)	12mg, q.d.	200mg, b.i.d; 250, b.i.d.; or 250mg, q.d.
Size	128	117	110 (69 in China)
Primary endpoint	ORR, safety (e.g. AE)	PFS, safety (e.g. AE)	ORR
Secondary endpoint	PFS, TTP, DoR	DCR, ORR, OS, QOL	DR, TTR, DCR, PFS, OS, AE, QOL
Registration #	CTR20150279	CTR20130315	CTR20140093

Could be single-arm or with control group (placebo or standard-of-care), masking could be open-label or double blinded

ORR and PFS as well as AEs are commonly used primary endpoints for

Source: CFDA, Goldman Sachs Global Investment Research

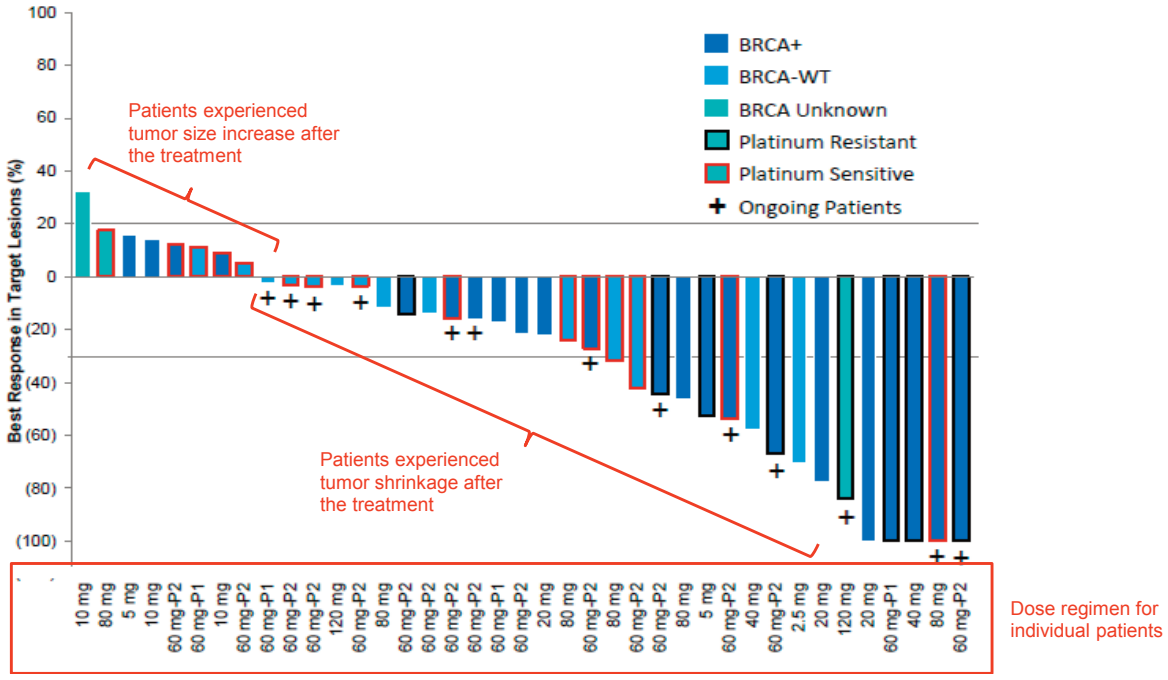
- **Sample size:** From about 100 to a couple of hundred patients. In some cases (e.g. rare diseases, or potent agents), the size of phase II could be smaller than 100, e.g. 60-90 for the phase II trials of Hengrui/BGNE/Junshi's anti-PD1 inhibitor on Hodgekin's lymphoma.
- **Primary endpoints:** Since the primary goal in phase II is to determine if there is sufficient evidence showing anti-tumor activities to warrant further investigation, the overall response rate (ORR) or the reduction of a tumor biomarker are appropriate

endpoints as they both measure the anti-tumor activities. In a randomized trial, progression free survival (PFS) is also an appropriate endpoint for phase II. However, it is worth noting that tumor shrinkage (e.g. ORR) does not measure the survival benefit to patients, and the evaluation of ORR is subject to measurement error, despite the standardized practice laid out in RECIST (Response Evaluation Criteria in Solid Tumors).

Waterfall plots

Waterfall plots are commonly used to demonstrate response data, e.g. maximal changes in tumor size among patients in phase II trials. It is also now more common for waterfall plots to be used to show best response data in enlarged phase I trials or phase I/II trials.

Exhibit 56: Waterfall plot example: Pamiparib (BGNE) phase I/II data as of June 1, 2017 (ESMO 2017)



Source: Company data

Phase-III trials: Confirmation in larger scale

Phase III oncology trials are the most expensive and time-consuming step of the whole drug development process. By enrolling a large number of patients (300+ as requested by CFDA), phase III trials compare the investigational therapy (single agent or in combination with standard treatment) with the standard treatment ("standard-of-care", SOC) or placebo when no SOC is available. The key purpose of phase III trials is to further confirm the efficacy and safety profile demonstrated in phase I/II trials.

Phase III trial design

A multi-center, double-blinded, randomized controlled trial (RCT) is considered to be the most rigorous design for a phase III trial, minimizing the bias for more reliable results.

- **Sample size:** Based on the CFDA's guidelines, at least 300 patients need to be enrolled in a phase III trial. The actual enrollment amount will be determined based on assessment of clinicians and statisticians .
- **Primary endpoints:** There are only two ways in which patients can benefit from a treatment: i.e., live longer (survival benefit) or live better (quality of life), thus the most appropriate endpoints of phase III trials are overall survival (OS) and quality of life (QoL, which is based on a scoring system). Any other endpoints are surrogate endpoints and should be shown to be correlated with OS or QoL.

  In oncology phase III trials, OS is the gold standard. However, considering the length of study with OS as the endpoint, particularly in an adjuvant setting, progress free survival (PFS) is commonly used as the primary endpoint. The advantages of PFS also include the fact that it is not affected by subsequent therapies. However, longer PFS does not necessarily translate into longer OS, and there have been cases of drugs being approved with superior PFS data showing no OS benefits in subsequent trials, e.g. Iressa (gefitinib) from AstraZeneca in treating non small cell lung cancer.

Exhibit 57: Comparison of widely used clinical trial endpoints

Endpoint		Overall survival (OS)	Progression-free survival (PFS) / Time to progression (TTP)	Disease-free survival (DFS)	Objective response rate (ORR)
Study design	Randomized	Essential	Essential	Essential	Randomized, or single-arm studies
	Blinding	Not essential	Preferred	Preferred	Preferred (in comparative studies)
	Blinded review	-	Recommended	Recommended	Recommended
Pros		Gold standards: direct measure of benefits, easy to measure, precise	Smaller size / shorter follow-up vs. survival studies; stable disease included; not affected by crossover / sequential therapies; generally objective and quantitative	Smaller size / shorter follow-up vs. survival studies	Works in single-arm studies; smaller size / earlier assessment vs. survival studies; effect attributable to drug
Cons		Large sample size (longer time); noncancer related deaths included; maybe affected by crossover / sequential therapies	Not precise (tumor assessment bias, esp. in open-label studies); definition of "progression free" vary among studies; involves balanced timing of assessments among treatment arms; frequent radiological or other assessment	Not precise (tumor assessment bias, esp. in open-label studies); definition of "disease free" vary among studies	Not a direct measure of benefit; not a comprehensive measure of drug activity; only a subset of patients (i.e. those responded)

Source: US FDA, Goldman Sachs Global Investment Research

Understanding Kaplan-Meier (K-M) curves

First developed in the 1950s, Kaplan-Meier (K-M) curves and estimates of survival data have been widely used to estimate a population's survival curve from a sample, even when patients drop out or stay in the trial for different lengths of time. In the presentation of phase III survival data – e.g., overall survival (OS) or progression-free survival (PFS) or diseases free survival (DFS) – K-M curves are one of the most commonly used plots.

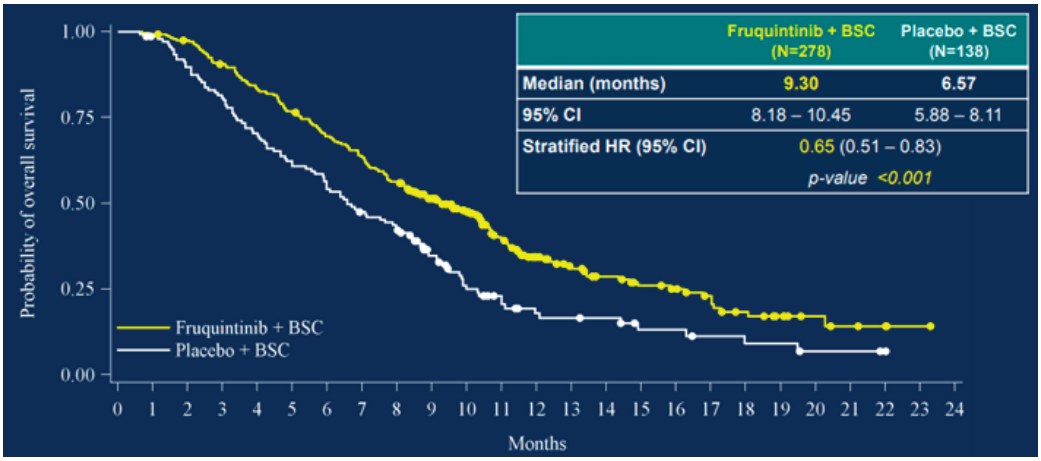
When data on a K-M curve is presented, a table of survival data is usually showed, and the details covered in the table usually include: the median OS/PFS (in months or weeks), sample size (n), 95% confidence interval (CI), hazard ratio (HR) at 95% CI and p value for statistical significance (see HCM's fruquitinib phase III FRESCO study OS K-M curve as an example).

- **P-value (statistical significance)**: When comparing the clinical endpoints data (e.g. OS) between test arm and control arm, p value (i.e., the observed results/difference between the groups is purely by chance alone) can help determine the robustness of the results. In general, $p<0.05$ (i.e., there is less than a 5% chance that the observed results are due to chance rather than due to the treatment) is the threshold for statistical significance, i.e., the two groups are statistically different, while $p<0.001$ as statistically highly significant.
- **95% confidence interval**: The 95% confidence interval is defined as the mean plus or minus 2 standard deviations (the extent of variability around the mean due to chance), this means that if the trial was repeated an infinite number of times, the mean of the study would fall within this range 95% of the time. The narrower the

confidence interval, the better. Wide confidence intervals may imply that the sample size is not large enough.

- **Hazard ratio (HR)**: In its simplest form, the hazard ratio is the chance of an event occurring in the treatment arm divided by the chance of the event occurring in the control arm, or vice versa, of a study. In oncology trials, hazard ratios are often referred to as the ratio of death probabilities. For example, in fruquitinib phase III data, the hazard ratio of 0.65 means the risk of death decreased by 35% in the treatment group vs. the placebo group.

Exhibit 58: Kaplan-Meier (K-M) curves: Fruquitinib phase III OS data as an example



Source: ASCO 2017, company reports

A few key concepts to highlight for better understanding of K-M curves:

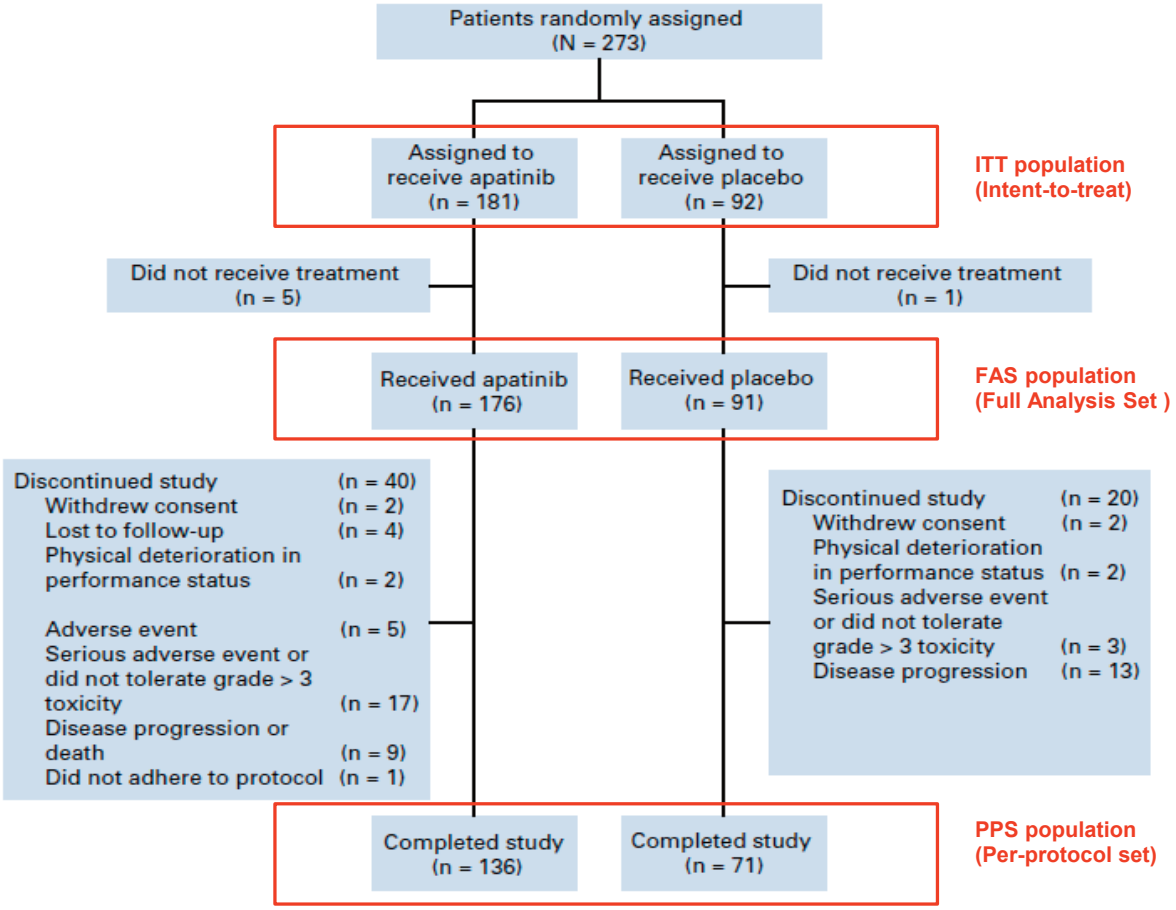
- K-M curves used in cancer literature mostly fall under three types: OS curves, DFS curves (lower than OS curves) and PFS curves.
- Each sample is characterized by three variables: 1) the study group it is in, the test arm or the control arm; 2) length of stay in the study; 3) status at the end of the their serial time, i.e. event of interest (e.g., death in measuring OS, tumor growth or spread in measuring PFS, disease relapse in DFS) or censored, which could be due to drop-outs, lost to follow-up, or required data is not available.
- The shape of a K-M curve matters: 1) curves with more steps have a higher number of participants; 2) the wider the two curves separate (test arm and control arm), the more potentially significant the difference is, though p-value is the key to telling whether the significance is statistically meaningful.
- The amount of censored subjects is important as a large number of patients censored may lead to questions about whether the treatment was not effective enough, causing many patients to leave the study to pursue other treatments. A K-M curve that does not included censored patients should be examined with caution.

Data analysis: ITT, FAS and PPS

We would also like to highlight a few concepts in data analysis in phase III trial:

- **Intent-to-treat (ITT) analysis:** All the patients after the randomization will be included in the analysis, regardless of drop-outs (i.e., patients quit the trial), any slight change in protocols (e.g., a switch between treatment groups), and noncompliance (not taking medicines according to prescription). ITT is considered to be the most conservative analysis with minimal bias.
- **FAS and PPS analysis:** ITT is more a principle, while in clinical trials some patients could withdraw right before they received the first dose and even do not have baseline medical records (i.e., the starting points, including a series of basic tests done before treatment). Adding those patients might not bring additional data points. In that case, ITT will be modified, i.e. mITT. There are two most widely used mITT – FAS (full analysis set), which is closest to ITT, while PPS (per-protocol set) is the subset of FAS only including patients without major protocol violations. The results from FAS and PPS might be similar in most cases, but could lead to different conclusions in a few cases.
- **Interim analysis:** Before the trial is completed, interim analysis might be conducted under different conditions: 1) timely monitor, particularly for side-effects; 2) early termination because of efficacy, which could be either promising or below expectations; and 3) sample resizing. It is important to note that the protocol for interim analysis must be pre-specified before the trial starts.

Exhibit 59: ITT/FAS/PPS population: Apatinib Phase-III enrollment as an example



Source: Company data

Phase 0 & IV trials - Exploratory studies and post-marketing surveillance

Other than the conventional phase I/II/III trials that almost all new therapies have to go through before obtaining regulatory approval for marketing, there are two other types of clinical trials:

- **Phase 0 trials or exploratory studies:** These in-human studies aim to test initial interaction between drugs and the human body, as well as anti-cancer activities before initiating the later phase of clinical trials. Only a very few patients are enrolled (e.g. 10-15), and the doses of the drug are low.
- **Phase IV trials or post-marketing studies:** Trials undertaken after a drug is launched in the market could be due to a CFDA request related to assessing the drug's long-term effects and potentially rare but clinically serious side-effects, which may not have been assessed adequately in phase III. However, in most cases, pharma companies leverage post-marketing studies to better position the product in the marketplace and facilitate product recognition among physicians.

Unconventional biomarker-driven trial as a new option

Traditionally, phase I trials are conducted with a mixture of different cancers while phase II/III oncology trials focus on a specific cancer, which is defined by histopathologic tests, e.g. lung cancer means the primary site of the cancer is in the lung. However, with the improving understanding of the role of key genes or gene mutations in the genesis of cancers, more studies have been conducted on the molecular profiling of tumors (e.g., the distribution of EGFR mutation in lung cancer). Some findings suggest biomarkers might be more predictive of patients' sensitivity to targeted therapies vs. histology of tumors (e.g., all HER2+ cancer patients respond better to anti-HER2 treatment, regardless of the location of the tumor, which could be in the breast or the stomach), leading to the development of biomarker-driven clinical trials.

Two major types of biomarker-driven trials:

- **Basket trial:** Single treatment for histologically different tumors with the same biomarker. Basket trials could increase the number of patients that are eligible to receive certain therapies, thereby accelerating the study. The first FDA approval of a treatment for solid tumors based on a basket study was granted to Keytruda in 2017, targeting cancer patients with MSI-H/dMMR biomarkers (microsatellite instability-high or mismatch repair deficient).
- **Umbrella Trial:** For a single cancer type, multiple treatments each matched to multiple biomarkers are covered in one trial. This is particularly useful when the biomarker prevalence is low. Combining basket trials and umbrella trials could create so-called super umbrella trials, e.g. NCI-MATCH trial, which covers 18 biomarkers, 12 treatments and patients with both the most prevalent and rare cancers.

In China, biomarker-driven trials have not been utilized so far.

Access to clinical trial design and clinical data

Access to clinical trial details has improved notably since September 2013, when the CFDA began to request trial sponsors to: 1) register clinical trials conducted in China, including bioequivalent studies, PK studies, and phase I/II/III/IV trials, at CDE's online platform (www.chinadrugtrials.org.cn) before the first patient enrollment and keep the disclosed information updated along with the progress of the trials; and 2) more and more China trials have also been registered at clinicaltrials.gov, which is provided by the U.S. National Library of Medicines and has become one of the largest clinical trial databases worldwide.

Selected medical conferences

The availability of the results of clinical trials depends on biotech/pharma companies' disclosure, which can be in the format of company announcements/press releases, publications on medical journals or presentations at major medical conferences. With leading Chinese biotech/pharma companies' growing focus on building their reputations in the global medical community, we have been seeing an increasing number of presentations at global conferences (either poster presentations or oral presentations).

Among the numerous medical conferences hosted every year with a focus on various therapeutic areas, we picked a few of the most important ones related to cancer treatment, such as the annual meeting of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology Congress (ESMO). Over the last several years, we have seen a growing number of clinical studies sponsored by China-based pharma/biotech companies and conducted by Chinese principal investigators (PIs) being selected to present to the global medical community. The China version of ASCO, i.e. CSCO, has also become one of the key platforms to understanding the most updated trends in clinical treatment for cancers and development of key domestic novel therapies.

Exhibit 60: Selected medical conferences over the next 12 months (2Q18 to 1H19)

Date	Short	Conferences	Focus	Location
Oncology				
Apr 11 - Apr 14, 2018	ELCC	European Lung Cancer Congress 8th Edition	Lung cancer	Geneva, Switzerland
Apr 14 - Apr 18, 2018	AACR	The American Association For Cancer Research Annual Meeting 2018	All cancers	Chicago, IL, US
Jun 01 - Jun 05, 2018	ASCO	The Annual Meeting of the American Society of Clinical Oncology 2018	All cancers	Chicago, IL, US
Jun 20 - Jun 23, 2018	World GI	ESMO World Congress on Gastrointestinal Cancer 2018	Gastrointestinal cancers	Barcelona, Spain
Sep 19 - Sep 23, 2018	CSCO	The 21st Annual Meeting of Chinese Society of Clinical Oncology	All cancers	Xiamen, China
Sep 23 - Sep 26, 2018	IASLC WCLC	IASLC 19th World Conference on Lung Cancer	Lung cancer	Toronto, Canada
Oct 19 - Oct 23, 2018	ESMO	The European Society for Medical Oncology Congress 2018	All cancers	Munich, Germany
Nov 08 - Nov 11, 2018	EMUC	10th European Multidisciplinary Congress on Urological Cancers	Urological cancers	Amsterdam, Netherlands
Nov 23 - Nov 25, 2018	ESMO Asia	ESMO Asia 2018 Congress	All cancers	Singapore
Dec 04 - Dec 08, 2018	SABCS	The San Antonio Breast Cancer Symposium	Breast cancer	San Antonio, TX, US
Dec 13 - Dec 16, 2018	ESCO IO	ESMO Immuno-Oncology Congress 2018	Cancer immunotherapy	Geneva, Switzerland
Jan 17 - Jan 19, 2019	GICS	The ASCO Gastrointestinal Cancers Symposium 2019	Gastrointestinal cancers	San Francisco, CA, US
Feb 14 - Feb 16, 2019	GUCS	The ASCO Genitourinary Cancers Symposium 2019	Genitourinary cancers	San Francisco, CA, US
Feb 28 - Mar 02, 2019	-	The ASCO-SITC Clinical Immuno-Oncology Symposium 2019	Cancer immunotherapy	San Francisco, CA, US
Mar 14 - Mar 16, 2019	-	Multidisciplinary Thoracic Cancers Symposium	Lung cancers	San Diego, CA, US
May 02 - May 04, 2019	-	ESMO Breast Cancer Annual Congress	Breast cancer	Berlin, Germany
Jun 18 - Jun 22, 2019	ICML	15th International Conference on Malignant Lymphoma	Lymphoma	Lugano, Switzerland
Other diseases				
Mar 10 - Mar 12, 2018	ACC	American College of Cardiology's 67th Annual Scientific Session & Expo	Cardiology	Orlando, FL, US
Mar 16 - Mar 20, 2018	EAU	33rd Annual European Association of Urology Congress	Urology	Copenhagen, Denmark
Apr 29 - May 03, 2018	ARVO	Annual Meeting of Association for Research in Vision and Ophthalmology	Eye diseases	Honolulu, HI, US
Apr 11 - Apr 15, 2018	ILC	The International Liver Congress 2018	Liver diseases	Paris, France
May 18 - May 21, 2018	AUA	American Urological Association Annual Meeting	Urology	San Francisco, CA, US
Jun 13 - Jun 16, 2018	EULAR	Annual European Congress of Rheumatology	Rheumatology	Amsterdam, Netherlands
Jun 14 - Jun 17, 2018	EHA	23rd European Hematology Association Annual Congress 2018	Hematology	Stockholm, Sweden
Jun 22 - Jun 28, 2018	ADA	American Diabetes Association, 78th Scientific Sessions	Diabetes	Orlando, FL, US
Sep 20 - Sep 23	ISH	ISH 2018 Scientific Meeting	Hypertension	Beijing, China
Oct 01 - Oct 05, 2018	EASD	54th Annual Meeting of the European Association for the Study of Diabetes	Diabetes	Berlin, Germany
Oct 06 - Oct 10, 2018	CHEST	American College of Chest Physicians (AACP) Annual Meeting	Chest-related diseases	San Antonio, TX, US
Oct 19 - Oct 24, 2018	ACR/ARHP	American College of Rheumatology's Annual Meeting	Rheumatology	Chicago, IL, US
Oct 23 - Oct 28, 2018	ASN	American Society of Nephrology Annual Meeting 2018	Nephrology	San Diego, CA, US
Nov 09 - Nov 13, 2018	AASLD	American Association for Study of Liver diseases, Liver Meeting	Liver diseases	San Francisco, CA, US
Nov 10 - Nov 14, 2018	AHA	American Heart Association's Scientific Sessions 2018	Heart diseases	Chicago, IL, US
Dec 01 - Dec 04, 2018	ASH	60th American Society of Hematology Annual Meeting & Exposition	Hematology	San Diego, CA, US
Feb 06 - Feb 08, 2019	ISC	International Stroke Conference 2019	Stroke	Honolulu, HI, US

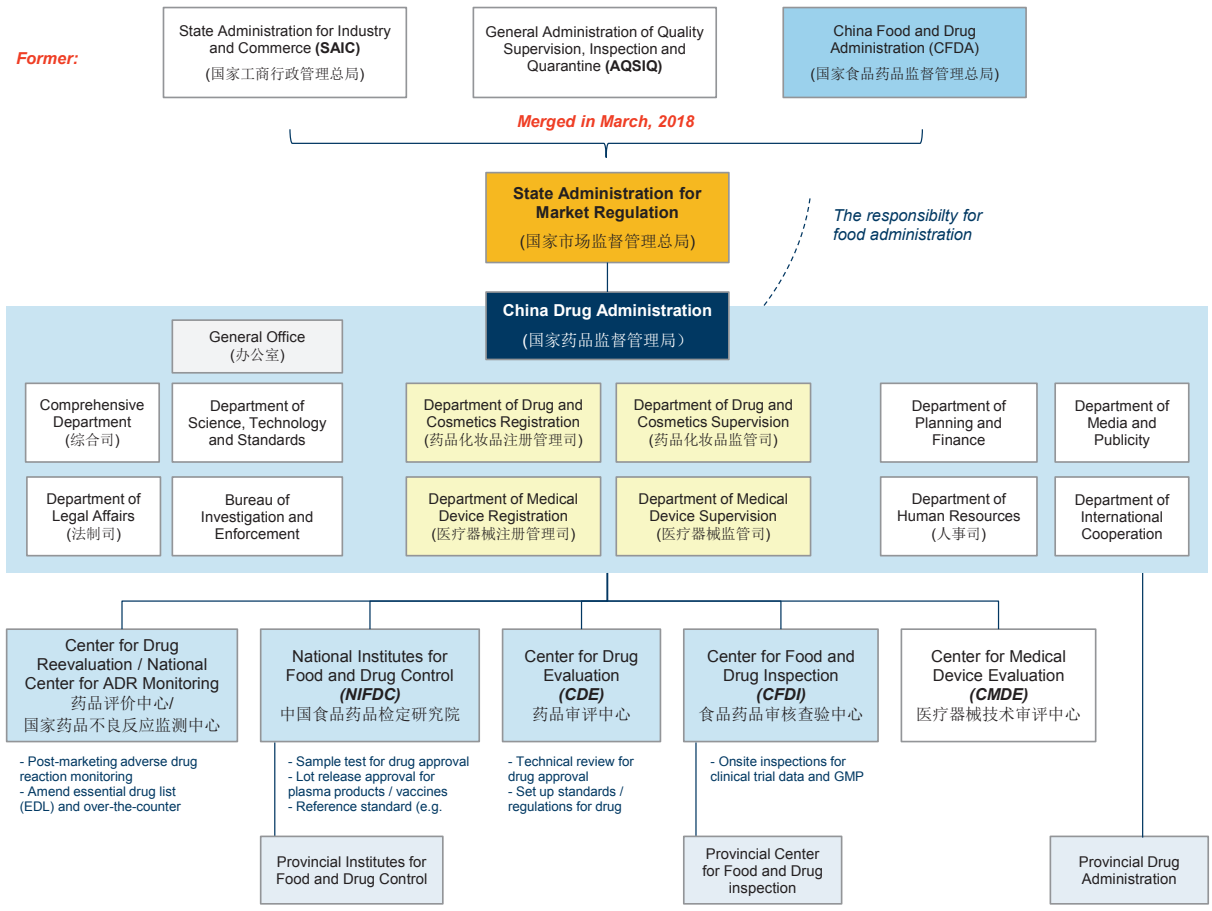
Source: Compiled by Goldman Sachs Global Investment Research

Regulator's role in drug development - gatekeeping at IND/NDA

New organizational changes at CFDA in 2018

The CFDA is the key regulator of drug approval and post-marketing supervision in China. After the State Council organization reform in March 2018, the CFDA merged with the State Administration for Industry and Commerce (SAIC) and the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) to form the State Administration for Market Regulation, while the CFDA's responsibility has been inherited by the China Drug Administration (CDA), except the responsibility for food administration and supervision. Since the transition is still ongoing, we still use "CFDA" throughout the report.

Exhibit 61: CFDA (now CDA) organization chart



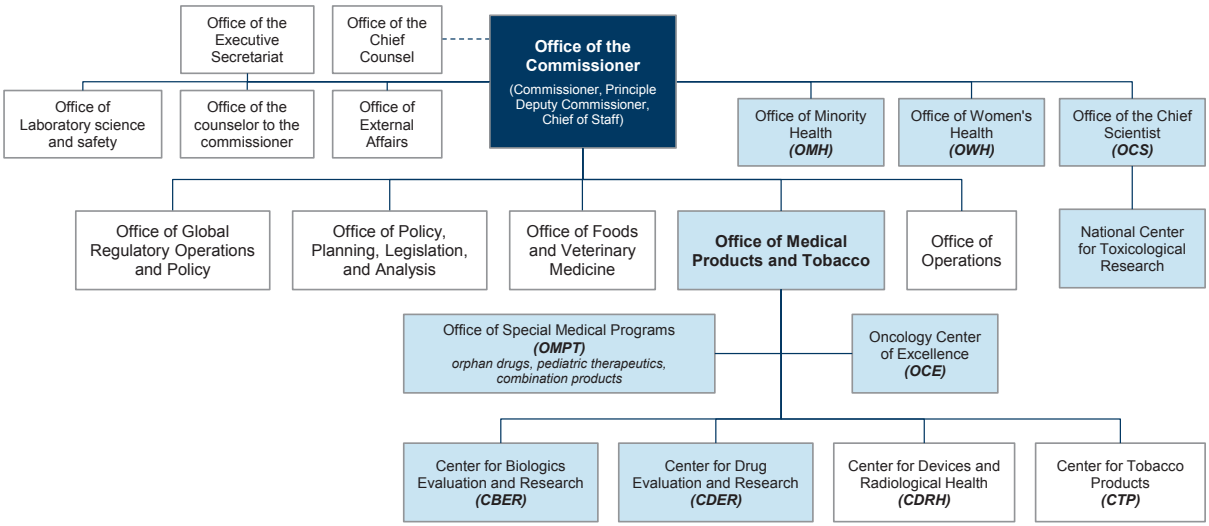
Source: CFDA, Goldman Sachs Global Investment Research

The drug approval function is jointly overseen by three key entities under the CFDA:

- **The Center for Drug Evaluation (CDE),** which takes the lead in assessing the efficacy and safety of new therapies. The technical review of clinical trial data is conducted at the CDE.
- **The National Institutes for Food and Drug Control (NIFDC)** is responsible for the registration test for an investigational drug's samples, and the testing reports are sent to the CDE to facilitate the technical review.

- **The Center for Food and Drug Inspection (CFDI)** conducts onsite inspection of clinical trials and manufacturing facilities (i.e., GMP inspection) before the final approval of an investigational drug.

Exhibit 62: US FDA Organization Chart



Source: US FDA

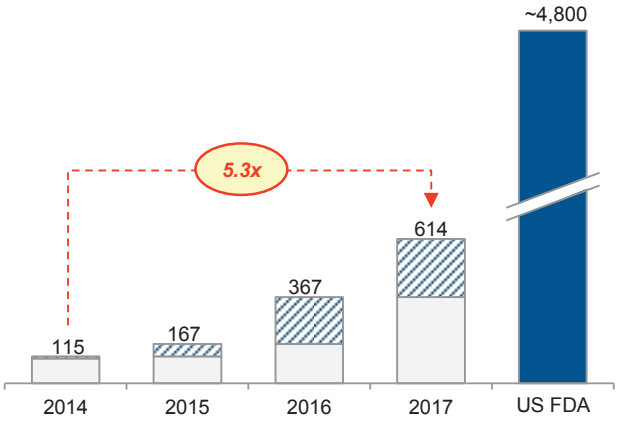
When the organizational structures of the CFDA and the US FDA are compared, there are similarities, e.g. the CDE in China has largely the same function as the Center for Drug Evaluation and Research (CDER) under the FDA. However, we see room for the CFDA to catch up to the FDA (e.g., specialized toxicological research, oncology center of excellence and special medical programs at the FDA).

CDE capacity expansion as the foundation for accelerating drug approval

One of the key bottlenecks that has contributed to the slower drug approval process in China as been significant capacity constraints at the CDE, which had a staff of only about 100-120 people before 2015, vs. over 5,000 at the US FDA. One of the key reforms at the CFDA starting from 2015 has been the acceleration of talent recruitment, which we believe is the foundation for driving a more efficient drug approval system in China.

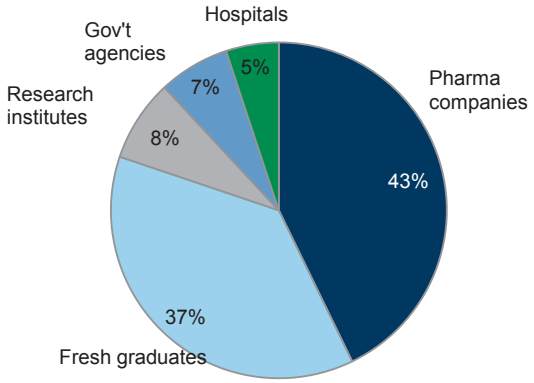
In 2014-2017, the CDE's headcount increased by 5X, up to 614 by end-2017, and could rise above 1,000 in 2018-2019, according to the Commissioner of the CFDA. Our analysis of the CDE's recruitment announcements also suggests that pharma companies are the key source for the CDE's talent pool, contributing over 40% of the new recruits, which should help migrate industry expertise from corporates to the regulator.

Exhibit 63: Headcount at the CDE increased by 5X in the past three years
# of headcounts at CDE in 2014-2017 vs. the US FDA (CDER)



Source: CFDA, US FDA

Exhibit 64: Over 40% of the CDE's new recruits have come from pharma companies
Breakdown of CDE recruitment by source



Source: CFDA

Investigational new drug (IND)/clinical trial application (CTA)

In China, before conducting clinical trials in humans, official approval must be obtained from the CFDA. An application for clinical trials (CTA in China, equivalent to IND in the US), together with: 1) the full set of data from preclinical studies; 2) a clinical trial design proposal; and 3) the approval from hospitals where the clinical trials will be conducted, will be reviewed by the CFDA/CDE (Center for Drug Evaluation, under the CFDA) and the process can take 6-12 months or even longer. In the ongoing CFDA reform, the CFDA aims to cut the CTA review time to ~60 work days (vs. 30 days at the US FDA), and this could become effective beyond 2018.

New drug application (NDA) and biological license application (BLA)

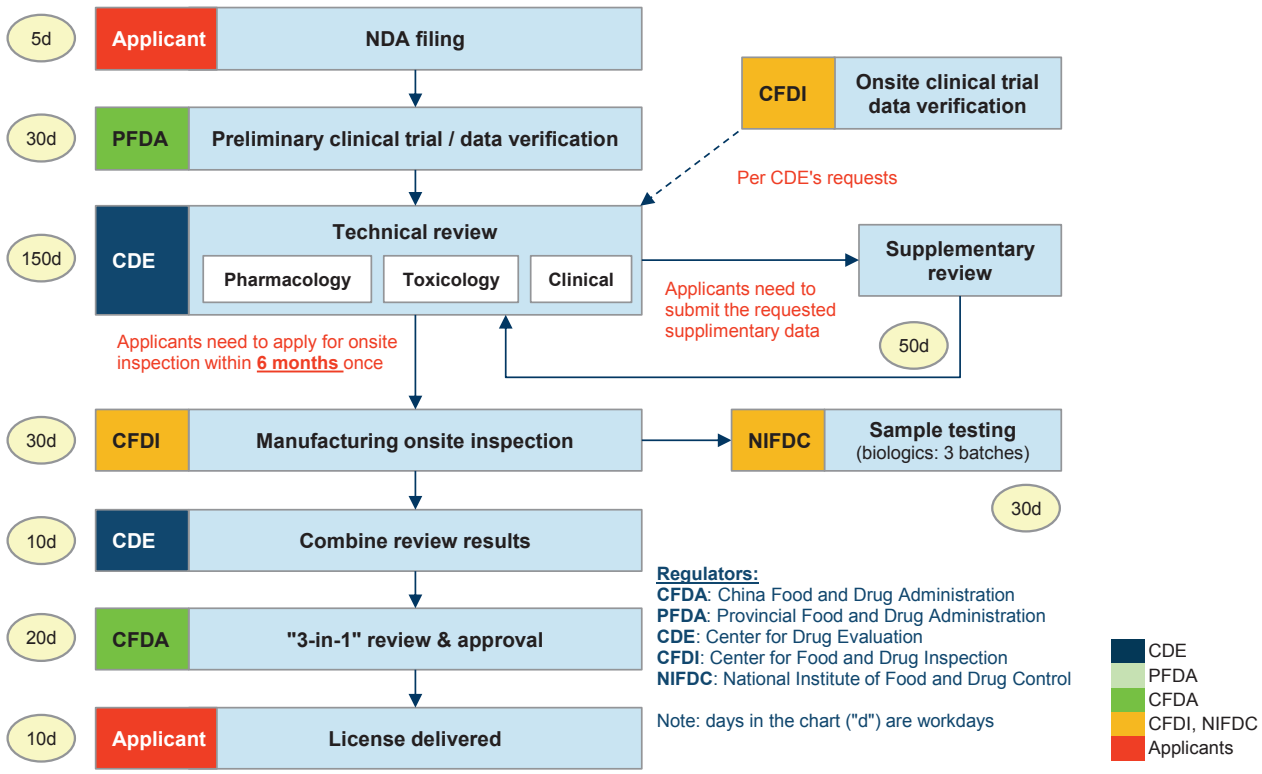
If a drug candidate has proven to be effective with manageable side-effects, a new drug application (NDA, or BLA for biologics in the US) containing preclinical data, clinical results, and manufacturing and quality control procedures can be submitted to the CFDA for review.

The core and the most time-consuming part of the NDA review is the technical review conducted by the CDE (the counterpart of the US FDA's Center for Drug Evaluation and Research (CDER) plus the Center for Biological Evaluation and Research (CBER), which can take at least 4-5 months. In most cases, the time from the NDA filing entering the queue for CDE review to the completion of the full review process can be substantially longer, given: 1) the time spent on the waiting list; and 2) the CDE's request for supplementary data, which can require multiple rounds. Since 2016, the CDE has been able to request clinical trial data verification during the review process, and the verification is done by the CFDA's Center for Food and Drug Inspection (CFDI).

Once the CDE review is done, an onsite inspection of the manufacturing facility is conducted with three batches of samples being tested for quality consistency. The

result of two inspections (facility and samples) and the CDE technical review report are then submitted to the CFDA for final review and decision-making.

Exhibit 65: New drug application (NDA) process in China



Source: CFDA, Goldman Sachs Global Investment Research

Establishing accelerated review system in China

As part of the major CFDA reforms aimed at driving an industry-wide enhancement of drug quality and innovation, the CFDA released preliminary guidance on priority review for drugs on February 26, 2016. An updated version was released on December 28, 2017, after a two-year trial run, marking the establishment of an official accelerated review system in China. The CFDA priority review aims to cut the review timeframe for: 1) clinical trial applications (CTA, or investigational new drug (INDs) for novel drugs); 2) NDAs for novel drugs; and 3) abbreviated NDAs (ANDAs) for generics. The first batch of priority review candidates was released in early March 2016, and as of end-2017 the CFDA's Center for Drug Evaluation (CDE) had announced 25 batches, covering a total of 191 molecules (or 392 applications).

Comparison of the newly established accelerated review system in China, including priority review and conditional early approval, with similar systems in the US, the EU and Japan show that while China is similar to developed regions in granting priority to innovative therapies with superior clinical benefits in treating major diseases, affordability and basic accessibility are more valued as the review of high-quality generics is prioritized, including potential first-to-market generics, i.e. those for which an ANDA is filed within one year before the patent expiry of originator drugs, and those being approved/marketed in the US and the EU.

Exhibit 66: Accelerated review system for drugs in China vs. US/EU/Japan

	Accelerated review system	Designation requirement	Benefits
China CFDA	Priority review	● Novel drugs ● Drugs in innovative formulations, new therapies, drugs with superior clinical benefits ● First-to-market generics; US/EU approved generics ● TCM/ethnic medicines with weill defined clinical benefits ● New drug development projects listed as National Key R&D projects ● Drugs with superior clincial benefits in treating AIDS, tuberculosis, hepatitis, rare disease, cancers, most prevalent disease in elarly population, pediatric drugs ● Drugs with clinical demand while in supply shortage ● For serious public health issue ● ANDA refiling post withdrawal	CFDA will decide priority review designation within 30 days post application
	Conditional early approval	● Good surrogate / intermediate clinical endpoint results ● Good preliminary clinical results ● US / EU launched drugs for rare diseases	
US FDA	Fast track	● Serious condition + Unmet medical need ● Infectious disease product	● Actions to expedite development and review ● Rolling review
	Breakthrough Therapy	● Serious condition + Substantial improvement on a clinically significant endpoint	● Intensive guidance ● Organizational commitment ● Rolling review ● Other actions to expedite review
	Accelerated Approval	● Serious condition + meaningful advantage + good surrogate / intermediate clinical endpoint results	Earlier approval based on surrogate / intermediate clinical endpoint results
	Priority Review	● Serious condition + significant improvement ● Pediatric study ● Infectious disease product ● Priority review voucher	6 months for review (vs. regular ~10 months)
EU EMA	PRIME (Priority Medicine)	Products of a major interest to public health and therapeutic innovation	● Identify candidates for accelerated assessment ● Early rapporteur appointment ● Reinforced scientific and regulatory support ● Dedicated contact person
	Accelerated assessment	Products of a major interest to public health and therapeutic innovation	150 days for review
	Conditional Marketing Authorization	● Life-threatening diseases ● Emergency situations ● Orphan medicinal products	● Earlier authorization of medicines ● Comprehensive data generated post authorization
	Compassionate use	● Life threatening disease ● For a “group of patients” ● Centralized MAA or clinical trials ● Falling under mandatory or optional scope of centralized procedure	● Benefit seriously ill patients ● Recommendations to member states
Japan PMDA	Priority review	● Orphan drugs ● Improvement for severe diseases	9 months for review
	SAKIGAKE (forerunner designation)	● Innovative medical products ● For serious diseases ● Development & NDA in Japan ● World’s first ● Prominent results on preliminary studies	6 months for review
	Conditional early approval	Earlier approval based on surrogate / intermediate clinical endpoint results	

Source: CFDA, US FDA, EMA, Japan Pharmaceuticals and Medical Devices Agency (PMDA), Goldman Sachs Global Investment Research

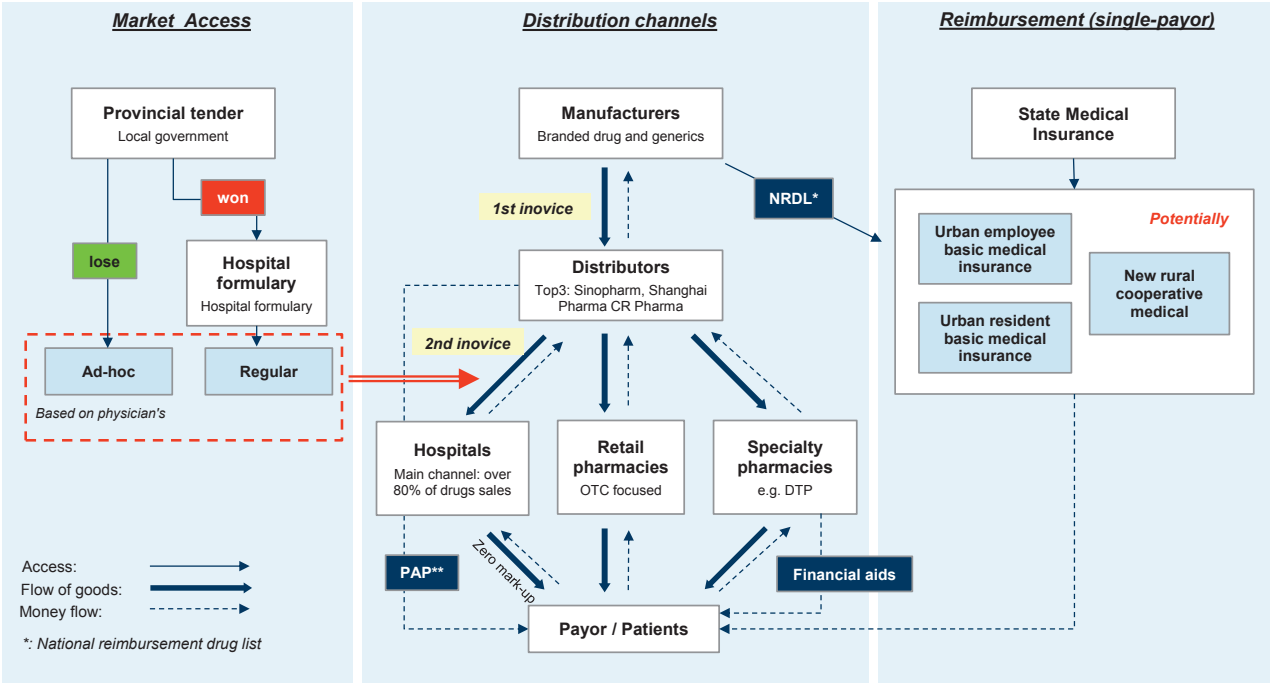
Commercialization: Pricing, reimbursement and sales model

- Market access - drug tendering + enter hospital formulary
- Distribution channels - hospital as mainstream, but DTP pharmacies emerging
- Reimbursement coverage expanded to cover more advanced therapies

Commercialization - improving affordability and transparency

After obtaining the CFDA's approval for production and marketing, a new drug enters the commercialization stages in China, which primarily deals with three aspects: 1) obtaining the qualification for access to the hospital channel, which dispenses over 80% of prescription drugs; 2) establishing a distributor network for efficient delivery of products to different channels; and 3) gaining access to medical insurance in China.

Exhibit 67: The market access, distribution and reimbursement system for drugs in China



Source: Goldman Sachs Global Investment Research

Market access - drug tendering + enter hospital formulary

Public hospitals captured over 85% of patient flow in China and over 80% of drug sales were generated in hospitals, thus access to hospitals is essential for a new prescription drug to generate meaningful sales. There are two major steps:

- **Provincial tenders:** This step is conducted by the local government; the frequency can vary from province to province, but normally provincial tenders are done once every one to two years. In the case of losing the tender or missed a tender cycle, sales can be generated by ad hoc procurement, which will be small in volume given that the procurement is based on physicians' requests and involves tedious paperwork.
- **Hospital formulary entry:** Winning the provincial tender represents the drug has been granted the qualification to be marketed within the province, but being listed in individual hospital's formulary will rely on the sales/marketing activities done by the sales reps/market access team. The frequency for hospitals' formulary review

committee to review the drug list varies – it can be on a quarterly basis, a half-year basis or even longer.

Distribution channels - hospital as mainstream, but DTP pharmacies emerging

Under the "two invoice" regulation for distribution, there is only one-layer of distributor allowed for drugs sold to hospitals. Though hospitals are likely to remain as a key channel for drug sales, direct-to-patient (DTP) pharmacies are emerging as a supplementary channel for higher-priced novel therapies, particularly in the initial commercial stage when access to hospitals has not been granted without tenders and the reimbursement coverage is missing. DTP pharmacies, many of which controlled by top-ranked distributors in China (e.g., Sinopharm, Shanghai Pharma, China Resources Pharma), collaborated with pharma/biotech companies to launch dedicated financial assistance programs (e.g., payment in installments in MediTrust Health-AstraZeneca's Tagrisso project to help patients manage short-term cash flows) and direct-to-patient delivery services to improve patient penetration.

Exhibit 68: Major channels for drugs in China

	In-Hospital pharmacy	Large chain pharmacy	Retail pharmacy	On-line pharmacy
Service model	Self-Financing Rx pharmacy	Direct to patient pharmacy (DTP)	Medical Treatment Management (MTM)	Online to offline (O2O)
Key participants	Hospitals & Pharmacies & Distributors	Pharmaceutical companies & Pharmacies	Pharmaceutical companies & Pharmacies	Pharmacies & Internet platform
Examples	TASLY pharmacy vs. Tianjin Medical University general hospital	Roche vs. GuoDa Drugstore (Sinopharm)	Phyizer vs. Tianjin Richpharm pharmacy	Tmall medical center
Rx Category	Targeted therapies, Premium drugs, Orphan drugs, etc.	Premium specialty drugs indicated in Oncology, HCV, autoimmune etc.	Chronic disease drugs	OTC, RX drugs without safety concerns
Positioning	Maximize the market access and drug listing	Improve prescription amount in such strict const-control environment	Improve compliance rate by offering treatment guidance and high quality services	Channel Innovation

Source: Insight database

Reimbursement coverage expanded to cover more advanced therapies

The major medical insurance system run by the government (the single-payor system) covers over 90% of China's population via three programs: 1) two urban medical insurance programs for employees and non-employees (residents), previously run by the Ministry of Human Resources and Social Security; and 2) a rural program (new rural cooperative medical insurance) covering the rural population, previously run by the National Health and Family Planning Commission. In addition, a medical aid program run by Ministry of Civil Affairs provides additional coverage for the lower-income population. With the creation of a new State Medical Insurance Administration in May 2018, the

supervision of three major medical insurance program as well as medical aid, drug pricing and tendering (previously regulated by the National Development and Reform Commission) will be consolidated under a single authority, potentially increasing the efficiency of the policy-making process.

Drugs that are covered by medical insurance are included on a drug reimbursement list at both the national level (NRDL) and the provincial level (PRDL):

- The NRDL was previously revised in 2009 and 2017, and the government has guided that revisions will be more frequent going forward, potentially once every two years. There are two catelogs in the NRDL: 1) Catalog A: mostly drugs with long prescription histories in China with relatively lower costs, 100% reimbursed by the government; 2) Catalog B: more newer drugs are included, including specialty drugs, with the reimbursement rate <100% (50-90% in most cases), which varies from city to city;
- PRDL is the reimbursement list actually implemented locally. Based on NRDL, provinces have the option to replace ~15% of the drugs on Catalog B to adapt to local medical demand or prescription habits. Provinces have the flexibility to adjust reimbursement rates depending on the provinces' local policies and balance of medical funds. The major revision of the PRDL will be following NRDL revision, while there could be minor revisions to cover newly launched products between major revisions. Moreover, the number of PRDLs that a new drug has entered is also one of the criteria for NRDL inclusion.

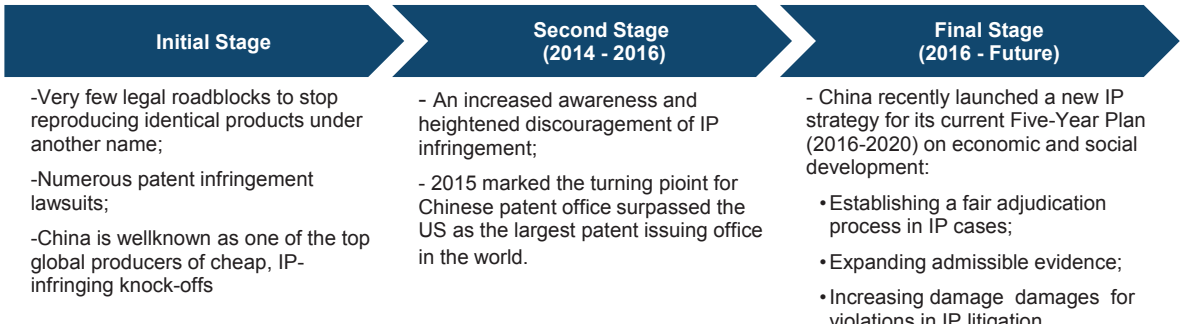
Intellectual property protection in China

- Overview of Intellectual property rights protection
- Current effective rules for new protection
- When to file and expire for a patent

Intellectual property protection in China

Western innovators may get the impression that China's patent system favors local agencies and discriminates against foreigners. Hence, most innovators are reluctant to invest time and money to pursue patents in China.

Exhibit 69: China's progress on intellectual property protection



Source: Insights

China's government has noted that this problem can also discourage domestic innovation. It has therefore put into place a series of steps to reform the IP protection system, including the restructuring of legal organization, limiting the possibility of protectionism and bias against foreign litigants, modifying IP laws to expand admissible evidence and increasing damages for violations.

Even though the current situation is far from satisfying, the changes still represent a positive trend in China's domestic innovation environment. Most importantly, they have enhanced innovators' confidence by providing protection for investments in research and development.

Overview of Intellectual property rights protection

Within China's existing legal framework, biological and pharmaceutical enterprises receive intellectual property rights protection, mainly in the form of patents and administrative protection.

Patent protection is classified into three types: inventions, utility models, and industrial designs.

Besides patent protection, administrative protection of drugs is a supplementary measure unique to China. Similar to intellectual property rights protection, administrative protection grants an enterprise certain exclusive rights, giving it a competitive edge. Administrative protection of drugs is subject to approval by the SFDA.

Current effective rules for new protection

In China, invention patents and utility model & design patents have terms that last 20 years and 10 years, respectively, from the filing date of the patent application to the expiration date.

When to file a patent, and when patents expire

A period of 20 years from the filing of a patent application will be granted to the patent owner. Patent rights are territorial in nature and take effect only when the patentee has applied and received recognition.

It takes a long time (10-15 years on average) for a pharmaceutical product to finally enter the market. As a result, a significant period of patent protection time can be lost. In the past 20 years, the average period between the date of filing a patent application and the granting of marketing approval was 12.8 years, but it has declined since 2008. This has a significant impact on the actual effective patent life. Due to the long development process before marketing, the US and Japan have extended patent protection periods, but existing Chinese law does not yet provide for this.

In general, the filing of a patent application is usually done before launch. However, it is generally not advised to publish early if the relevant product is still far from being market ready, as this would allow others to potentially find ways to work around the design or even copy the product. So close collaboration among internal stakeholders (R&D, registration, marketing and intellectual property departments) is needed to achieve thoughtful planning based on the development progress and market needs in the related countries.

Besides the extension of the patent protection period, market exclusivity and higher prices are provided as a reward for the risk undertaken by innovators that finance research and development that leads to new technologies.

A patent is not the only path to exclusivity. Actually, drugs were primarily protected by administrative measures in 1984-1993 when no patent protection law existed. Market exclusivity is granted to originators to balance between new drug innovation and generic drug competition. The difference is that patents can be issued or expire at any time (most commonly during clinical trials and after launch) while market exclusivity takes effect upon marketing approval.

Below we present a case study on biotech IPR protection in China:

Exhibit 70: Changes to IPR protection in China (both patent and administrative new drug protection)

Classfication of new drugs*	Administrative protection measures			Patent Protection	
	1985 -1999 Drug controlling law	1999-2002 New drug registration act & Notice on new drug protection and technology transfer	2002-Present Revised drug management law & Drug Management Act	1985 -1993	1993-Present
Category I: Innovative new drugs not marketed anywhere in the world	8 years	12 years	5 years	For regular drug patents: 15 years For utility model and design patents: 5 years	For regular drug patents: 20 years For utility model and design patents: 10 years
Category II: Improved new drugs not marketed anywhere in the world	6 years	8 years	4 years		
Category III: Generic drugs, with equivalent quality and efficacy to the originator's drugs, that are marketed in other countries, but not yet in China.	4 years	8 years	3 years		
Category IV: Generic drugs, with equivalent quality and efficacy to the originator's drugs, that are already marketed in China.	3 years	6 years	3 years		
Category V: Drugs that have been marketed in other countries, but not yet in China.	3 years	6 years	3 years		

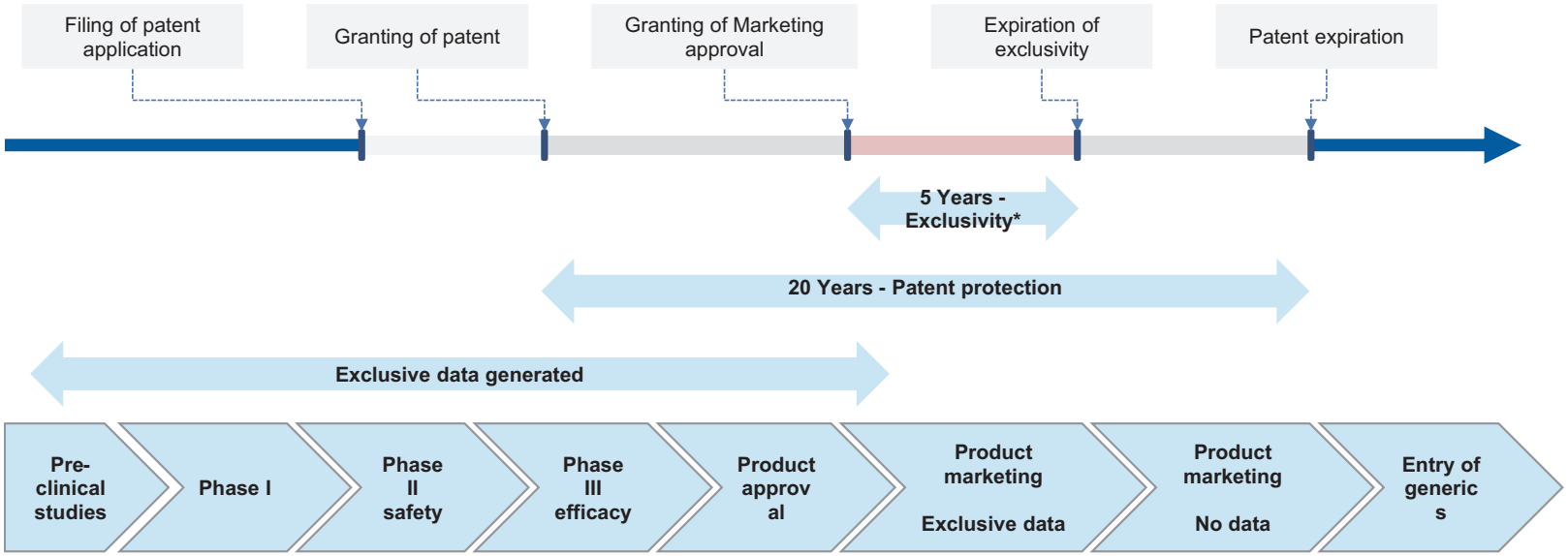
Source: Goldman Sachs Global Investment Research

Exhibit 71: Patent classification

Patent types	Invention patent	Utility models patent	Appearance design patent
Subject matter	Physical products and processes	New solution or improvement to items	External features
Terms of protection	20	10	10
Primary consideration for granting a patent	Novelty, inventiveness and industrial applicability but inventiveness requirement for invention patents is higher.		
Timing of application	Suggest to be applied immediately after animal tests, without having to wait until clinical tests have been completed.	File simultaneously with invention patent to make sure at least 1 patent can be granted	No requirement
Advantage	Exclusive rights to manufacture, market, use, etc.	Can provide broad patent protection making it difficult for a competing product	Usually faster and cheaper patent protection
Disadvantage	Once a patent expires, interests might be seriously compromised	Longer and more expensive than design patent	Difficult to protect different variations of product.
Examination and patentability evaluation	~ 3-5 years	~6months	3-6 months
	Full substantive examination	Only a formality examination	Only a formality examination
Costs	An invention patent costs more to complete prosecution (Similar costs of drafting and preparing applications plus different examination procedure)		
Examples	Patents on combination products/manufacturing processes/different crystal forms	Formulation patent	Ornamental design

Source: Goldman Sachs Global Investment Research

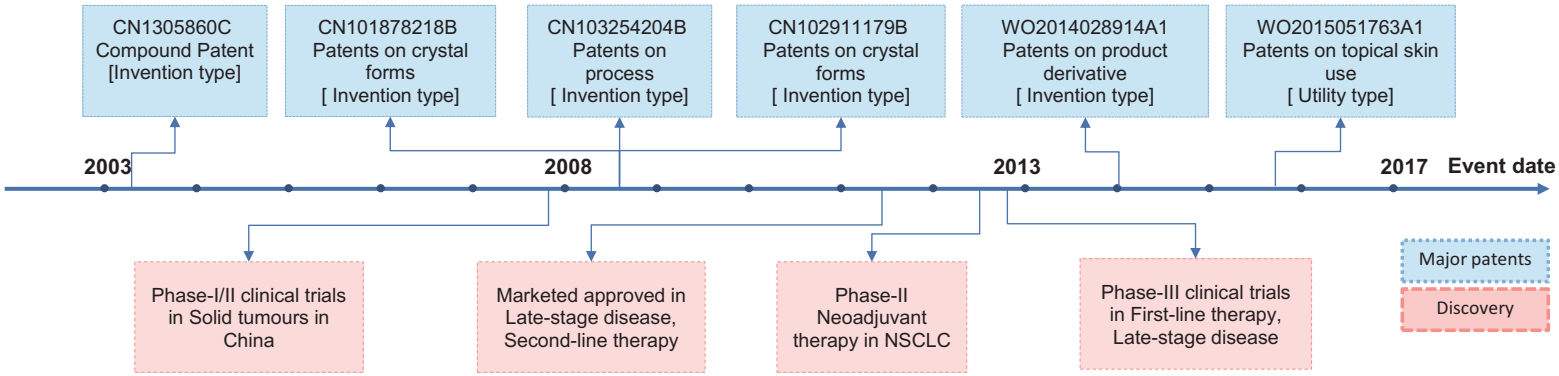
Exhibit 72: Drug discovery process



*Patents and exclusivity may or may not run concurrently and may or may not cover the same aspects of the drug product.

Source: Goldman Sachs Global Investment Research

Exhibit 73: Icotinib from Zhejiang Beta Pharma



Source: Patent search and analysis, springer

Cancers and their treatment

Cancer has become the leading cause of death in China with over 3mn patients diagnosed with cancer and 2.2mn people dying from cancer each year. Cancers of the lung, stomach, and liver are the three major types of cancers in China (vs. prostate, breast, and lung in the US; breast, prostate, and colorectal in the EU and Japan).

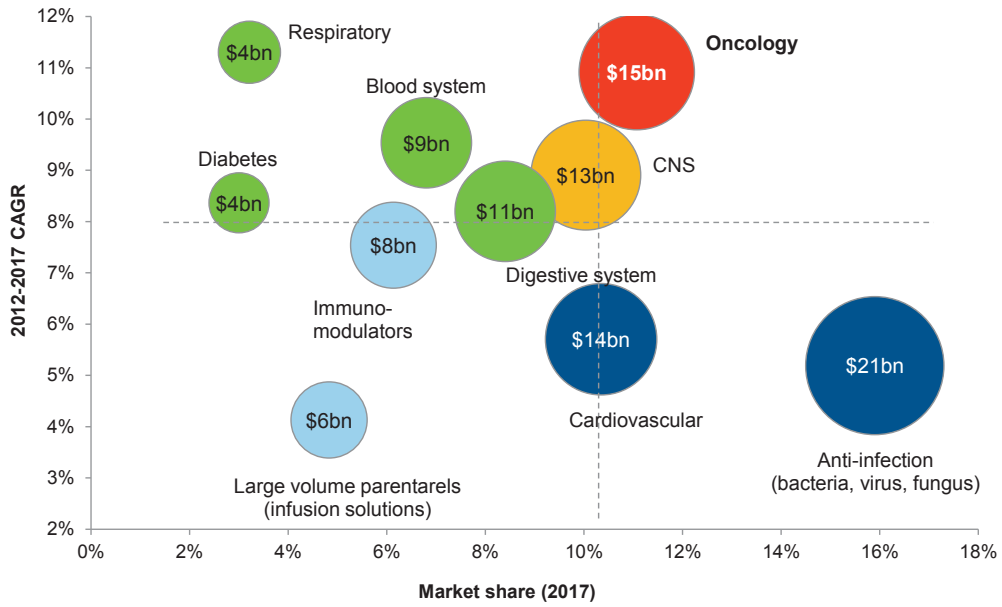
- Lung cancer - No.1 cancer in China and globally
- Breast cancer - an emerging killer for women
- Gastric cancer - H. pylori infection as the key risk factor
- Esophageal cancer - higher prevalence in developing world
- Colorectal cancer - catching up with developed regions in incidence
- Liver cancer - China accounts for more than half of global incidence
- Lymphoma - major category of blood cancers
- Cancer immunotherapies (I/Os) - potential game changers

Cancer in China: Demographics and treatment paradigm shift

The second-largest therapeutic category in China: ~US$15bn market

We estimate China's oncology drug market was worth ~US$15bn in 2017, on the back of a 10% growth rate in the past five years vs. market growth in the single digits. Cancers have become the leading cause of death in China with over 4mn patients diagnosed with cancers and 2.2mn people dying from cancer each year.

Exhibit 74: Oncology is the second-largest category in China
Chinese Rx drug market breakdown by key specialties



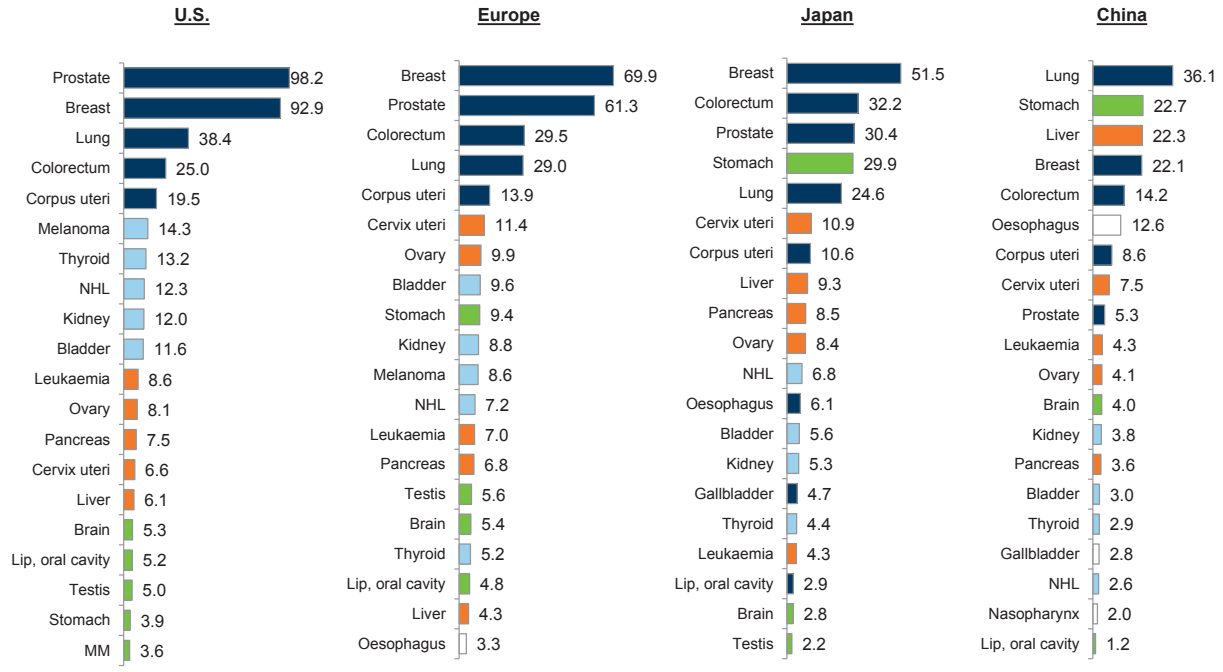
Source: PDB database, Goldman Sachs Global Investment Research

Cancer demographics are different in China vs. the US/EU

Cancer demographics are different in China vs. developed regions: cancers of the lung, stomach, and liver are the three major types of cancers in China (vs. prostate, breast, and lung in the US; breast, prostate, and colorectal in EU and Japan).

The differentiated cancer types and large patient population potentially make China a unique market for some cancer indications.

Exhibit 75: The major cancer types in China are quite different than those in developed countries/regions
Incidence rates across various countries/regions



Source: Globocan 2012

Roche, Hengrui and AZ are the top-three players in China's oncology market

The oncology market in China remains fragmented with the top 10 players only capturing 62% market share in 2017 (unchanged vs. 62% in 2012). Among the 15 largest players, there are 7 MNCs. Roche, Hengrui and AstraZeneca have consistently been the top three players in the past five years in the field, with collective market share of 44%.

Exhibit 76: Top players in China's oncology market

2012		
#	Company	Market share
1	Roche	14.0%
2	Hengrui	8.9%
3	AstraZeneca	6.9%
4	Pfizer	6.6%
5	Qilu	6.0%
6	Sanofi	4.5%
7	Hansoh	4.5%
8	Luye	4.3%
9	Novartis	3.5%
10	Yibai	3.0%
11	Eli Lilly	2.8%
12	Lunan	2.3%
13	Aosaikang	2.3%
14	BMS	2.2%
15	Main Luck	2.1%

2017		
#	Company	Market share
1	Roche	14.1%
2	Hengrui	8.1%
3	AstraZeneca	7.0%
4	Luye	5.9%
5	Qilu	5.5%
6	Pfizer	5.2%
7	Sanofi	4.7%
8	Hansoh	4.8%
9	Novartis	4.5%
10	Lunan	2.6%
11	BMS	2.4%
12	Eli Lilly	1.9%
13	Yibai	1.6%
14	Aosaikang	1.6%
15	Orion	1.5%

MNCs
Chinese players

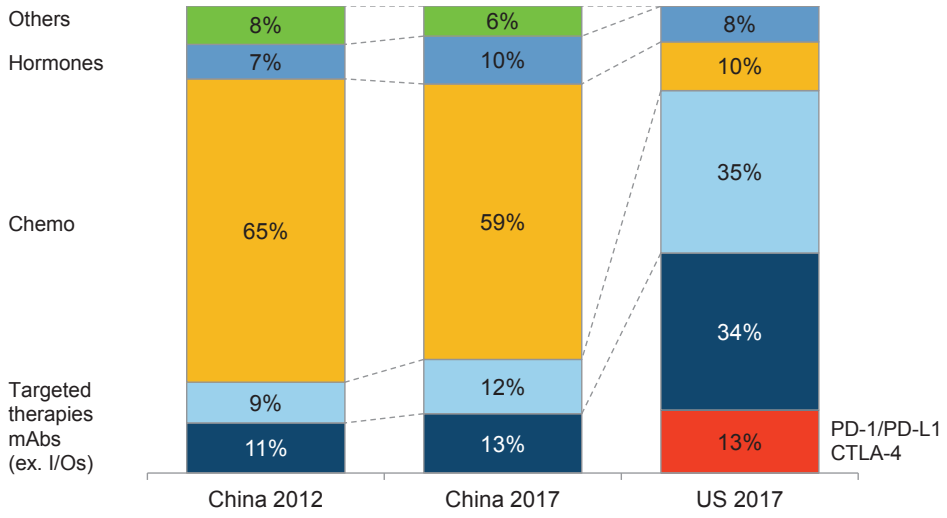
Source: PDB database

Cancer treatment paradigm to shift targeted therapies and I/Os

Compared with the prescription mix in the US in oncology, which has been dominated by targeted therapies (TKIs and monoclonal antibodies) and cancer immunotherapies (or immuno-oncology drugs, I/O), China is in the early stages of shifting from older-generation chemotherapies to more advanced treatment regimens. Chinese patients have limited access to state-of-the-art cancer therapies and only 29 out of 105 targeted therapies approved by the US FDA were available in China as of May 2018. The insufficient reimbursement coverage further confines the treatment choices. We expect the treatment paradigm shift process to accelerate in 2018 and beyond, given:

- The CFDA's accelerated approval of imported oncology drugs with overseas clinical data.
- Emerging domestic players in the space focusing on developing both me-too/me-better treatment and bioequivalent but lower-priced generics.
- Improving affordability with expanded reimbursement coverage.

Exhibit 77: mAbs/targeted therapies are emerging in China



Source: PDB database

Biologics are emerging as top-selling anti-cancer drugs in China

The top-selling anti-cancer drugs are still traditional chemotherapies, particularly taxanes (paclitaxel and docetaxel). Monoclonal antibodies (mAbs) and targeted therapies are emerging; among this category, Rituxan and Herceptin and Avastin are best-selling mAbs while Gleevic and Iressa, including their generic versions, are the mostly widely prescribed TKIs.

Exhibit 78: Top 20 anti-cancer drugs in China

2012			2017		
#	Drug	Market share	#	Drug	Market share
1	Paclitaxel	10.1%	1	Paclitaxel	8.7%
2	Docetaxel	8.7%	2	Pemetrexed	6.1%
3	Pemetrexed	5.7%	3	Docetaxel	5.6%
4	Oxaliplatin	5.4%	4	TGO/S1	5.0%
5	Capecitabine	4.7%	5	Rituximab	4.6%
6	Gemcitabine	4.0%	6	Oxaliplatin	4.4%
7	TGO/S1	4.0%	7	Capecitabine	4.0%
8	Rituximab	3.7%	8	Trastuzumab	3.8%
9	Trastuzumab	2.9%	9	Imatinib	3.0%
10	Epirubicin	2.7%	10	Gemcitabine	2.9%
11	Irinotecan	2.6%	11	Temozolomid	2.8%
12	Gefitinib	2.4%	12	Goserelin	2.8%
13	Imatinib	2.3%	13	Bevacizumab	2.4%
14	Goserelin	2.0%	14	Letrozole	2.1%
15	Letrozole	1.9%	15	Irinotecan	2.1%
16	Temozolomid	1.9%	16	Gefitinib	1.8%
17	Erlotinib	1.6%	17	Bicalutamide	1.7%
18	Nedaplatin	1.6%	18	Elemene	1.6%
19	Anastrozole	1.5%	19	Doxorubicin	1.6%
20	Pirarubicin	1.5%	20	Epirubicin	1.6%

mAbs

TKIs

Source: PDB database

Cancer immunotherapy as next game-changing category

Cancer immunotherapy (or immuno-oncology [I/O]) has reached several milestones in the past few decades, with immune checkpoint inhibitors (PD-1/PD-L1 inhibitors) and CAR-T (chimeric antigen receptor T-cell therapy) as the two most prevailing breakthrough therapies for cancers, raising the prospects for cancers to be managed or even cured in future. As the education of physician communities progresses, cancer treatment in China could shift gradually from chemotherapies to targeted therapies and immunotherapies. We examine the I/O space in China to map the landscape of the PD-1/L-1 pipelines, and we expect the first regulatory approval of a PD-1/L1 agent in China at end-2018 or early 2019.

Exhibit 79: Five PD-1/L1 filed NDAs in China as of May 2018
PD-1/L1 development road map in China

		anti-PD1							anti-PD-L1				
	Developer	BMS	Merck	Novartis	Innovent	Hengrui	Beigene	Junshi	Roche	AZ	Merck	Cstone	Alphamab / 3DMED
	Candidates	Nivolumab (Opdivo)	Pembrolizumab (Keytruda)	PDR001	IBI308	SHR-1210 (Camrelizumab)	BGB-A317 (Tislelizumab)	JS001	Atezolizumab (Tecentriq)	Durvalumab (Imfinzi)	Avelumab (Bavencio)	CS1001	KN035
Solid tumors	NSCLC	1L, +chemo 2L, mono	1L, +P/C 2L, mono		2L, mono	1L, +P/C 2L, mono/+apatinib	1L, +chemo 2/3L, mono	2/3L, +P/C	1L, mono/+P/C 2/3L, mono	1L, +trem 1L, mono	1L, mono		
	Esophageal	1L, +ipi / chemo	2L, mono		2L, mono	2L, mono +radiotherapy	2L, mono 1L, +chemo	2/3L, mono			Mono		
	GC/GEJ	1L, +ipi Adjuvant,mono	2L, mono			1L, +apatinib	1L, +chemo	2/3L, mono					
	Bladder	Mono					2/3L, mono	2L, mono	1L, mono	1L, mono or +trem			
	HCC	1L, mono	2L, mono	+ cMETi		2L, mono/+apatinib	1L, mono 2L, mono			1L, +trem 1L, mono			
	Melanoma		2L, mono			Mono		1L, mono					
	SCLC	2L, mono / +ipi				2/3L, +apatinib			+ etoposide / carboplatin				
	NPC			Mono		1L, +GP		2/3L, mono					
	Prostate								2/3L, +Xtandi				
	Ovarian								+ chemo / Avastin				
	Mesothelioma	1L, +ipi											
	FTC								+ chemo / Avastin				
	PPC								+ chemo / Avastin				
	Breast							2/3L, +radio Mono					
	H&N							2/3L, mono					
	RCC	+ ipi						2/3L, +axitinib					
	NET							Mono					
	Cholangiocarcinoma												2L, mono
Blood cancer	HL				3L, mono	Mono	2L, mono	Mono				2L, mono	
	ENKL, nasal				Mono	Mono							
	T/NK cell lymphoma						2L, mono					2L, mono	
	NHL							Mono					

NDA
Ph 3
Ph 2/1b
Ph I

Diesease abbreviations:

NSCLC: Non-small cell lung cancer; HCC: Hepatocellular carcinoma; SCLC: Small cell lung cancer; NPC: Nasopharynx cancer; H&N: Head and Neck cancer; RCC: Renal cell carcinoma; NET: Neuroendocrine tumor; FTC: Fallopian tube cancer; PPC: Primary peritoneal carcinoma; HL: Hodgekin's lymphoma; ENKL, nasal; Extranodal NK/T-cell lymphoma (nasal type); NHL: non-Hodgekin's lymphoma

Source: Company data, Insight database

LUNG CANCER In China

733,300 New cases per year
610,200 Death per year
51.9 / 100K Incidence rate
43.2 / 100K Mortality rate
19.8% 5-year survival rate (2010-14)

Most common type: NSCLC (92%)
Most common genotype: EGFR+ (48%) and ALK+(6%) in adenocarcinoma type of NSCLC
Staging at diagnosis: Stage I 14%, Stage II 7%, Stage III/IV 79%
Targeted therapies in China: Gefitinib, erlotinib, afatinib, icotinib for 1st-line EGFR+; osimertinib for 2nd-line EGFR+ with T790M mutation; crizotinib: for 1st-line ALK+

Disease demographics

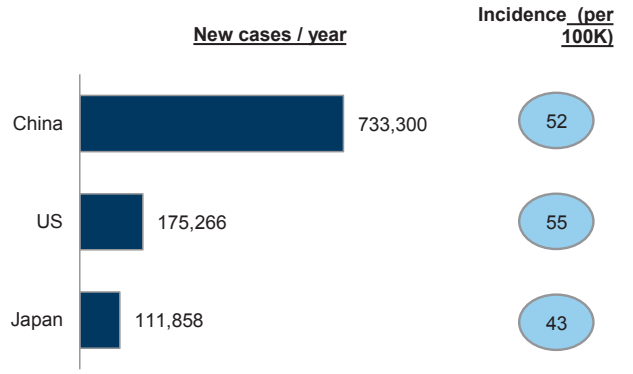
Lung cancer is the leading cause of death and the largest diagnosed cancer type in China. Globally, it is also one of the most common types of cancers that lead to death. There are an estimated 733,000 new cases of lung cancer in China per annum.

The epidemic of lung cancer is a major health issue confronting both developed and developing countries, given the high mortality rates across all countries. There are two major types: 1) non-small cell lung cancer (NSCLC), which accounts for more than 90% of all lung cancer cases; and 2) small cell lung cancer (SCLC). NSCLC and SCLC grow and spread in different ways and therefore have different treatment procedures. More so, lung cancer can be broken down into two different histologic types, i.e. adenocarcinoma (more prevalent in China, 60%-70%) and squamous cell carcinoma, which could also lead to differences in treatment and prognosis.

Incidence and survival rate vs. global peers

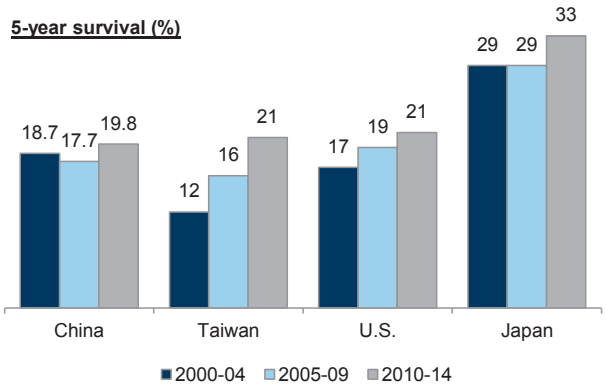
There is no significant difference in terms of both incidence and mortality in China, Japan and the US (ranked as one of the top three cancers with an incidence rate in the range of ~40-55 per 100,000 population). The best-recognized risk factor for lung cancer is smoking, and other risk factors for lung cancer include lung disease history (e.g., COPD, chronic obstructive pulmonary diseases), cancer history, family history of lung cancer, and exposure to other carcinogens. The rise of tobacco use among the Chinese population and exposure to air pollution could be the major driver for growing lung cancer incidence in China.

Exhibit 80: Number of new cases and incidence of lung cancers in China, Japan and the US



Source: Cancer Statistics in Japan 2013, Cancer China Statistics 2015, American Cancer Society

Exhibit 81: Five-year survival rate of lung cancer in various regions, 2000-2014

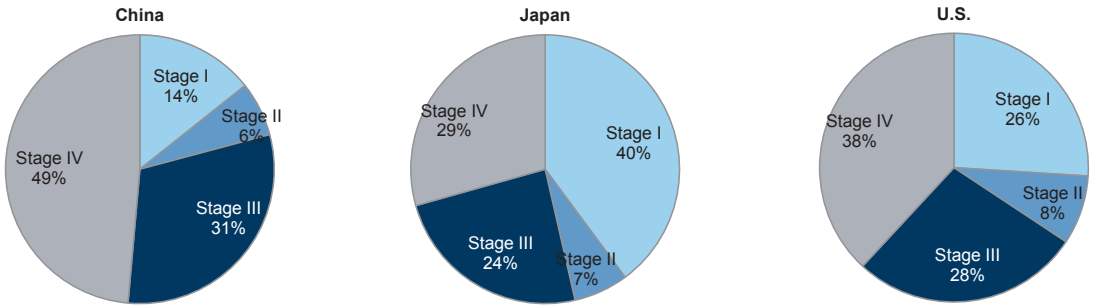


Source: Global surveillance of trends in cancer survival 2000-2014

Distribution of cancer stages

The survival rate of patients with lung cancer is highly related to the stage of lung cancer they are diagnosed with. Unfortunately, because of the nonspecific nature of lung cancer symptoms (e.g., cough), most lung cancer patients are not diagnosed until the cancer has progressed into the advanced stage (49% of lung cancers in China are detected with metastases at first diagnosis, vs. 29% in Japan and 38% in US). In addition, variations in the genotypes of lung cancer also lead to differences in survival - the survival rates of lung cancer patients in Japan are substantially better than in the US, and one of the key reasons could be the higher prevalence of EGFR mutation-positive patients, which are suitable for targeted therapies.

Exhibit 82: Half of lung cancer patients diagnosed with metastatic cancers
Lung cancer patients by cancer stage: China vs. US /Japan



Source: Clinical characteristics and survival of lung cancer patients associated with multiple primary malignancies; Are hospitals in Japan with larger patient volume treating younger and earlier-stage cancer patients? An analysis of hospital-based cancer registry data in Japan; Trends in Stage Distribution for Patients with Non-small Cell Lung Cancer: A National Cancer Database Survey

Treatment paradigm

According to China's treatment guidelines and recognized practice, we summarize common treatment and therapy below:

- **Stage I-III (local) NSCLC:** Surgery still offers the best option for a cure and is highly recommended for patients with tumors still could be removed. Adjuvant therapies, which could be chemotherapy or chemo plus radiation, are recommended to improve survival and reduce the relapse rate. Platinum-based regimens are the most widely used in an adjuvant setting.

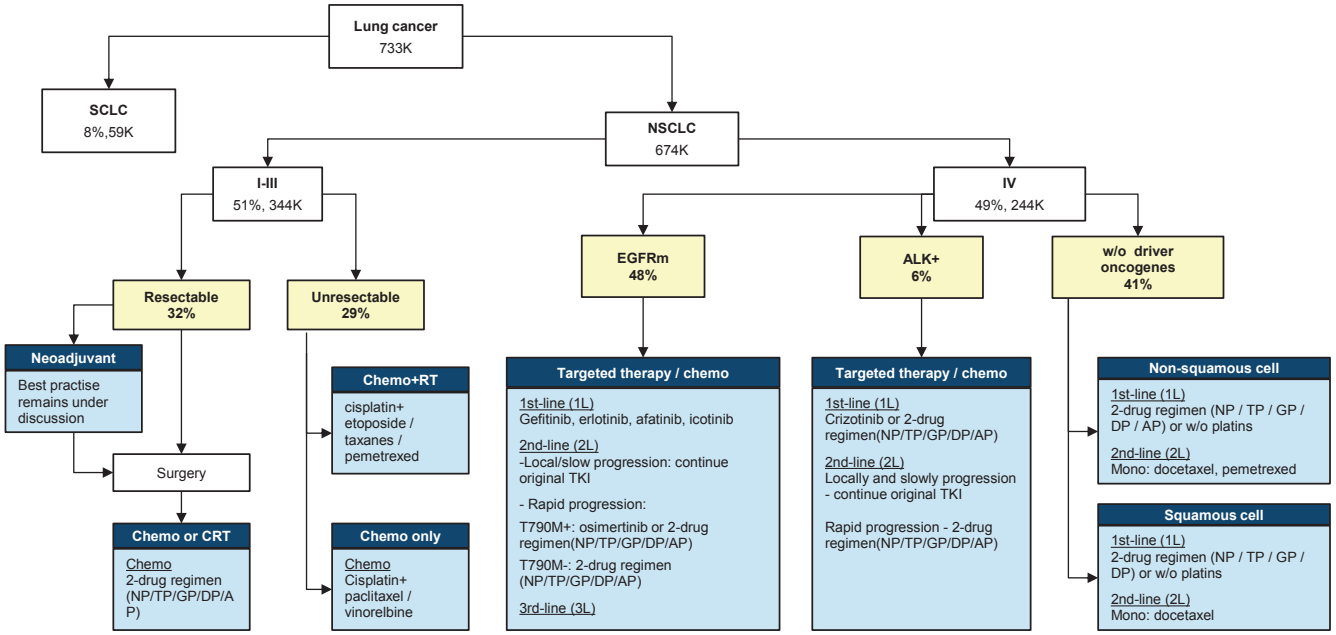
- **Stage IV (metastatic) NSCLC:** Biomarker testing is recommended to late-stage NSCLC patients before receiving treatment, and should include the mutations/fusions of EFGR (epidermal growth factor receptor), ALK (anaplastic lymphoma kinase) and ROS1. Moreover, the histologic type (squamous cell carcinoma or non-squamous) will also be determined. Both the histologic and genetic information are important in indicating the following treatment:
  - **EGFR+:** In China, 48% of the patients with adenocarcinoma of NSCLC have EGFR mutation, which is less observed in squamous cell type. Four EGFR TKIs are recommended: 1) in a first-line setting: gefitinib, erlotinib, afatinib and Icotinib; and 2) osimertinib (Tagrisso) is for second-line treatment for patients with T790m mutation. Chemotherapies will also be considered when both 1L and 2L therapies have failed. Bevacizumab can be regarded as an optional choice for all the nonsquamous NSCLC in combination with platinum-based two-drug therapy or mono therapy.
  - **ALK+:** Less common than EGFRm in China - about 5-6% of NSCLC patients are treated using ALK+. The first-line targeted therapy is crizotinib while platinum-based two-drug regimens are considered as second-line.
  - **Patients without driver oncogene mutations/fusions:** Conventional chemotherapy combinations are the recommended regimens for patients without alteration in driver oncogene (i.e., EGFR/ALK/ROS1). For non-squamous cell type NSCLC (mostly adenocarcinoma), platinum-based two-drug regimens are the first-line choice, i.e., either cisplatin or carboplatin combined with one of the five drugs - gemcitabine, docetaxel, paclitaxel, vinorelbine and pemetrexed. In a second-line setting, docetaxel and pemetrexed are used as a single agent. For squamous cell type, the treatment regimens are similar, with the only difference being that pemetrexed is not recommended for those patients, either as single-agent therapy or in combination with platins. There is no standard-of-care treatment for third-line in China, while the newly approved anlotinib from Sino Biopharm could potentially fill the gap once it is officially launched in the market.

Exhibit 83: China's EGFR TKI market is valued at around Rmb2.5 bn
EGFR market model

	Unit	2011A	2012A	2013A	2014A	2015A	2016A	2017A	2018E	2019E	2020E
EGFR mutated late-stage / metastatic NSCLC											
Incidence rate (crude rate) - lung cancer	1/105	48.3	52.1	53.9	55.6	57.3	59.0	60.7	62.6	64.4	66.4
Diagnosed new cases - lung cancer	'000	651	705	733	760	787	815	843	873	904	935
i.NSCLC patients	'000	553	599	623	646	669	693	717	742	768	795
ii.Late-stage NSCLC	'000	382	410	424	436	448	461	473	486	499	513
EGFR genotype:											
EGFR tested	'000	8	49	85	118	143	166	194	238	285	318
as % of late-stage NSCLC patients	%	*2.0%*	*12.0%*	*20.0%*	*27.0%*	*32.0%*	*36.0%*	*41.0%*	*49.0%*	*57.0%*	*62.0%*
- EGFR mutated (m)	'000	3	19	32	45	55	63	74	91	108	121
- EGFR wild-type (wt)	'000	5	30	52	73	89	103	120	147	176	197
EGFR untested	'000	374	361	339	318	305	295	279	248	215	195
Patients on EGFR-TKIs (1st line)											
Total NSCLC patients on EGFR-TKIs	**'000**	**30.3**	**38.5**	**44.2**	**47.3**	**51.9**	**60.3**	**108.7**	**120.2**	**156.5**	**192.4**
Penetration (as % of all NSCLC patients)	%	*5.5%*	*6.4%*	*7.1%*	*7.3%*	*7.8%*	*8.7%*	*15.2%*	*16.2%*	*20.4%*	*24.2%*
-Patients received 1st-line EGFR-TKIs	'000	23.5	29.6	33.8	35.9	39.2	45.2	78.8	81.1	99.4	115.4
as % of total EGFR-TKI treated patients	%	*77.5%*	*77.0%*	*76.5%*	*76.0%*	*75.5%*	*75.0%*	*72.5%*	*67.5%*	*63.5%*	*60.0%*
-Patients received 2nd/3rd-line EGFR-TI	'000	6.8	8.9	10.4	11.3	12.7	15.1	29.9	39.1	57.1	77.0
as % of total EGFR-TKI treated patients	%	*22.5%*	*23.0%*	*23.5%*	*24.0%*	*24.5%*	*25.0%*	*27.5%*	*32.5%*	*36.5%*	*40.0%*
Total EGFR TKI market	**Rmb mn**	**1,435**	**1,782**	**2,036**	**2,111**	**2,295**	**2,178**	**2,482**	**2,511**	**3,082**	**3,751**
Growth y/y			*24.2%*	*14.2%*	*3.7%*	*8.7%*	*-5.1%*	*13.9%*	*1.2%*	*22.7%*	*21.7%*

Source: Goldman Sachs Global Investment Research

Exhibit 84: Non-small cell lung cancer treatment paradigm in China



Note: NP/TP/GP/DP/AP: cisplatin or carboplatin (P) plus gemcitabine (G), docetaxel (D), paclitaxel (T), vinorelbine (N) or pemetrexed (A)

Source: CSCO (Chinese Society of Clinical Oncology), Goldman Sachs Global Investment Research

Small cell lung cancer (SCLC) - lack of targeted therapies

SCLC is known for its rapid progression and early development of widespread metastases. It is sensitive to initial chemotherapy and radiotherapy, but most patients will relapse. For SCLC, most doctors use a two-stage system that divides SCLC into the

limited stage and the extensive stage (or extensive-disease ED-SCLC). This helps determine if a person might benefit from more aggressive treatments such as chemotherapy combined with radiation therapy to try to cure the cancer (for limited stage cancer), or whether chemotherapy alone is likely to be a better option (for extensive stage cancer).

- **Limited stage:** The goal of treatment is to cure the patient using chemotherapy and radiotherapy. Etoposide and cisplatin (EP regimen) is the most commonly used initial combination chemotherapy regimen.
- **Extensive-stage:** Platinum-based regimens can palliate symptoms and prolong survival in most patients. So far, no treatment has shown notable survival benefits for ED-SCLC patients, while some investigational therapies are on trials, e.g. PD-1/PD-L1 inhibitors.

Targeted therapies to highlight

There are three major categories of targeted therapies approved by the CFDA in China in treating stage IV NSCLC: 1) EGFR TKIs (tyrosin kinase inhibitors); 2) ALK TKIs; and 3) drugs targeting tumor blood vessel growth (i.e., VEGR inhibitors).

EGFR TKIs

There are five EGFR TKIs being approved in China: First-line therapies include gefitinib (Iressa from AZ), erlotinib (Tarceva from Roche), icotinib (Commana from Chinese player Betta Pharma) and afatinib (Giotrif from Boehringer Ingelheim); osimertinib (Tagrisso from AstraZeneca) has been approved as a second-line treatment. The first generation TKIs (gefitinib, icotinib, erlotinib) are reversible inhibitors to EGFR, while second-generation afatinib is an irreversible inhibitor to EGFR/HER2/ErbB4 signal pathways, and third-generation osimertinib is targeting patients with T790M mutation, which is the trigger for resistance to first-line EGFR TKI treatment. Icotinib is the first domestic developed novel EGFR TKI in China, capturing ~40% market share in 2017, while the sales trajectory of Tagrisso might be the steepest among all five, hitting sales of ~Rmb700 mn in the first year in China since its official launch in April 2017.

Exhibit 85: Comparison of five novel EGFR TKIs approved in China

Drug Brand in China	**Conmana (Icotinib)** 凯美纳	**Iressa (Gefitinib)** 易瑞沙,	**Tarceva (Erlotinib)** 特罗凯,	**Giotrif (Afatinib)** 吉泰瑞	**Tagrisso (osimertinib)** 泰瑞沙
Generation	1st-gen (reversible inhibition)	1st-gen (reversible inhibition)	1st-gen (reversible inhibition)	2nd-gen (irreversable inhibition, also inhibits HER2, ErbB4)	3rd-gen (targeted T790M mutation)
Manufacturer	Betta Pharma	AstraZeneca	Roche	Boehringer Ingelheim	AstraZeneca
Global first approval	-	2002, July in Japan	2004, Nov. in US	2013, July in US	2015, Nov in US
China approval	2011, June	late 2004	2006, April	2017, Feb	2017, Feb
Line of treatment	1st-line	1st-line	1st-line	1st-line	2nd-line
Sales in China (2017)	Rmb1,026m	~Rmb990m (US$144m)	~Rmb300m (estimates)	N/A	~Rmb700m
Dose strength	125mg / tablet	250mg / tablet	100mgor150mg / tablet	40mg / tablet	80mg / tablet
Daily dose	375mg	250mg	150mg	40mg	80mg
Treatment costs					
Latest national price cuts	Mid May, 2016	Mid May, 2016	2016, Aug - voluntary (-30%) Late July, 2017 - NRDL price negotiation	-	-
Monthly cost					
- Before price cut	~Rmb12,000	~Rmb14,000-Rmb15,000	~Rmb16,000-Rmb17,000	~Rmb9,500-10,000	~Rmb51,000 (or ~Rmb17,000 with PAP)
- After price cut	~Rmb5,500	~Rmb6,000-7,000	~Rmb5,850		
Reimbursement					
2017 NRDL	√	√	√	X	X
Clinical trial data	China trial		China trial	Global trial	Global trial
Trials	ICOGEN (Phase III, head-to-head)		TRUST (China)	LUX-Lung 8	AURA3
1st/2nd/3rd-line	2L/3L		2L/3L	2L vs. gefitinib	2L vs. platinum-pemetrexed
Sample size	200 (icotinib) : 199 (gefitinib)		6,665 (519 in China)	6,665 (519 in China)	419 T790M+ (48 in China)
mPFS	Icotinib 4.6 mth vs. gefitinib 3.4 mth		3.25 mth (6.44 mth China)	2.4 mth vs. Iressa 1.9 mth	10.1 mth vs. control 4.4 mth
mOS	Icotinib 13.3 mth vs. gefitinib 13.9 mth EGFR+: icotinib 20.9 mth vs. gefitinib 20.2 mth EGFR-: icotinib 7.8 mth vs. gefitinib 6.9 mth		7.9 mth (15.37 mth China)	7.9 mth vs. Iressa 6.8 mth	Not reached, HR 0.72

Source: Company data, Goldman Sachs Global Investment Research, PDB database

ALK/ROS1 inhibitors

Crizotinib (Xalkori from Pfizer) was approved by the CFDA in 2013 (NDA review only took 11 months) and is recommended as a first-line treatment for ALK+ and ROS1+ patients. In a global phase III trial, crizotinib showed superior PFS (median 7.7 months vs. 3 months for chemo) and ORR of 65% vs. 20% for chemo.

Anti-VEGFR TKIs and antibodies

In 2015, bevacizumab combined with carboplatin and paclitaxel was approved by the CFDA as a first-line therapy in China for metastatic non-squamous NSCLC, based on a China-specific phase III trial (BEYOND study), which showed that the combo could extend PFS by 2.7 months and OS by 6.6 months, reducing the risk of tumor progress by 60% and the risk of death by 32%. Moreover, Sino Biopharm's anlotinib, which is a multi-target kinase inhibitor with primary inhibitory activity against VEGFR, was recently approved by the CFDA as the third-line treatment for NSCLC patients. Phase III data of anlotinib (ALTER-0303 study) implied the potency of the novel therapy in a third-line setting: OS of 9.63 months/PFS of 4.37 months vs. placebo 6.3/1.4 months, respectively.

Key candidates in pipeline for NSCLC

EGFR TKI remains the most crowded area for developing targeted therapies for NSCLC, followed by anti-ALK, anti-VEGFR, and anti-cMET agents. Given the significant patient base for lung cancer in China, almost all first-batch PD1/L1 inhibitors targeting the Chinese market included NSCLC in one or more phase II/III trials.

Among ~50 novel therapies under development in the space, we would like to highlight a few late-stage ones with potential:

- **PD-1 antibodies as potential new options**: With the encouraging data from Keytruda's trials on treating NSCLC in both a first-line and second/third-line setting, NSCLC is now a most valued area for anti-PD-1/L1 agents under development, and Keytruda's NDA with CFDA is targeting NSCLC indication. So far, not much China-specific data for PD-1 inhibitors on NSCLC has been released. Hengrui submitted a 27-patient phase Ib data to ASCO 2018, showing ORR of 41.2% and DCR of 94.1% for the combination of SHR-1210 and apatinib in a third- or later-line setting.
- **High bar for new EGFR TKIs**: The bar for developing better EGFR TKIs has been raised notably in past years, given that the third-generation EGFR TKI Tagrisso (osimertinib) has demonstrated strong efficacy in both second-line and first-line settings, and has also showed encouraging activities in the central nervous system (FLAURA Trial), which implies effectiveness in patients with brain metastases (a relatively difficult-to-treat group of NSCLC patients). Some late-stage candidates in the pipeline, e.g. dacomitinib, have generated positive clinical data (better PFS) than first-generation EGFR TKIs, but the clinical impact remains debatable given the presence of a potent same-class drug.
- **VEGF TKIs**: Anlotinib is the first CDFA approved domestic VEGF TKI, followed by a few domestic candidates, including HCM's fruquitinib and Hengrui's apatinib (gastric cancer indication already approved) at ongoing phase 3 trials, which primarily target late-line (third/fourth-line) patients without standard-of-care treatment in China. Fruiquitinib's phase 2 data showed improved PFS data vs. placebo (3.8 months vs. placebo 1.1 months), though OS benefits have not been proven yet. The concerns with apatinib might be the dose-dependent side-effects (500-850mg daily vs. fruiquitinib 5mg once daily).

Exhibit 86: Pipelines for lung cancer (M for drug from multinational companies)

Candidates	Type	Target	Company	China Status	Global status
EGFR					
M Dacomitinib	TKI	EGFR-2nd gen	Pfizer	NDA filed	NDA filed US FDA;NDA filed EU EMA
Epitinib	TKI	EGFR	Chi-Med	Ph3	
M Avitinib	TKI	EGFR-3rd gen	ACEA Bio	Ph2	Ph 1/2 US
Pyrotinib	TKI	EGFR	Hengrui	Ph2	
AZD3759	TKI	EGFR	Alpha Biopharma	Ph1 / 2	
ASK120067	TKI	EGFR-3rd gen	Aosaikang	Ph1 / 2	
AST2818 (Alflutinib)	TKI	EGFR-3rd gen	Allist	Ph2	
Simotinib	TKI	EGFR	Simcere	Ph1b	
Beita-tinib	TKI	EGFR-2nd gen	Jinghua	Ph1	
BPI-15086	TKI	EGFR-3rd gen	Betta	Ph1	
HS-10296	TKI	EGFR-3rd gen	Hansoh	Ph1	
YZJ-0318	TKI	EGFR-3rd gen	Yangtze River Pharma	Ph1	
Mihuatinib	TKI	EGFR-3rd gen	Huadong	Ph1	
SH-1028	TKI	EGFR-3rd gen	Sanhome	Ph1	
ES-072	TKI	EGFR-3rd gen	Bossan	Ph1	
D-0316	TKI	EGFR	Yifang	Ph1	
GR1401	TKI	EGFR	Genrix	Ph1	
BPI-7711	TKI	EGFR	Beta pharma	Ph1	
GMA204	TKI	EGFR-3rd gen	Gmax Bio	IND filed	
ZL-2303 (Olmutinib)	TKI	EGFR-3rd gen	Zai Lab	IND filed	
ALK					
M Zykadia (Ceritinib)	TKI	ALK / ROS1-2nd gen	Novartis	Approved (June 1, 2018)	Approved as 2L in US in 2014, 1L in ALK+ NSCLC in 2017
M Alecensa (Alectinib)	TKI	ALK-2nd gen	Roche	NDA filed	Approved in 2015 in US/EU
X-396 (Ensartinib)	TKI	ALK-2nd gen	Betta	Ph3	
HS-10168	TKI	ALK	Hansoh	Ph1	
PLB1003	TKI	ALK	Pearl Biotech	Ph1	
M Lorlatinib	TKI	ALK / ROS1-3rd gen	Pfizer	IND approved	NDA in US/EU/Japan
ZL-2302	TKI	ALK	Zai Lab	IND approved	
M TPX-0005 (Ropotrectinib)	TKI	ALK-4th gen	TP Therapeutics	IND filed	Ph 1/2 in US
RF-A089	TKI	ALK	Humanwell	IND filed	
VEGFR					
M Ofev (Nintedanib)	TKI	VEGFR, FGFR, PDGFR	Boehringer Ingelheim	Ph3	Approved in 2014 by EU EMA
HMPL-013 (Fruquintinib)	TKI	VEGFR1/2/3	Chi-Med	Ph3	
ATAN (Apatinib)	TKI	VEGFR2	Hengrui	Ph3	
M Erdafitinib	TKI	FGFR	Johnson & Johnson	Ph2	Ph2 in US
c-MET					
M INC280 (Capmatinib)	TKI	c-Met	Novartis	Ph2	Ph2 in US
Savolitinib	TKI	c-Met	Chi-Med	Ph2	
M MSC2156119J (Tepotinib)	TKI	c-Met	Merck	Ph1b / 2	Ph2 in US
CT053PTSA (Ninggetinib)	TKI	c-Met, VERRF	HEC Pharma	Ph1b	
BPI-9016M	TKI	c-Met	Betta	Ph1	
Borui-tinib	TKI	c-Met	Pearl Biotech	Ph1	
PD-1/L1					
M Opdivo (nivolumab)	Biologics	PD-1	BMS	NDA filed	Approved in US 2015
M Keytruda (Pembrolizumab)	Biologics	PD-1	Merck/MSD	Phase 3	Approved in US 2015
SHR-1210	Biologics	PD-1	Hengrui	Phase 3, 2	Single agent, or + apatinib / platinum regimen
BGB A317	Biologics	PD-1	Beigene	Phase 3	Single agent
IBI308	Biologics	PD-1	Innovent	Phase 3	Single agent
M Tecentriq (Atezolizumab)	Biologics	PD-L1	Roche	Phase 3	Approved in US 2016
M Imfinzi (durvalumab)	Biologics	PD-L1	AstraZeneca	Phase 3	Approved in US 2018
M Bavencio (avelumab)	Biologics	PD-L1	Merck	Phase 3	Ph3 in US
JS001	Biologics	PD-1	Junshi	Phase 2	Combo
c-MET					
M Portrazza (Necitumumab)	Antibody	EGFR	Eli Lilly	IND approved	Approved in 2015 in US, 2016 in EU
CDK					
HcHAb18 (mertuzumab)	Antibody	CD147	Pacific Meinuoke	Ph1	

M Drug from multinational company

Source: Insight database

BREAST CANCER In China

272,400 New cases per year
70,700 Death per year
19.3 / 100K Incidence rate
5.0 / 100K Mortality rate
83.2 % 5-year survival rate (2010-14)

Most common type: Invasive carcinoma (88%)
Most common genotype: HER2+ (25%-30%)
Staging at diagnosis: Stage I 14%, Stage II 42%, Stage III/IV 44%
Targeted therapies in China Herceptin (trastuzumab) for 1st-line HER2+ patients; Tykerb (lapatinib) for 2nd-line HER2+

Disease demographics

Breast cancer is now the most common cancer in Chinese women, with 272,400 new cases each year. Breast cancer is also a highly heterogeneous disease. The selection of treatment is based on tumor histology, clinical and pathologic characteristics of the primary tumor and molecular types. Based on the status of three important biomarkers: 1) two hormone receptors (HR), i.e. estrogen receptor-alpha (ER) and progesterone receptor (PR); and 2) human epidermal growth receptor 2 (HER2), breast cancer patients can be classified under four major types:

- Luminal A type: ER+ and/or PR+, HER2-
- Luminal B type: ER+ and/or PR+, HER2+
- Triple-negative type (TNBC for short): ER-, PR- and HER2-
- HER2 type: HER2+, ER-, and PR-

The prognosis of HER2+ and TNBC subtypes are poorer, with lower survival outcomes, and the two types accounted for ~30% and 13% of breast cancer patients in China, respectively.

Exhibit 87: Over 30% of breast cancer patients are HER2+
Four major molecular subtypes of breast cancer in China

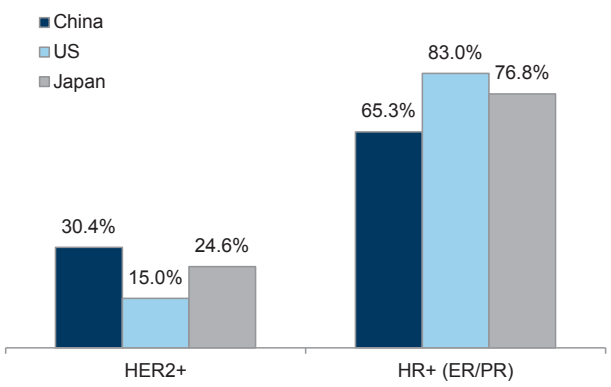
HER2+ patients

Molecular subtype	Luminal A	Luminal B	HER2	TNBC*
Biomarker:				
- ER and/or PR	+	+	- (both)	- (both)
- HER2	-	+	+	-
%	48.6%	16.7%	13.7%	12.9%
5-year survival:				
- Overall survival	92.9%	88.6%	83.2%	80.7%
- Disease free survival	88.6%	85.1%	79.1%	76.0%

Note:
1. based on a study covering 2791 patients in China
2. Other than the 4 types, ~8% of patients are "HER2 borderline" i.e. showed weak positive HER2
3: TNBC: tripple negative breast cancer

Source: Su et al. BMC Cancer 2011 11:292

Exhibit 88: Higher HER2+ prevalence in China
HER2+/HR+ status in China vs. Japan/US

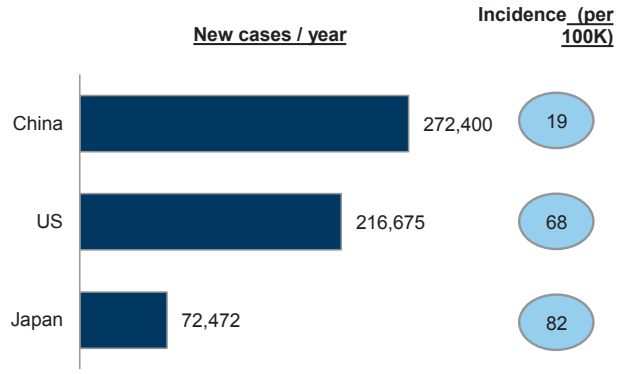


Source: National surveys in China, Japan and US, Goldman Sachs Global Investment Research

Incidence and survival rate vs. global peers

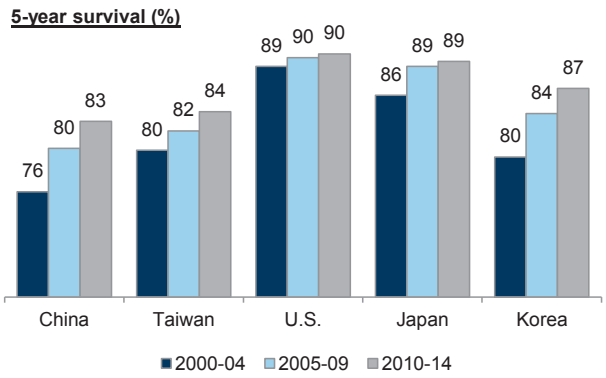
The incidence of breast cancer has been increasing in China, as well as in other developing countries/regions, due to improving life expectancy and the adoption of the lifestyle in more developed regions along with urbanization, including delayed childbearing and fewer children, less breast-feeding, a more sedentary workforce, and a more Westernized diet.

Exhibit 89: Breast cancer incidence may increase in China
Incidence of breast cancer in China is lower vs. Japan/US



Source: Cancer Statistics in Japan 2013, Cancer China Statistics 2015, American Cancer Society

Exhibit 90: Improving survival rate for breast cancer in China
Breast cancer 5-year survival in China vs. Asian peers/US

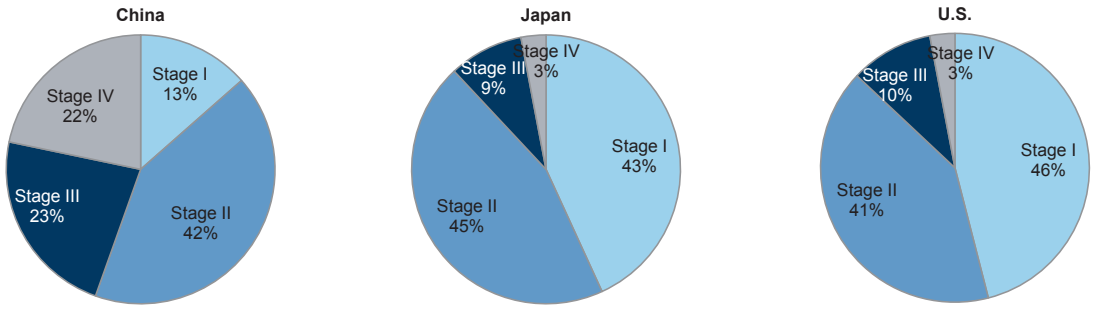


Source: Global surveillance of trends in cancer survival 2000-14

Distribution of cancer stages

More importantly, early detection in China for breast cancer, such as mammography, is still underdeveloped: ~45% of patients in China were diagnosed with Stage III/IV breast cancer vs. <15% in Japan/US. However, the five-year survival rate has improved notably in the past 10 years due to the availability of effective treatment in China, e.g. the approval of Herceptin in 2002, the gold-standard treatment for HER2+ breast cancer globally.

Exhibit 91: Early diagnosis of breast cancer in China is notably lower
Breast cancer patient by cancer stage: China vs. US/Japan

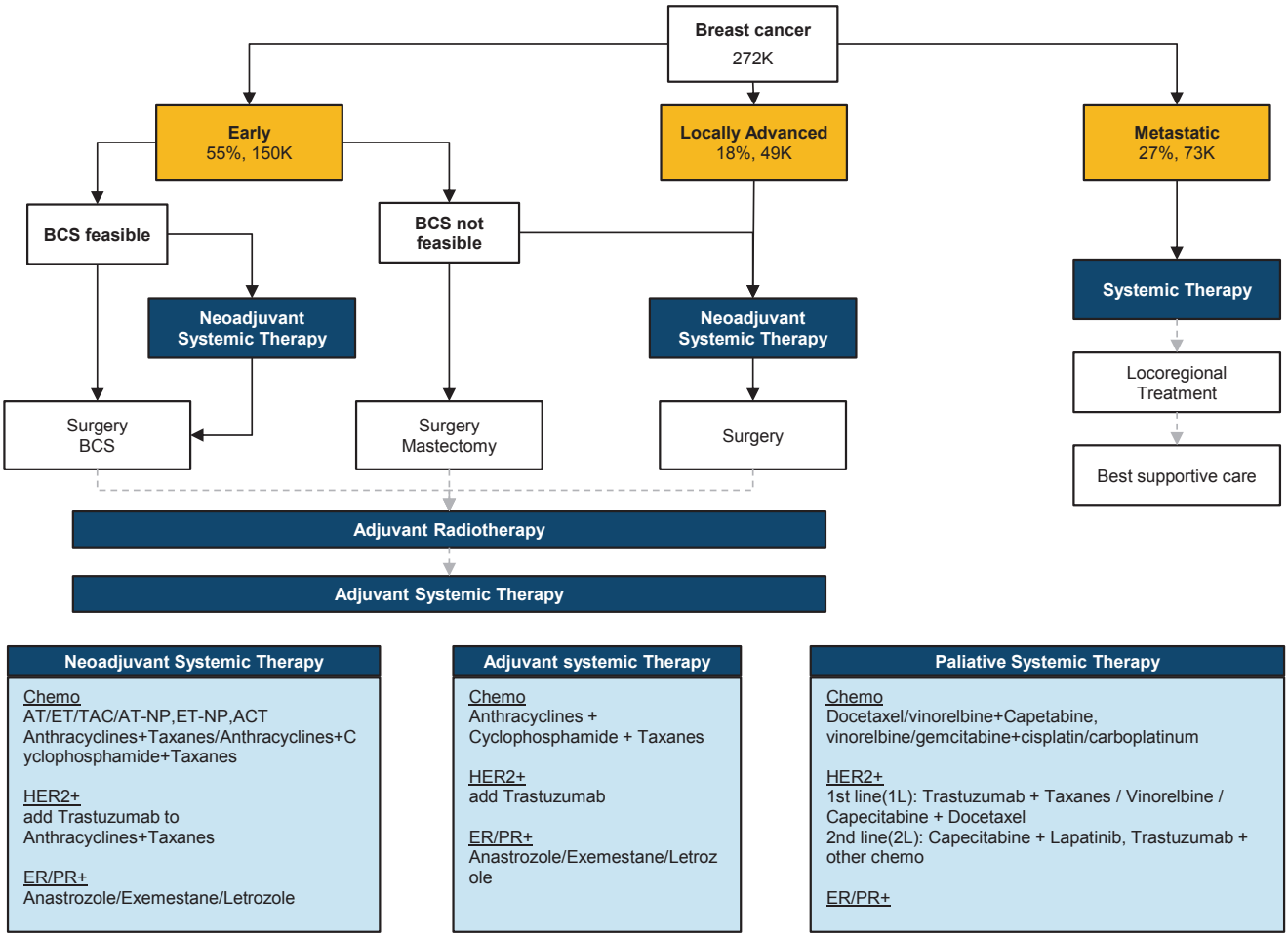


Source: A Nation-Wide multicenter 10-year (1999-2008) retrospective clinical epidemiological study of female breast cancer in China, Disparities in Medical Care Among Commercially Insured Patients With Newly Diagnosed Breast Cancer Opportunities for Intervention, Characteristics and prognosis of Japanese female breast cancer patients: The BioBank Japan project

Treatment paradigm

Radical mastectomy, i.e. removal of the entire breast, the underlying chest muscle and all the lymph nodes nearby, is widely perceived as the curative treatment. In most cases surgery is followed up with adjuvant radiation therapy, chemotherapy, and hormone therapy. The medication is based on the status of hormone receptors (ER/PR) and HER2.

Exhibit 92: Treatment paradigm of breast cancer in China



Note:
Systemic therapy includes endocrine therapy and/or targeted therapy and/or Chemotherapy
BCS - Breast conserving surgery

Source: CSCO, Goldman Sachs Global Investment Research

- **Early stage (I-II):** Primary surgery (breast-conserving surgery/BCS or mastectomy) with or without radiation therapy can potentially be the cure for early-stage breast cancer patients. BCS allows patients to preserve their breast but can only be applied to very early-stage patients. Neoadjuvant therapy will be considered when the size of the tumor does not meet the criteria. Post-surgery adjuvant therapy including medication and radiation are also necessary.
- **Locally advanced stage (IIIA,IIIB):** Surgery is still recommended, but with pre-surgery neoadjuvant therapy: 1) anthracycline-based (i.e., doxorubicin) with or without a taxane is standard therapy; 2) for HER2 positive patients, trastuzumab will be added; and 3) for ER/PR positive patients, endocrine therapy will be applied,

which include anastrozole/letrozole/exemestane/tamoxifen. After the surgery, adjuvant therapies also help to reduce the risk of local recurrence.

- **Metastatic stage (IIIC, IV):** For HER+ patients, trastuzumab remains the first-line therapy and lapatinib plus capecitabine is the second line. Taxane-/platin-based regimens are recommended for other patients. Fluvestrant (marketed under the brand of Faslodex) is normally only prescribed to ER/PR+ post-menopausal women.

Targeted therapies to highlight

There are two targeted drugs approved by the CFDA for treating breast cancer, all targeting HER2+ patients:

- **Herceptin (Trastuzumab) from Roche:** Herceptin is approved to be used in adjuvant therapy and first-line palliative therapy for patients with HER2+ alone or in combination with other standard chemotherapy. Herceptin provides overall survival benefits (reduces the risk of death by 39%) and has reduced the risk of recurrence (risk down by 48%). With proven clinical efficacy and consistent recommendation from key opinion leaders (oncologists) in China, Herception has become one of the best-selling monoclonal antibodies in China, capturing more than Rmb2.5bn of sales in 2017, triggering significant interest in biosimilar development. In 2017, Herceptin was included into a new NRDL, post a price cut of ~65%.
- **Tykerb (Lapatinib) from GSK:** Different from Herceptin, which is an anti-HER2 antibody, lapatinib is a small molecule in oral formulation. It is indicated for second-line treatment of HER2+ breast cancer, and CFDA approval was granted in 2013 for lapatinib plus capecitabine regimen, which could extend the PFS by four months (8.4 months vs. capecitabin only 4.4 months), based on phase III data. Similar to Herceptin, Tykerb's price was cut by 40% in 2017 before being included into the new version of the NRDL.

Key candidates in pipeline for breast cancer

Over 20+ of novel therapies are at various clinical trials in China for breast cancer treatment, and six Herceptin biosimilar candidates are in the pipeline. While HER2 remains as one of the key targets for both smaller-molecule drugs and biologics, which are targeting post-Herceptin second-line treatment, PARP inhibitors and CDK4/6 inhibitors represent a new class of drugs in this space; we highlight a few late-stage candidates below:

- **Herceptin biosimilars:** Six Herceptin biosimilars are in clinical trials with more at earlier stages (IND or preclinical). Fosun Pharma's biotech arm Henlius is one of the leaders in this space, with phase III targeting to finish the patient enrollment by end-2018 and potential NDA in 2019. GenorBio and Hisun Pharma are also at phase III.
- **Novel anti-HER2 antibodies:** Roche has filed NDA in China for pertuzumab (brand name Perjeta), which combined with trastuzumab and chemo regimen has been approved in the US/EU/Japan for breast cancer patients in different settings (first-line, neoadjuvant and adjuvant). Though pertuzumab is also a monoclonal

antibody that blocks HER2, it binds to a different antigenic region of the HER2 extracellular domain vs. trastuzumab. Phase III data suggest the two anti-HER2 antibodies can extend PFS by 6.1 months vs. Herceptin only.

- **Anti-HER2 ADCs (antibody-drug conjugates):** ADCs are antibodies with a toxic agent linked to the antibody to make it more potent in killing tumors. Kadcyla (T-DM1, or ado-trastuzumab emtansine) is one of the few ADCs approved globally and is now in phase III trials in China. In a EMILIA phase III trial, T-DM1 improves the OS by 5.8 months for patients already resistant to Herceptin treatment. Several domestic players (BioThera, RemeGen and Zhejiang Medicine) are also targeting the space via in-house R&D or license-in deals.
- **HER2 TKIs:** Hengrui's pyrotinib is an oral irreversible EGFR/HER2 inhibitor, and the NDA has been filed with pivotal phase II data. The CDE technical review has been completed, and the onsite inspection was scheduled at late April. If things go smoothly, we believe late 2Q/3Q18 might be a reasonable timeframe to expect CFDA's conditional approval. The phase II data presented at the 2017 San Antonio Breast Cancer Symposium (SABCS) suggests that, compared with the current second-line therapy lapatinib, pyrotinb showed better ORR (78.5% vs. 57.1%) and longer PFS (18.1 months vs. 7 months), implying a potentially more potent therapy in a post-Herceptin setting.
- **PARP inhibitors (-parib):** PARP inhibitors target BRCA-mutated HER2 negative breast cancer (germline BRCA mutation can be found in 20%-30% of breast cancer patients). Olaparib (Lymparza from AZ) is the first drug approved globally for this subgroup (approval in January 2018), based on data showing 2.8 months longer PFS vs. chemotherapy. The drug is now at phase III in China. BeiGene's BGB-290 is also targeting breast cancer as part of its clinical development strategy, though the current indication for the pivotal phase III is gBRCA-mutated ovarian cancer.
- **CDK4/6 inhibitors (-ciclib):** This class of drug tends to target ER+/HER2- patients. Both Ibrance (palbociclib) from Pfizer and Verzenio (abemaciclib) have been approved in the US and are at phase III trials in China. Palbociclib, the first-in-class CDK4/6 inhibitor, was approved for use in combination with endocrine therapy for metastatic breast cancer, while abemaciclib was the first CDK4/6 inhibitor approved as a stand-alone treatment. Hengrui's CDK4/6 inhibitor SHR6390 is also at Phase Ib/II trials for HR+/HER- breast cancer.
- **PI3K pathway:** Among new targets, PIK3CA (which belongs to the PI3K family) is one of the potential targets for drug development for breast cancer, particularly ER+ patients, given the common PIK3CA gene mutation in this group of patients. Roche's potential first-in-class taselisib, according to a Phase III trial (SANDPIPER study) results presented at ASCO 2018, modestly delays tumor progression in ER+ breast cancer by two months, and lowers the risk of tumor progression by 30% (i.e. HR=0.70).

Exhibit 93: HER2, PARP and CDK4/6 as focused targets in breast cancer therapy development
Key novel therapies for breast cancer under development in China

Candidates	Type	Target	Company	China Status	Global status
HER2					
M Perjeta (Pertuzumab)	Biologics	HER2	Roche	NDA filed	Approved in US in 2012; EU/Japan in 2013
Pyrotinib	Chemical	HER2	Hengrui	NDA filed	Ph1 in US
M Kadcyla (T-DM1)	ADC	HER2 + DM1	Roche	Ph3	Approved in US/EU/Japan in 2013
BAT8001	ADC	HER2 + IgG1	Bio-thera	Ph3	-
RC48-ADC	ADC	HER2	RemeGen	Ph1b / 2	-
HS627	Biologics	HER2	Hisun	Ph1	-
LZM005	Biologics	HER2	Livzon	Ph1	-
ARX-788 (HER2-AS269)	ADC	HER2	Zhejiang Medicine	Ph1	Licensed from Ambrx in 2013
CDK4/6					
M Ibrance (Palbociclib)	Chemical	CDK4/6	Pfizer	Ph3	Approved in US,2015; EU, 2016; Japan,2017
M Verzenio (Abemaciclib)	Chemical	CDK4/6	Eli Lilly	Ph3	Approved in US, 2017 and NDA filed in EU and Japan
SHR6390	Chemical	CDK4/6	Hengrui	Ph1b / 2	-
PARP					
M Lynparza (Olaparib)	Chemical	PARP	AstraZeneca	Ph3	Approved in US in Jan 2018 for gBRCA+ / HER-BC
BGB-290 (Pamparib)	Chemical	PARP	Beigene	Ph1	-
IMP4297	Chemical	PARP	Impact Therapeutics	Ph1	-
Fluzoparib	Chemical	PARP	Hansoh	Ph1	-
M ABT-888 (Veliparib)	Chemical	PARP1 / PARP2	AbbVie	IND approved	Ph3 in the US
EGFR					
QLNC-120	Chemical	EGFR / HER2	Qilu	Ph2	-
Hemay022	Chemical	EGFR / HER2	Hemey Bio	Ph1	-
Allitinib	Chemical	EGFR	Allist	Ph1	-
mTOR					
M Afinitor (Everolimus)	Chemical	mTOR	Novartis	Ph2	Approved in US and EU, 2012
LXI-15029	Chemical	mTOR	Luoxin Pharma	Ph1	-
PI3K					
M Taselisib	Chemical	PIK3CA	Roche	Ph3	Ph3 in US
M BKM120 (Buparlisib)	Chemical	PI3K	Novaritis	IND approved	Ph2 in the US
VEGFR/FGFR multiple targets					
M ENMD-2076	Chemical	VEGFR, FGFR, c-KIT, FLT-3, CSF1R	CASI Pharma	Ph2	Ph2 in US
PD-1/L1					
JS001	Biologics	PD-1	Junshi Bio	Ph1	For TNBC

Source: Insight database

GASTRIC CANCER In China

679,100 New cases per year
498,000 Death per year
48.0 / 100K Incidence rate
35.2 / 100K Mortality rate
35.9% 5-year survival rate (2010-14)

Most common type: Adenocarcinoma (90%)
Most common genotype: HER2+ (12%)
Staging at diagnosis: Stage I 13%, Stage II 22%, Stage III/IV 65%
Targeted therapies in China Herceptin (trastuzumab) for HER2+ patients; apatinib: for 3rd-line treatment

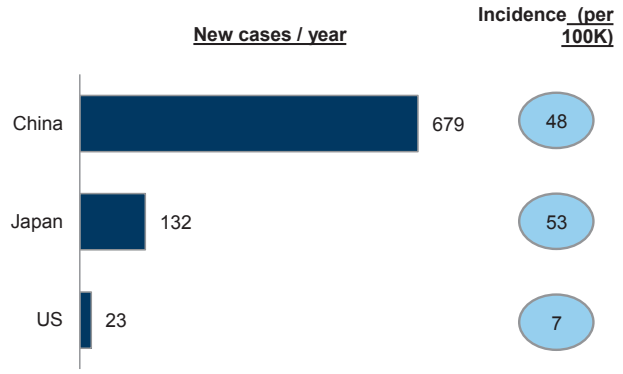
Disease demographics

Gastric cancer (or stomach cancer) is the second-largest cancer in China, in terms of both incidence rate and mortality rate. Based on data from Cancer Registry in China, the country sees about 679,100 new cases of stomach cancer each year. More than 70% of gastric cancer patients in China, as well as in other Eastern Asian countries, develop a tumor in the lower part of their stomach (i.e., antrum and pylorus), while the major type of gastric cancer in the US/EU occurs in the main body/upper part of the stomach (e.g., the junction with the esophagus), which entails different treatment.

Incidence and survival rate vs. global peers

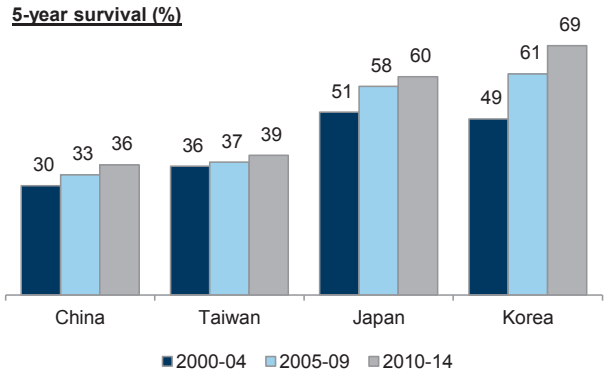
The incidence of gastric cancer is substantially higher in China and other East Asian countries (one of the top-five cancers in both China and Japan, ~50 per 100,000 population, vs. <10 in the US and Europe), which poses a substantial opportunity for therapies targeting gastric cancer. Key risk factors for gastric cancer include: 1) the high incidence of helicobacter pylori (H. pylori) infection (62% based on a study in Jiangsu province in China); 2) smoking; and 3) diet, e.g. high salt intake. Less affluent/developing countries have higher exposure to these risk factors. Gastric cancer incidence has been declining globally since the 1930s, so we expect the incidence rate in China to gradually decline.

Exhibit 94: Higher incidence of gastric cancer in Eastern Asia
Incidence of gastric cancer in China vs. US/Japan



Source: Cancer China Statistics 2015, Cancer Statistics in Japan 2013, American Cancer Society

Exhibit 95: Poorer prognosis of gastric cancer in China
Gastric cancer five-year survival in China vs. Asian peers

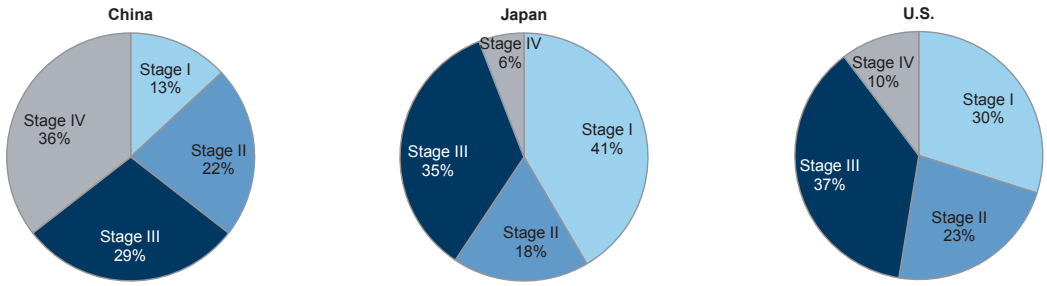


Source: Global surveillance of trends in cancer survival 2000-14

Distribution of cancer stages

The five-year survival rate (which is widely used to assess the prognosis of cancer) for gastric cancer in China was 35.9%, which is an improvement over the last 10 years, but still below Asian peers (e.g., 60%-70% in Japan/South Korea), largely due to a lower rate of early diagnosis: over 65% of patients are diagnosed with local advanced (stage III) and metastatic gastric cancers (stage IV), for which surgery might no longer be an option, and only 13% are diagnosed at the early stage (stage I), vs. the ratio of 41% in Japan. A lack of screening programs and relatively low penetration of annual medical check-ups in China are likely to be key reasons for this.

Exhibit 96: Over 65% of gastric cancer diagnosed at mid to late stage in China
Gastric cancer patients by cancer stage: China vs. US/Japan



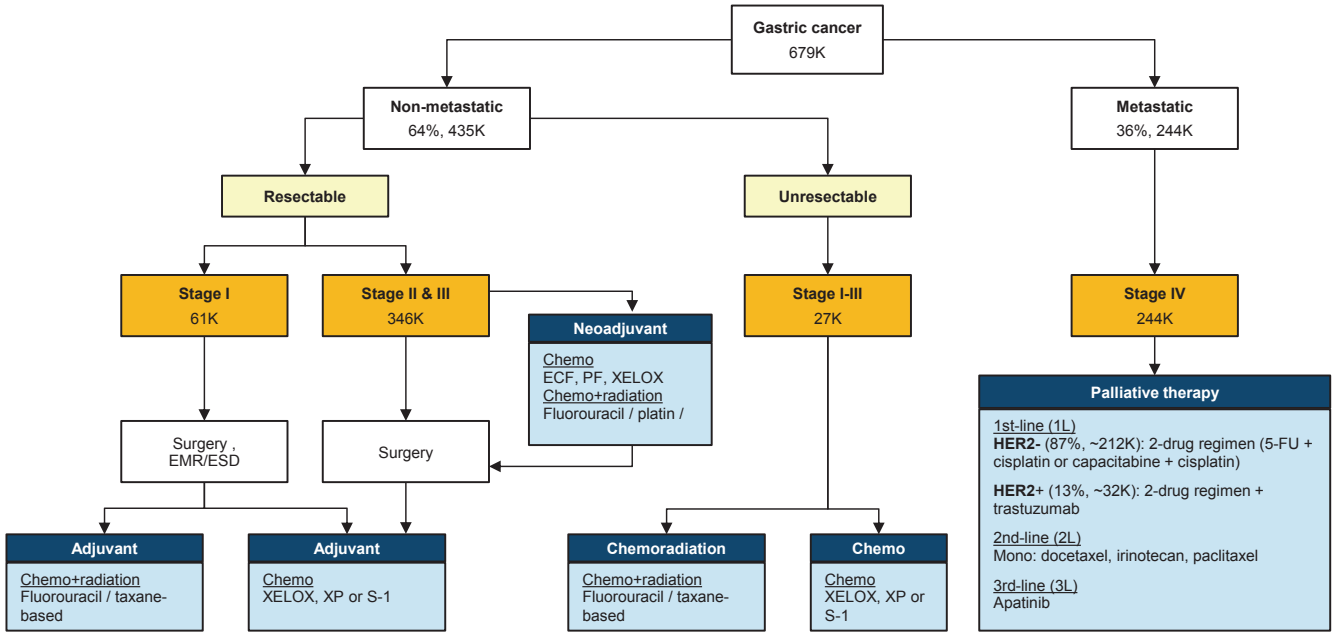
Source: Clinical features and treatment of patients with esophageal cancer and a history of gastrectomy: a multicenter, questionnaire survey in Kyushu, Japan; Survival analysis of patients with gastric cancer in Shanghai; Lymph Node Staging in Gastric Cancer: Is Location More Important Than Number?

Treatment paradigm

Below we summarize the most common approaches to treating gastric cancer in China, based on Chinese clinical guidelines and feedback from oncologists:

- **Stage I-III (local) gastric cancer:** Surgery is the primary treatment, which can be followed by adjuvant chemotherapies or concurrent chemoradiation therapies. In some cases, the chemo/chemoradiation is applied before the surgery (i.e., neoadjuvant therapies). For stage I-III patients with unresectable tumors, chemo/chemoradiation will be the first treatment choice.
- **Stage IV (metastatic) gastric cancer (mGC):** As mGC is not curable with available therapies, managing the symptoms and slowing the progress of the disease, thereby prolonging survival, is the key focus of the treatment:
  - **First-line (1L):** HER2 genetic testing is recommended for all patients with metastatic disease at the time of diagnosis (12% of gastric cancer patients are HER2 positive in China, less common vs. 30%-40% for breast cancer in China). For HER2-negative (HER2-) mGC, a two-drug regimen (5-FU or capacitabine plus cisplatin) is the most commonly prescribed treatment, while trastuzumab, the anti-HER2 antibody, is added into the two-drug regimen for HER2+ patients.
  - **Second-/third-line (2L/3L):** For relapsed/refractory patients that have failed 1L treatment, taxanes (docetaxel and paclitaxel) and irinotecan will be used. Hengrui's apatinib (brand name is ATAN) is the only recommended third-line targeted therapy in China for gastric cancer.

Exhibit 97: Gastric cancer treatment paradigm in China



Source: Chinese Society of Clinical Oncology (CSCO), Goldman Sachs Global Investment Research

Targeted therapies to highlight

There are two targeted therapies approved by the CFDA for treating gastric cancers:

- **Herceptin (trastuzumab) from Roche:** The combination of trastuzumab plus capecitabine or 5-FU and cisplatin (i.e., trastuzumab added to XP or PF regimen) was approved by the CFDA in 2012 as a first-line therapy for patients diagnosed with HER2+ metastatic gastric and gastroesophageal junction adenocarcinoma. Roche's ToGA phase III open-label, randomized controlled trial: trastuzumab plus chemo could improve overall survival (OS) by 2.7 months vs. chemo only (OS of 13.8 months vs. chemo 11.1 months).
- **ATAN (apatinib) from Hengrui:** Apatinib is first domestic targeted therapy developed for gastric cancer. The novel VEGFR2 inhibitor was approved by the CFDA as a third-line therapy in 2014, with phase III data showing improvement in OS (6.5 months vs. placebo 4.7 months) and progression free survival (PFS, 2.6 months vs. placebo 1.8 months). More trials are being conducted on apatinib to: 1) move to earlier line of treatment; and 2) expand to new indications (e.g., lung, liver, esophageal, breast and colorectal cancers). Apatinib was included in the 2017 edition of the NRDL, after the price cut of ~35% in 2016.

The most commonly used chemotherapies are fluoropyrimidines (capecitabine and 5-FU) and cisplatin/oxaliplatin, while taxane (paclitaxel and docetaxel) is also recommended for second-line setting and adjuvant/neoadjuvant therapies.

Exhibit 98: Commonly used targeted therapies/chemotherapies used to treat gastric cancer

Targeted therapy	
Apatinib (ATAN, Hengrui)	For 3rd-line gastric cancer treatment
Trastuzumab (Herceptin, Roche)	For HER2+ metastatic patients' 1st-line treatment
Chemo regimens	
XELOX	Capecitabine (XEL) + Oxaliplatin (OX), also known as CAPOX / CAPE-OX
XP	Capecitabine (X) + Cisplatin (P)
PF	Cisplatin (P) + Fluorouracil (5-FU, F)
S-1	Tegafur+gimeracil+oteracil potassium compound, also one of the "standard-of-care" treatment in Japan
ECF	Epirubicin (E) + Cisplatin (C) + 5-FU (F)
Fluoropyrimidine	A type of anti-cancer drugs, most commonly used ones include: 5-FU, capecitabine and floxuridine
Taxane	A class of anti-drugs, paclitaxel and docetaxel are widely used

Source: CSCO

Key candidates in pipeline for gastric cancer

The vascular endothelial growth factor (VEGF) pathway is a key focus in the development of targeted therapies for treating gastric cancers, and PD-1 is emerging in the space. HER2 is also one of the targets (e.g. pyrotinib from Hengrui), but we are more cautious on the success rate, given the failure of lapatinib (anti-HER2 therapy) in its phase-III trial on gastric cancer.

Among the candidates, we highlight:

- **Cyramza (Ramucirumab) from Eli Lilly**: An anti-VEGFR antibody at phase-III trials in China. The biologic was approved by the US FDA in 2014 for treatment of

late-stage gastric cancers patients in second-line as a single agent (OS of 5.2 months vs. placebo 3.8 months, phase III REGARD trial) or combined with paclitaxel (OS of 9.6 months vs. paclitaxel only 7.4 months, phase III RAINBOW trial). However, recent data from a phase III RAINFALL trial presented at the 2018 GI Cancers Symposium do not support use of ramucirumab in a first-line setting. Ramucirumab generated sales of US$758 mn in 2017.

- **Fruquitinib co-developed by Hutchinson Chin-Med (HCM) and Eli Lilly**: Fruquitinib (HMPL-013) is an oral VEGFR inhibitor; the phase III trial on gastric cancer is ongoing, testing the efficacy and safety of the combo of the molecule with paclitaxel in a second-line setting. An NDA for the drug was filed for colorectal cancer indication in June 2017 with positive phase III data (more details in the colorectal cancer section).
- **PD-1 antibodies**: Opdivo/Keytruda have been approved for the treatment of late-stage gastric cancers, as the trials showed survival benefits in a second-line/third-line setting. The Chinese Society of Clinical Oncology (CSCO) has already recommended PD-1 inhibitors in clinical guidelines released earlier this year on gastric cancer, encouraging terminal patients to participate in clinical trials of PD-1. Among more than 25 PD-1/L1 candidates in China, four have already initiated phase II/III trials on gastric cancer.

Exhibit 99: VEGFR inhibitors and PD-1 as focus in gastric cancer research
Key pipeline of targeted therapies/immunotherapies for gastric cancer

Candidates	Type	Target	Company	China Status	Global status
FGFR, VEGFR, Cmet					
HMPL-013 (Fruquintinib)	Chemical	VEGFR	HCM / Eli Lilly	Phase 3	-
M Cyramza (Ramucirumab)	Biologics	VEGFR2	Eli Lilly	Phase 3	First approval (US) in '14, US$758m in '17
M Erdafitinib	Chemical	FGFR	JnJ	Phase 2	Phase 2
Anlotinib	Chemical	VEGFR, FGFR, PDGFR, c-KIT, c-MET	Sino Biopharm	Phase 2	-
Savolitinib	Chemical	c-MET	HCM / AZ	Phase 2	Phase 2 in South Korea for GC
BMS-817378	Chemical	VEGFR-2, c-MET	Simcere / BMS	Phase 1b	BMS licensed out China rights to Simcere in 2010
Lucitanib / Delitinib	Chemical	FGFR/VEGFR	SIMM	Phase 1	-
CM082 (Vorolanib)	Chemical	VEGFR / PDGFR	Betta Pharma	Phase 1	-
CT053PTSA	Chemical	VEGFR/c-MET	HEC Pharma	Phase 1	-
HER2/neu					
SHR1258 (Pyrotinib)	Chemical	HER2	Hengrui Medicine	Phase 1	-
PD-1/L1					
M Keytruda (Pembrolizumab)	Biologics	PD-1	Merck/MSD	Phase 3	Approved in '17 in US as 3L for PD-L1+ patients
M Opdivo (Nivolumab)	Biologics	PD-1	BMS	Phase 3	Approved in '17 in Japan as 2L
SHR-1210	Biologics	PD-1	Hengrui Medicine	Phase 2	-
BGB-A317	Biologics	PD-1	BeiGene	Phase 2	-
GLS-010	Biologics	PD-1	Wuxi / Gloria	Phase 1	-

M *Products from multinational biotech / pharma companies*

Source: Insight database, FDA, Company data

ESOPHAGEAL CANCER In China

477,900 New cases per year
375,000 Death per year
33.8 / 100K Incidence rate
26.5 / 100K Mortality rate
29.7% 5-year survival rate (2010-14)

Most common type: Squamous cell carcinoma (i.e. ESCC, 95%)
Staging at diagnosis: Stage I 8%, Stage II 37%, Stage III/IV 55%

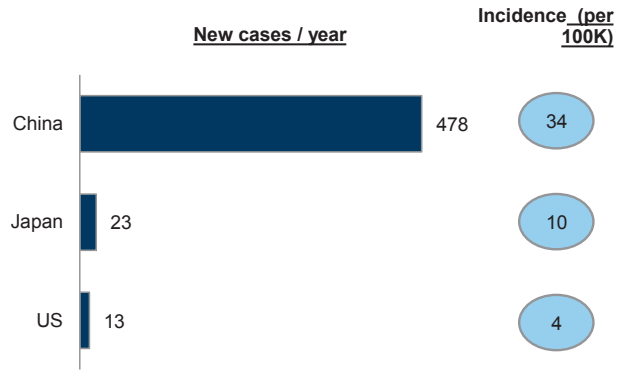
Disease demographics

Esophageal cancer affects the tissue of the esophagus, and is the third-largest cancer in China in terms of incidence (477,900 new cases per annum). Over 80% of new cases of esophageal cancer are in developing countries, and over 50% are in China. There are two types of esophageal cancer - i.e. squamous-cell type (abbreviated to ESCC), which is more common in China (over 95% of all esophageal cancer cases), and adenocarcinoma, which is more common in the US/EU (~75%).

Incidence and survival rate vs. global peers

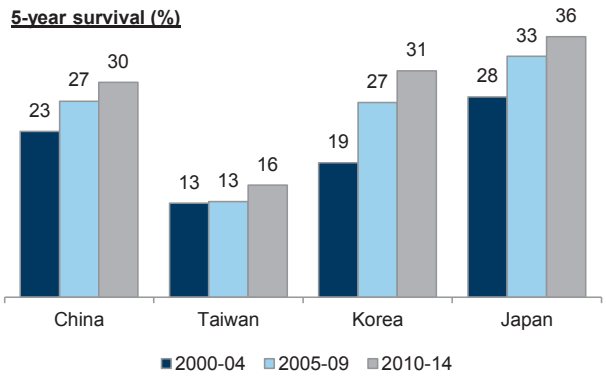
The incidence of esophageal cancer is notably higher in China vs. Japan/US. Key risk factors for ESCC include smoking, alcohol, hot drinks (particularly for those who smoke and drink alcohol) and chewing betel nut, which is popular in Southern China (e.g., Hunan, Fujian, Hainan and Taiwan).

Exhibit 100: Higher incidence of esophageal cancer in China
Incidence of esophageal cancer in China vs. US/Japan



Source: Cancer China Statistics 2015, Cancer Statistics in Japan 2013, American Cancer Society

Exhibit 101: Five-year survival is low due to a lack of effective therapies
Esophageal cancer five-year survival in China vs. Asian peers



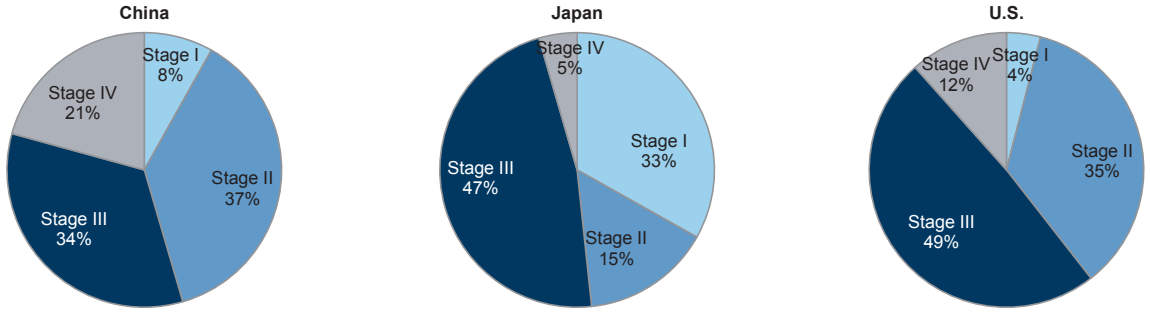
Source: Global surveillance of trends in cancer survival 2000-14

Distribution of cancer stages

The five-year survival of esophageal cancers is generally low: 30% in China and a similar level among Asian peers, largely due to: 1) slow progress in developing new therapies, particularly targeted therapies, for treating ESCC; and 2) difficulties in early detection of

esophageal cancer (55% of EC patients were diagnosed with Stage III/IV cancers, vs. 52% in Japan and 61% in the US, putting all these countries at a similar level).

Exhibit 102: 55% of esophageal cancer is diagnosed at mid to late stage in China
Esophageal cancer patients by cancer stage: China vs. US/Japan



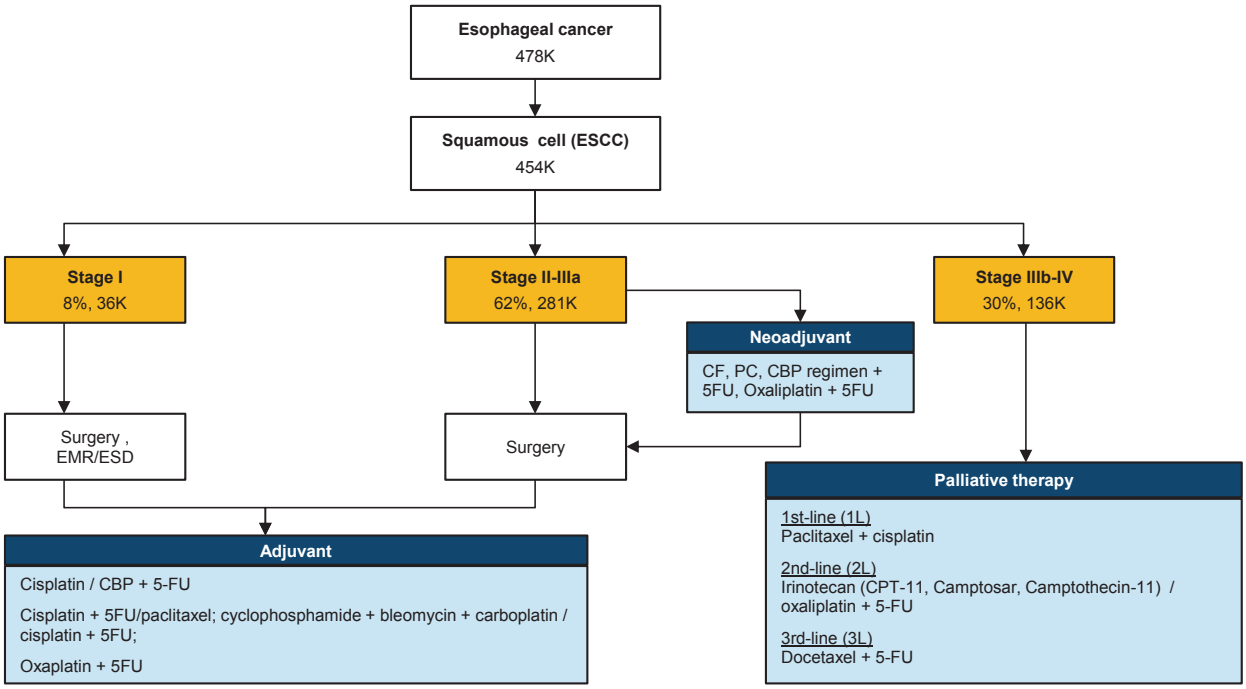
Source: Medical expenditure for esophageal cancer in China: a 10-year multicenter retrospective survey (2002–2011); Clinical features and treatment of patients with esophageal cancer and a history of gastrectomy: a multicenter, questionnaire survey in Kyushu, japan; A survey of oesophageal cancer: pathology, stage and clinical presentation

Treatment paradigm

Cisplatin-based (either cisplatin or oxaliplatin) chemo regimens are the first choice for most ESCC patients in adjuvant, neoadjuvant and palliative first-line settings, with 5-FU, taxanes (paclitaxel and docetaxel) and irinotecan often used in combination therapies.

While transtuzumab (Herceptin) is also recommended in the US for treating HER2+ esophageal cancers, the indication has not been approved in China and is rarely used in clinical practice as off-label therapy.

Exhibit 103: Esophageal cancer treatment paradigm in China



Source: CSCO (Chinese Society of Clinical Oncology), Goldman Sachs Global Investment Research

Key candidates in pipeline for esophageal cancer

Given the relatively lower incidence in the US/EU and differences in histology of esophageal cancer in different countries (i.e., more squamous cell cancer in China vs. more adenocarcinoma in the US/EU), the development of novel therapies for esophageal cancer has been slower than for more prevalent cancers. However, the emergence of cancer immunotherapy, (particularly PD-1/L1) has shown initial efficacy, and potential for being a new tool in managing esophageal cancer:

- **PD-1 antibodies**: Our track of the CDE database suggests there are more than 10 clinical trials to test the efficacy of 8 PD-1/L1 agents in treating esophageal cancers in both first-line and second-line settings, either as a single agent or combined with chemo regimens. Four are at phase-III trials, including Keytruda, Opdivo and two domestic PD-1 inhibitors from Hengrui and BeiGene.
- **VEGF inhibitors**: Hengrui's apatinib and Sino Biopharm's anlotinib are at phase-II trials for ESCC, pending more data to verify the efficacy and safety profile.

Exhibit 104: PD-1/L1 as emerging focus in anti-ESCC therapy development
Key pipeline of targeted therapies/IOs for esophageal cancer in China

Candidates	Type	Target	Company	China Status	Notes
VEGF / FGFR					
Apatinib	Chemical	VEGFR	Hengrui Medcine	Phase 2	Plus chemoradiation or S1 or as single-agent
Anlotinib	Chemical	VEGFR, FGFR, PDGFR, c-KIT, c-MET	Sino Biopharm	Phase 2	-
M Erdafitinib	Chemical	FGFR	JnJ	Phase 2	
Donafenib	Chemical	VEGFR, PDGFR, EGFR, Raf/MEK/ERK	Zelgen	Phase 1b	2L+
EGFR					
Nimotuzumab	Chemical	EGFR	BioTech Pharma	Phase 3	Pls PC regimen, 1L
Larotinib	Chemical	EGFR,HER2	HEC Pharma	Phase 1	-
PD-1/L1					
M Keytruda (Pembrolizumab)	Biologics	PD-1	Merck/MSD	Phase 3	2L setting, single agent
M Opdivo (nivolumab)	Biologics	PD-1	BMS	Phase 3	Combo plus Yervoy, 1L setting; single-agent
BGB-A317	Biologics	PD-1	Beigene	Phase 3	2L setting; +chemo in 1L
SHR-1210	Biologics	PD-1	Hengrui Medicin	Phase 3	Single agent
IBI308	Biologics	PD-1	Innovent	Phase 2	
JS001	Biologics	PD-1	Junshi	Phase 1b/2	
M Bavencio (Avelumab)	Biologics	PD-L1	Merck/MSD	Phase 1b	
GLS-010	Biologics	PD-1	Wuxi / Gloria	Phase 1	

Source: Insight database, Company data

COLORECTAL CANCER In China

376,300 New cases per year
191,000 Death per year
26.6 / 100K Incidence rate
13.5 / 100K Mortality rate
57% 5-year survival rate (2010-14)

Most common type: KRAS mutation (40%)
Staging at diagnosis: Stage I 5%, Stage II 25%, Stage III/IV 70%
Targeted therapies in China Avastin (bevacizumab), Erbitux (certuximab)

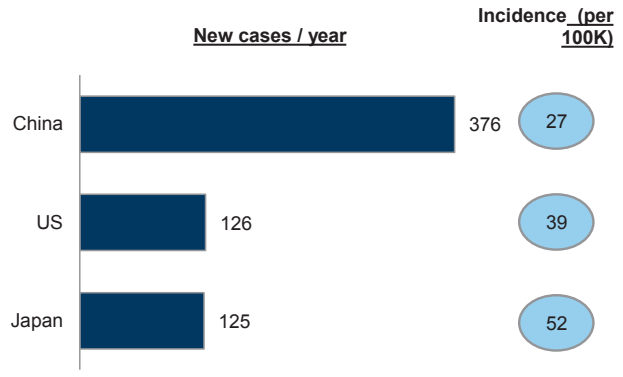
Disease demographics

Colorectal cancer (CRC), cancer developed in the colon and the rectum, is one of the top five cancers in China, and also one of the leading causes of cancer death globally. The most updated data from the Cancer Registry in China shows there are 376,300 new cases of CRC in China each year, and 40% of the patients harbour mutations in the KRAS gene, the status of which will lead to differences in choosing systematic treatment regimens.

Incidence and survival rate vs. global peers

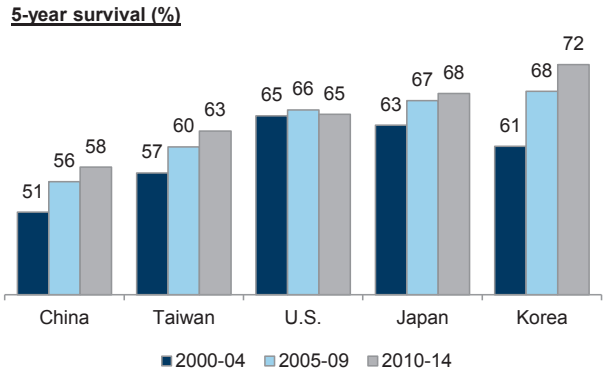
The incidence rate of CRC is higher in more developed countries, e.g. 39 per 100,000 population in the US and 52 in Japan, vs. 27 in China. While age is a major factor in the incidence of CRC, risk factors may include dietary habits (e.g., low-fiber diets, diets rich in red and processed meat, excessive alcohol intake), inflammatory bowel conditions (such as ulcerative colitis or Crohn's disease for many years), radiation exposure and a family history of colorectal cancer.

Exhibit 105: Incidence of CRC in China is lower vs. Japan/US
Incidence of gastric cancer in China, Japan and US



Source: Cancer Statistics in Japan 2013, Cancer China Statistics 2015, American Cancer Society

Exhibit 106: Poorer prognosis of CRC in China
Colon cancer five-year survival in China vs. Asian peers

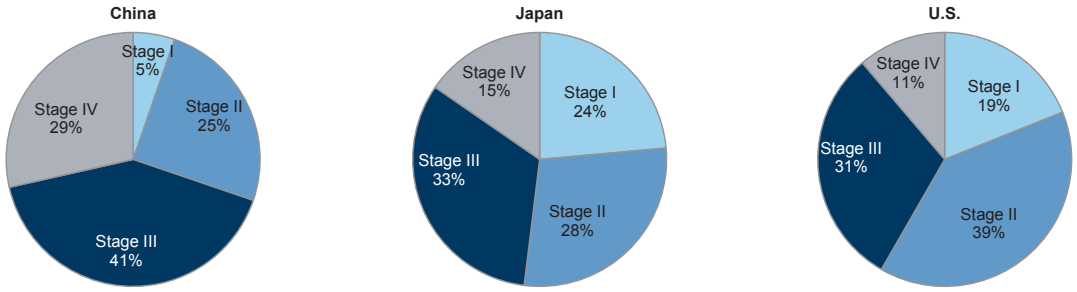


Source: Global surveillance of trends in cancer survival 2000-14

Distribution of cancer stages

The five-year survival rate of CRC in China is 58% vs. (vs. 65%+ in US/Japan/South Korea). The penetration of early detection remains the bottleneck to improving the survival rate, as <5% of CRC patients in China are diagnosed with Stage I tumors, over 75% of which stay alive for over five years, while ~70% of the patients are at Stage III/IV, which has a five-year survival rate that can be lower than 10%.

Exhibit 107: About 70% of CRC was diagnosed at mid to late stage in China
CRC patient by cancer stage: China vs. US/Japan



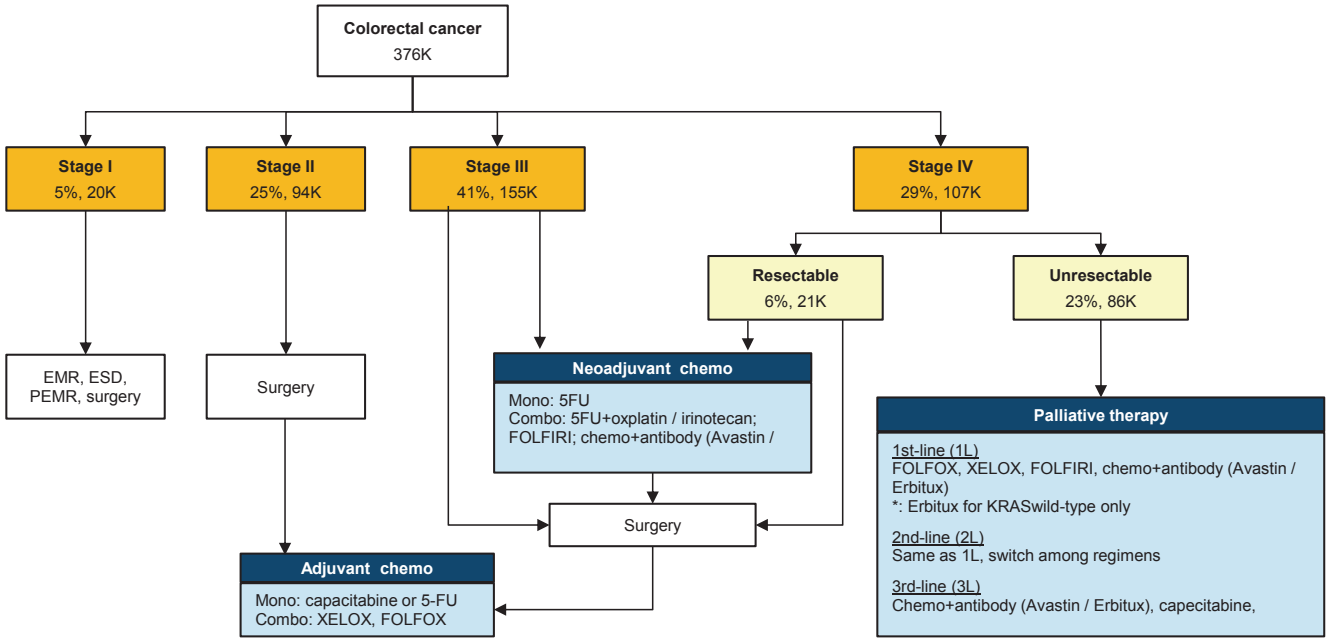
Source: Hospital-Based Colorectal Cancer Survival Trend of Different Tumor Locations from 1960s to 2000s, Characteristics and prognosis of Japanese colorectal cancer patients: The BioBank Japan Project, TNM Staging of Colorectal Cancer Should be Reconsidered According to Weighting of the T Stage

Treatment paradigm

Below we summarize the most common approaches to treating colorectal cancer in China, based on Chinese clinical guidelines and feedback from oncologists:

- **Stage I-III (local) CRC:** Various types of endoscopy-assisted resection and surgery are the primary treatment for resectable CRC. For Stage II CRC, post-surgery adjuvant chemo is recommended. For Stage III and resectable Stage IV, to improve the effectiveness of surgery in removing tumors, neoadjuvant chemo before the surgery is also recommended.
- **Stage IV (metastatic) CRC (mCRC):** Three chemo regimens and two mAbs were mostly prescribed in treating mCRC: i.e. 5-FU/capecitabine + platin based 2-drug/3-drug regimens (FOLFOX, XELOX and FOLFIRI) with or without Avastin/Erbitux. It is worth noting that:
  - KRAS testing is essential before receiving treatment with Avastin or Erbitux, as patients with KRAS gene mutation are unlikely to benefit from Erbitux but could benefit from Avastin.
  - Raltitrexed (Sino Biopharm as the sole player in China, sales of Rmb334m in 2017) and regorafenib (Bayer's noval oral multikinase inhibitor approved by the CFDA in 2017) are recommended for patients that have failed the first two lines of treatment.

Exhibit 108: Colorectal cancer treatment paradigm in China



Source: CSCO (Chinese Society of Clinical Oncology), Goldman Sachs Global Investment Research

Targeted therapies to highlight

There are three targeted therapies approved by the CFDA for treating colorectal cancers:

- **Two monoclonal antibodies - Avastin/Erbitux:** Both Avastin (bevacizumab, Roche) and Erbitux (cetuximab, Merck) were approved by the CFDA for treating metastatic CRC, in first/second/third-line settings. Roche accepted a 60% price cut in China for Avastin in the national price negotiation in July 2017, and the therapy was included in the NRDL, while Merck withdrew from the negotiation for Erbitux.
- **Stivarga (regorafenib, from Bayer):** Regorafenib is an oral multikinase inhibitor approved by the CFDA for mCRC indication in May 2017 as a recommended third-line therapy. While mAbs are in injection form and need to be combined with chemo regimens in a clinical setting, regorafenib is in oral form, inhibiting multiple targets including VEGFR, and can be used as single agent therapy. The phase III CORRECT study shows that regorafenib could improve the OS of mCRC patients in a third-line setting by 1.4 months (regorafenib 6.4 months vs. placebo 5.0 months), and shows survival benefits regardless of the status of the KRAS gene (i.e., works for either KRAS wild type or KRAS mutant).

Exhibit 109: Commonly used targeted therapies/chemotherapies in treating CRC

Targeted therapy	
Bevacizumab (Avastin, Roche)	Approved in China in Feb 2010 for mCRC
Cetuximab (Erbitux, Merck)	Approved in China in 2006, for KRAS wild-type mCRC
Regorafenib (Stivarga, Bayer)	Approved in China for mCRC indication in May 2017, oral single agent
Chemo regimens	
XELOX	Capecitabine (XEL) + Oxaliplatin (OX), also known as CAPOX / CAPE-OX
FOLFOX	Folinic acid (FOL) + 5FU (F) + Oxaliplatin (OX)
FOLFIRI	Folinic acid (FOL) + 5FU (F) + Irinotecan (IRI)

Source: CSCO

Key candidates in pipeline for colorectal cancer

Monocolonal antibodies targeting VEGF and EGFR pathways are still the key focus in the development of new therapies in treating CRC.

- **Anti-VEGF antibody**: Zaltrap (Ziv-aflibercept, Sanofi/Regeneron), which is approved in the US as a second-line therapy in combination with a FOLFIRI regimen, is undergoing phase III trials in China. The antibody-chemo regimen, according to its US pivotal phase III, could improve OS by 1.4 months vs. standard-of-care (13.5 months vs. 12.06 months for chemo-placebo group). Kanghong's KH903 is potentially a similar product to Zaltrap, still at phase I.
- **Anti-VEGF TKI**: Hutchinson Chi-Med (HCM)'s fruquintinib's phase III (FRESCO study) results were presented at ASCO 2017 and highlighted in CSCO 2018 clinical guideline for mCRC: in a third-line setting, fruquintinib improved the OS of mCRC patients by 2.7 months (9.3 months vs. placebo 6.57 months). Sino Biopharm is testing anlotinib, which is a multi-target TKI primarily targeting VEGFR, at a phase IIb trial on mCRC.
- **Anti-EGFR antibody**: Vectibix (Panitumumab, Amgen) was approved by the US FDA as a first-line therapy in combination with FOLFOX and as a second-line therapy, targeting patients with wild-type KRAS genotype. Growing evidence suggests panitumumab is similar to cetuximab in efficacy and safety profile, and thus can be used interchangeably.

Exhibit 110: Anti-VEGR and anti-EGFR as key pathways for CRC drug development
Key pipeline of targeted therapies for colorectal cancer in China

Candidates	Type	Target	Company	China Status	Global status
VEGF					
HMPL-013 (Fruquintinib)	Chemical	VEGFR	HCM / AZ	NDA filed	-
M Zaltrap (Ziv-aflibercept)	Biologics	VEGF	Sanofi / Bayer	Phase 3	First approval (US) in '12, US$1.6bn in '17
Anlotinib	Chemical	VEGFR, FGFR, PDGFR, c-KIT, c-MET	Sino Biopharm	Phase 2	-
KH903	Biologics	VEGF	Kanghong	Phase 1	-
EGFR					
M Vectibix (Panitumumab)	Biologics	EGFR	Amgen	Phase 3	First approval (US) in '06, US$642bn in '17
SCT200	Biologics	EGFR	Sinocelltech	Phase 2	-
GR1401	Biologics	EGFR	Genrix Bio	Phase 1	-
QL1203	Biologics	EGFR	Qilu Pharma	Phase 1	-
Others					
M AB1010 (Masitinib)	Chemical	KIT	AB Science	Phase 3	
APG-1387	Chemical	IAP	Ascentage	Phase 1b	

M *Products from multinational biotech / pharma companies*

Source: Insight database, FDA, Company data

We also would like to highlight that domestic players in China are investing heavily on developing biosimilars to Avastin and Erbitux:

- **Avastin biosimilars**: A total of 10 biosimilars are under development; Henlius's HLX04 began phase III trials on mCRC in April 2018, while the other players' candidates are still at phase I, including Hengrui, Qilu, Sino Biopharm, Hualan and Luye.
- **Erbitux biosimilars**: Six candidates with Kelun's KL140 at phase 3 trial, which began in early 2018. However, KL140 is not following the biosimilar pathway, as the phase III is a placebo-controlled trial (vs. head-to-head comparison against Erbitux).

LIVER CANCER In China

466,100 New cases per year
422,100 Death per year
33.0 / 100K Incidence rate
29.9 / 100K Mortality rate
14.1% 5-year survival rate (2010-14)

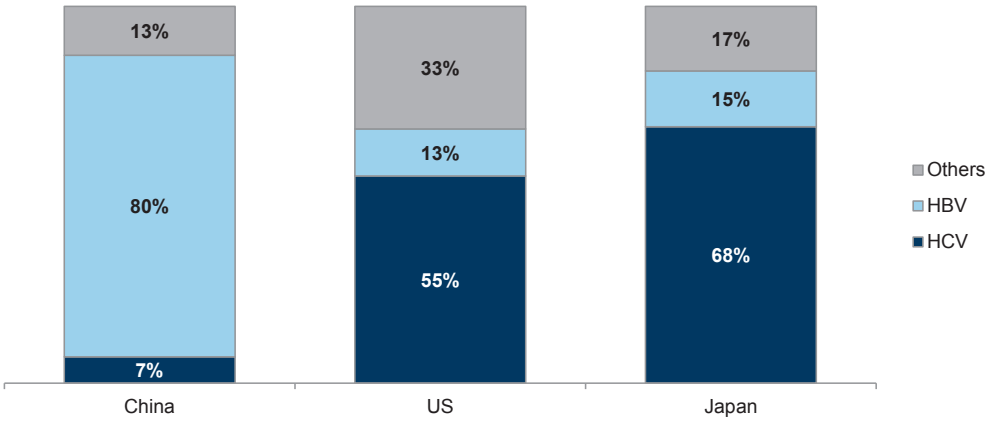
Most common type: Hepatocellular carcinoma (i.e. HCC 90%)
Staging at diagnosis: Stage I 15%, Stage II 34%, Stage III/IV 51%
Targeted therapies in China Nexavar (sorafenib) as 1st-line; Stivarga (regorafenib) as 2nd-line

Disease demographics

Liver cancer is the third most common malignancy cancer type in China in terms of mortality. It is also the world's fifth most common cancer and the third most common cause of cancer-related death. Most liver cancer is diagnosed in developing nations, and China makes up 55% of liver cancer incidence globally. The vast majority (90%) of primary liver cancers are hepatocellular carcinomas (HCCs).

Most cases of HCC are associated with hepatitis B or C virus infection (80% are associated with HBC or HCV infections), alcohol-induced cirrhosis, or other chemical carcinogens. In China, 80% of HCC patients are infected with HBV, while 7% are caused by HCV (in EU/US and Japan, the major cause of HCC is HCV).

Exhibit 111: 80% of HCC patients in China infected by hepatitis B virus
Breakdown of HCC patients by cause



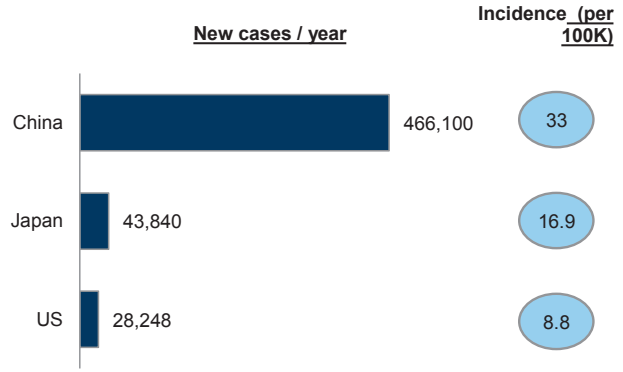
Source: NCCN guideline

Incidence and survival rate vs. global peers

The high incidence rate of HCC in China could be due to the high prevalence of hepatitis in the country. Based on WHO data, China has about 90mn chronic hepatitis B patients (one-third of total hepatitis B patients globally), with ~25-30mn needing anti-viral treatment and ~10mn chronic hepatitis C patients (~7% of hepatitis C patients globally) with ~2.5mn needing anti-viral treatment. Given the relatively low penetration of

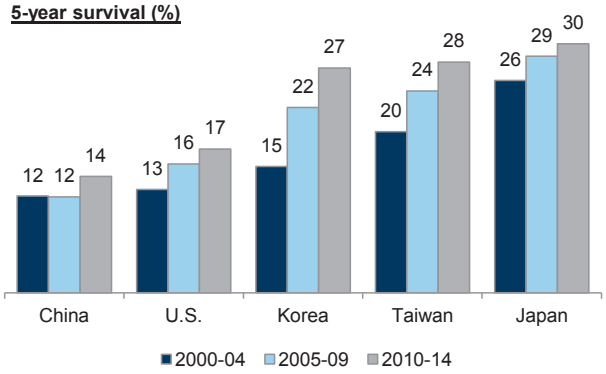
anti-viral treatment for both hepatitis B (~15%) and hepatitis C (<1%), both types of hepatitis remain as the key risk factors of HCC incidence.

Exhibit 112: Over 50% of liver cancer cases are in China
Incidence of liver cancer in China vs. US/Japan



Source: Cancer China Statistics 2015, Cancer Statistics in Japan 2013, American Cancer Society

Exhibit 113: Prognosis of liver cancer is generally poor
Liver cancer five-year survival in China vs. Asian peers

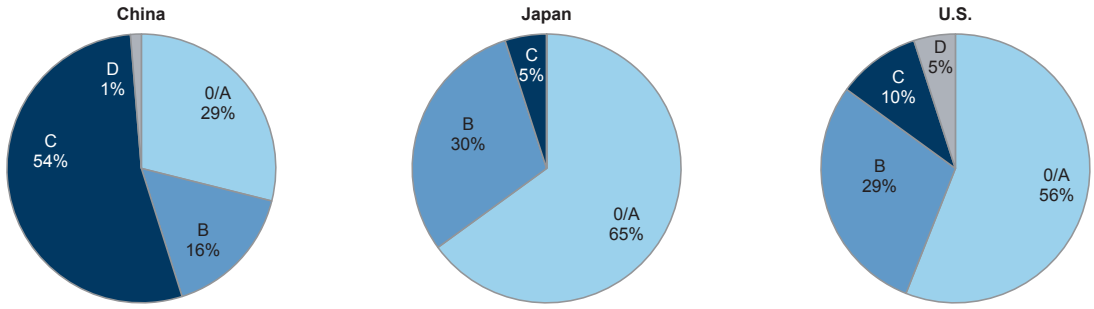


Source: Global Surveillance of Trends in Cancer Survival 2000-14

Distribution of cancer stages

The low five-year survival rate for liver cancer is largely due to the fact that most HCC patients do not show marked symptoms or early signs until the disease has progressed to the advanced stage. In China, more than 55% of patients are diagnosed with advanced HCC, while the rate is significantly lower in Japan and the US, due to the popularity of regular medical check-ups in those countries.

Exhibit 114: Notably lower early-detection rate in China for liver cancer
Liver cancer patients by cancer stage (BLCL system): China vs. US /Japan

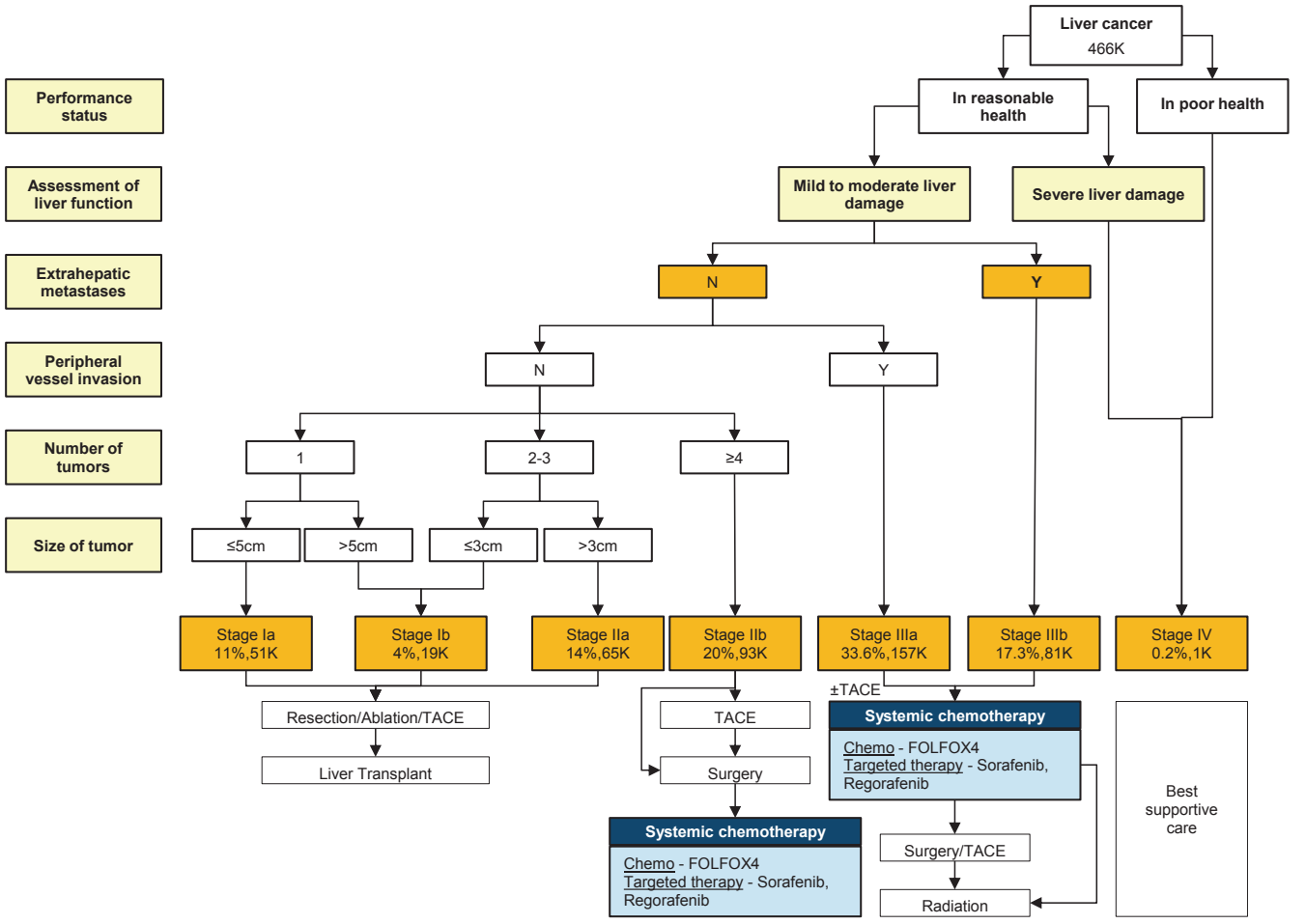


Source: Tumor stage and primary treatment of hepatocellular carcinoma at a large tertiary hospital in China: A real-world study; Liver Cancer Working Group Report; Etiology of hepatocellular carcinoma in Latin America: A prospective, multicenter, international study

Treatment paradigm

Based on clinical guidelines, there are two types of treatment for liver cancer: 1) radical therapies including hepatic resection, liver transplantation and local ablation; and 2) palliative therapies such as transarterial chemoembolization, radiotherapy, systemic chemotherapy, molecular targeted therapy, immunotherapy, and traditional Chinese medicine (TCM). Unfortunately, most HCC patients do not show marked symptoms or signs early on, so they are diagnosed only after the disease has reached an advanced stage and can only seek palliative therapies.

Exhibit 115: Liver cancer treatment paradigm in China



Source: Chinese Society of Clinical Oncology (CSCO), Goldman Sachs Global Investment Research

- **Early stage HCC (Ia-IIa):** Curable treatment is recommended for patients with early-stage HCC, resection, liver transplantation or local ablation (i.e., the liver tumors are destroyed using layer, radiofrequency, freezing or other techniques).
- **Intermediate-late stage HCC (IIb-IIIb):** Mainly those with a more severe situation, such as distant metastases, portal invasion or MORE tumor sites. Those patients are eligible for transarterial chemoembolization (TACE), which may shrink the tumor size, decrease tumor progression, and improve the possibility of surgery. Systemic therapy including chemotherapy and targeted therapy are recommended before or after the surgery/TACE or are used concurrently with TACE. The key chemo regimen for treating liver cancer is FOLFOX (folinic acid, fluorouracil and oxaliplatin). Sorafenib

(marketed under the brand Nexavar by Bayer) is the first-line targeted therapy, and the newly approved regorafenib (Stivarga, also from Bayer) is recommended as second-line.

- **Late stage with a poor health status (IV):** For patients that have progressed into a status of poor health performance and may not be able to tolerate the toxicity, best supportive care will be the choice.

Targeted therapies to highlight

There are two targeted drugs approved by the CFDA for treating HCC in China, both marketed by Bayer:

- **Nexavar (Sorafenib):** Sorafenib is the first targeted drug approved by the CFDA for HCC as a first-line treatment, and the phase III SHARP study showed sorafenib could improve the OS by 2.8 months on average compared with placebo (10.7 months vs. placebo 7.9 months). However, growing controversy on sorafenib's efficacy, particularly in older patients and patients with more severe symptoms, coupled with cost and side-effects, has limited the extensive use of sorafenib in clinical practice.
- **Stivarga (Regorafenib) from Bayer:** Regorafenib is an oral multi-kinase inhibitor that potently blocks multiple protein kinases involved in tumor angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF), metastasis (VEGFR3, PDGFR, FGFR) and tumor immunity (CSF1R). Regorafenib demonstrated clinical benefits in OS (10.6 vs 7.8 months for placebo) for patients that have failed first-line sorafenib treatment. It became the first drug to be approved for the second-line treatment for HCC by the CFDA in December 2017 (its indications of metastatic colorectal cancer and gastrointestinal stromal tumor or GIST were also approved earlier in 2017), and the second anti-HCC drug was approved by the CFDA after almost 10 years.

Key candidates in the pipeline for HCC

Tumor blood vessel (angiogenesis) remains one of the key focus areas in the development of new therapies for treating liver cancer. Meanwhile, checkpoint inhibitors are bringing new potential treatment to the arena:

- **VEGFR inhibitors:** Eisai's Lenvima (Lenvatinib, currently approved for differentiated thyroid cancer and renal cell cancer by the US FDA) has shown superior efficacy and survival benefits in Asian HCC patients in a phase III study (REFLECT study, 288 Asian patients) vs. sorafenib in first-line setting: OS 15 months (vs. sorafenib 10.2 months), PFS 9.2 months (vs. sorafenib 3.6 months), ORR 21.5% (vs. sorafenib 8.3%), showing its potential to be another first-line treatment for liver cancer in China. Hengrui's apatinib is also working on a phase-III study to tap the unmet medical needs in China (phase-II data: PFS = 4.2 months, OS = 9.7 months). In the biologics space, Lilly's ramucirumab has demonstrated survival benefits as a second-line treatment for HCC patients in a phase-III trial (REACH-2 study), though the targeted patient base has been narrowed to those with a high level of alpha-fetoprotein (AFP>=400mg/mL), which might cover ~50% of HCC patients.

- **PD-1/L1:** Five Pd-1/L1 inhibitors under development in China are undergoing trials targeting HCC, in either first-line or second-line settings. Among the five candidates, Opdiva's second-line HCC indication was approved by the US FDA in September 2017, based on data from a subgroup of CHECKMATE-040 trial: ORR of 14.3% with 91% of responders' duration of response over 6 months and 55% over 12 months.

Exhibit 116: Development of novel therapies for HCC focuses on VEGFR & I/Os
Key novel therapy pipeline for HCC in China

Candidates	Type	Target	Company	China Status	Note
VEGFR/VEGFR2					
M Lenvima (Lenvatinib)	Chemical	VEGFR	Eisai	Phase 3	Phase 3 in US
M Inlyta (Axitinib)	Chemical	VEGFR	Pfizer	Phase 3	Phase 2 in US
ATAN (Apatinib)	Chemical	VEGFR	Hengrui	Phase 3	-
M Cyramza (Ramucirumab)	Biologics	VEGFR2	Eli Lilly	Phase 3	Phase 3 in US
ZL-2301 (Brivanib)	Chemical	VEGFR	Zai Lab	Phase 2	Phase 3 by BMS in US
PD-1/L1					
M Keytruda (Pembrolizumab)	Biologics	PD-1	Merck/MSD	Phase 3	1L, vs. sorafenib
M Opdivo (nivolumab)	Biologics	PD-1	BMS	Phase 3	2L (approved in US)
SHR-1210	Biologics	PD-1	Hengrui	Phase 3	2L
M Imfinzi (durvalumab)	Biologics	PD-L1	AstraZeneca	Phase 2	Combo + Tremelimumab
M PDR001	Biologics	PD-1	Novartis	Phase 1b/2	Combo + INC
TGF-b					
M LY2157299 (Galunisertib)	Biologics	TGF-b	Eli Lilly	Phase 2	Phase 2 in US
CTLA-4					
M Tremelimumab	Biologics	CTLA-4	AstraZeneca	Phase 2	Phase 1/2 in US
FGFR					
M FGF401	Chemical	FGFR4	Novartis	Phase 1/2	Phase 1/2 in US
M Erdafitinib	Chemical	FGFR	JnJ	Phase 1/2	Phase 1 in US
Lucitanib / Delitinib	Chemical	FGFR/VEGFR	SIMM	Phase 1	-

Source: Insight database

LYMPHOMA In China

88,200 New cases per year
52,100 Death per year
6.2 / 100K Incidence rate
3.7 / 100K Mortality rate
61.1% 5-year survival rate (2010-14)

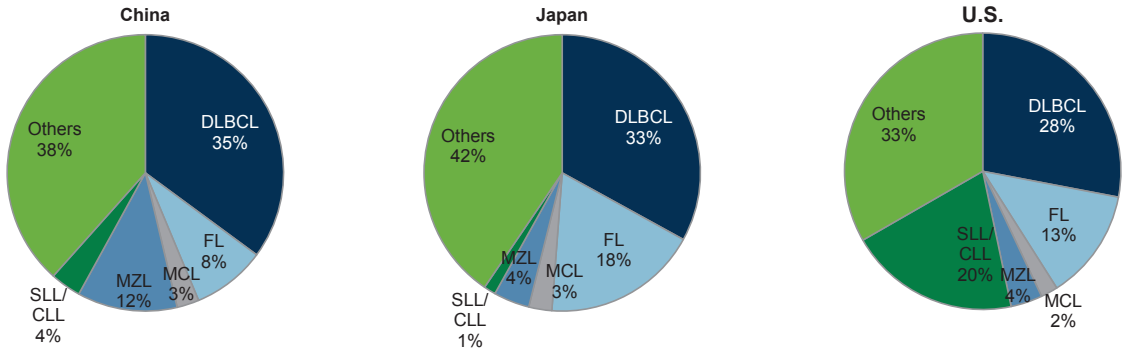
Most common type: Non-Hodgkin's lymphoma (91%) – DLBCL (diffuse large B-cell lymphoma, 35%) and FL (follicular lymphoma, 9%)
Most common genotype: CD20 expression (CD20+) in DLBCL (83%) and FL (72%)
Targeted therapies in China Rituxan (rituximab) for CD20+ DLBCL and FL; Imbruvica (ibrutinib): for SLL/CLL and MCL

Disease demographics

Lymphoma is a diverse group of blood cancers that originate from either B, T or NK cells, making up 2% of the new cases of cancer diagnosed in China. The overall incidence rate in China is relatively lower than for most solid tumors.

Lymphoma is generally divided into two major subgroups: Hodgkin's lymphoma (HL), which accounts for <10% of all lymphoma cases, and non-Hodgkin's lymphoma (NHL), which consists of more than 30 subtypes, including B-cell NHL and T/NK-cell lymphoma. The distribution of subtypes varies in different populations. Diffuse large B-cell lymphoma (DLBCL) is the major type of NHL in China, as well as in Japan and the US, but follicular lymphoma (FL) is more important in Japan/US than in China, and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is the second major type of NHL in the US, though it is less prevalent in Asia. The difference in demographics of lymphoma leads to differences in drug development focus.

Exhibit 117: DLBCL and FL are key types of NHL
Breakdown of NHL by subtype: China vs. Japan/US



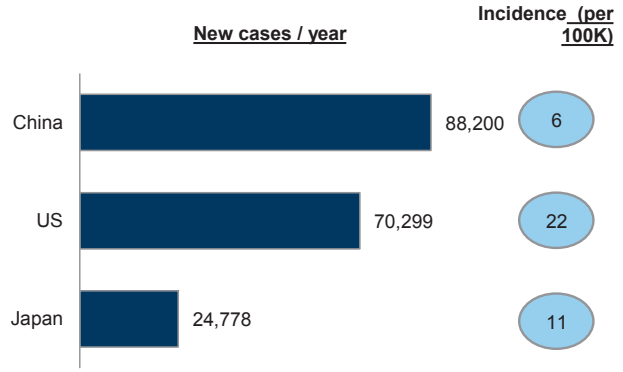
Source: Subtype distribution of lymphomas in Southwest China: Analysis of 6382 cases using WHO classification in a single institution, Epidemiology of Lymphoid Malignancy in Asia

Incidence and survival rate vs. global peers

The incidence rate (per 100,000 people) of lymphoma is substantially lower in China vs. more developed regions. Lymphoma is generally a less fatal cancer, with 70%–90% of treatment-naïve patients (i.e., first time to receive treatment post diagnosis) able to be cured. In the past decade, due to improvements in access to medications, the five-year survival rate of lymphoma in China improved from <50% to over 60%, and there

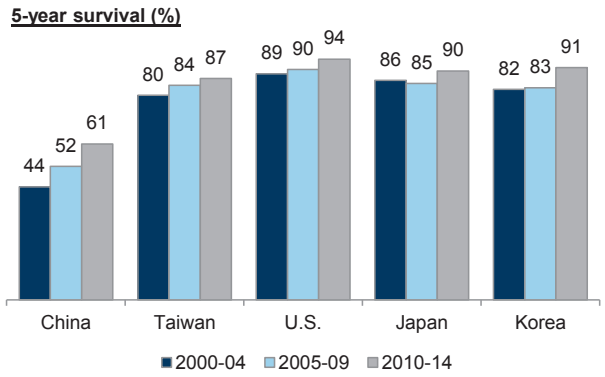
remains room to improve, compared with a five-year survival rate of more than 85% for US and Asian peers.

Exhibit 118: Lower incidence of lymphoma in China
Incidence of lymphoma in China vs. US/Japan



Source: Cancer China Statistics 2015, Cancer Statistics in Japan 2013, American Cancer Society

Exhibit 119: Notable improvement in lymphoma survival in China
Five-year survival of lymphoma in China vs. US/Asian peers



Source: Global surveillance of trends in cancer survival 2000-14

Treatment paradigm

For NHL, there are two first-line chemotherapies in China as standard-of-care treatment: CHOP (cyclophosphamide + doxurubicin + vincristine + prednisone) and CVP (cyclophosphamide + vincristine + prednisone). Rituximab (Rituxan or MabThera, from Roche) was introduced into China in 2000 and has become the first-line recommendation added to the two chemo regimens, i.e. R-CHOP and R-CVP. In 2017, the approval of the first BTK inhibitor ibrutinib (Imbruvica, from JnJ) in China brought a new therapy, particularly for patients with CLL/SLL and MCL (mantel cell lymphoma).

Other than systemic chemotherapy, radiation therapy and hematopoietic stem cell transplantation (HSCT) are also recommended for select patient groups.

Exhibit 120: Most common therapies for NHL in China

Targeted therapy	
Rituxan (MabThera, Roche)	For CD20+ NHL treatment
Ibrutinib (Imbruvica, J&J / AbbVie)	For SLL/CLL and MCL treatment
Chemo regimens	
CHOP	Cyclophosphamide(C)+doxorubicin(H) + vincristine(O) + Prednisone(P)
CVP	cyclophosphamide(C)+ vincristine(V) + Prednisone(P)

Source: CSCO

- **Ritaxan/MabThera (Rituximab) from Roche:** Rituxan was first approved by the CFDA in 2000, and the indication covers two of the most prevalent NHL types, i.e. DBCLC and FL. Backed by its strong clinical efficacy and Roche's marketing in China for NHL treatment, Rituxan became one of the best-selling monoclonal antibodies in China, with estimated sales of Rmb1.5b-2bn in 2017. The drug was included into the NRDL in 2017 after a price cut of ~40%.
- **Imbruvica (Ibrutinib) from J&J/Abbvie:** In 2017, the CFDA approved Imbruvica (Ibrutinib, J&J/AbbVie) as a second-line treatment for mantle cell lymphoma and

small lymphocytic lymphoma. Imbruvica generated US$2.6bn of worldwide sales in 2017 (first global approval in 2013), and is the first-in-class BTK inhibitor.

Key candidates in pipeline for lymphoma

A total of nine Rituxan biosimilars are under development in China. Henlius's filed an NDA for HLX01 in late 2017, so it could become the first company to market Rituxan biosimilar in China if the final approval is granted by the CFDA. Innovent's IBI301 and Sinocelltech's SCT400 are at phase III.

Exhibit 121: Henlius's HLX01 is potentially the first Rituxan biosimilar
The development status of key Rituxan biosimilars in China

Rituxan biosimilar	Company	Status
HLX01	Henlius (Fosun Pharma)	NDA filed
IBI301	Innovent	Ph3
SCT400	Sinocelltech	Ph3
Rituxan biosimilar	Hisun	Ph2
TQB2303	Sino Biopharm	Ph1
WBP263	Hualan	Ph1
LZM002C	Livzon	Ph1
H02	Lunan	Ph1
GB241	Genor Bio	Ph1

Source: CFDA

Other than biosimilars, novel therapies are also under development for treating lymphoma, particularly NHL, in China, primarily focusing on three targets:

- **Anti-CD20 antibody:** The mechanism of the target has already been verified by rituximab. The late-stage anti-CD20 candidate in China is obinutuzumab (Gazyva, also from Roche), which has already been approved in the US/EU and is at phase-III trials in China. Growing evidence (e.g., Roche's pivotal phase-III GALLIUM study) suggests obinutuzuamb could provide longer and sustained survival benefits (in PFS) compared with rituximab.
- **Bruton's tyrosine kinase (BTK)**: Globally, there are two BTK inhibitors available, ibrutinib (Imbruvica from JnJ), which is the first-in-class drug and was already approved in China in 2017, and acalabrutinib (Calquence, from AZ), which was approved by the US FDA in October 2017. In China, Beigene's BGB-3111 (Zanubrutinib) is at pivotal phase II trials on MCL/CLL/WM, three subtypes of NHL, and phase I data shows the candidate is well tolerated with manageable AEs, particularly the bleeding issues that ibrutinib is facing in clinical use.
- **PD1/L1 inhibitors**: I/Os are also tested in the lymphoma area. Three domestic anti-PD1 mAbs (Hengrui, Innovent and Beigene) are being tested in phase-II trials on classic Hodgkin's lymphoma (cHL) and T/NK cell lymphoma.

Exhibit 122: Novel therapies for lymphoma under development in China

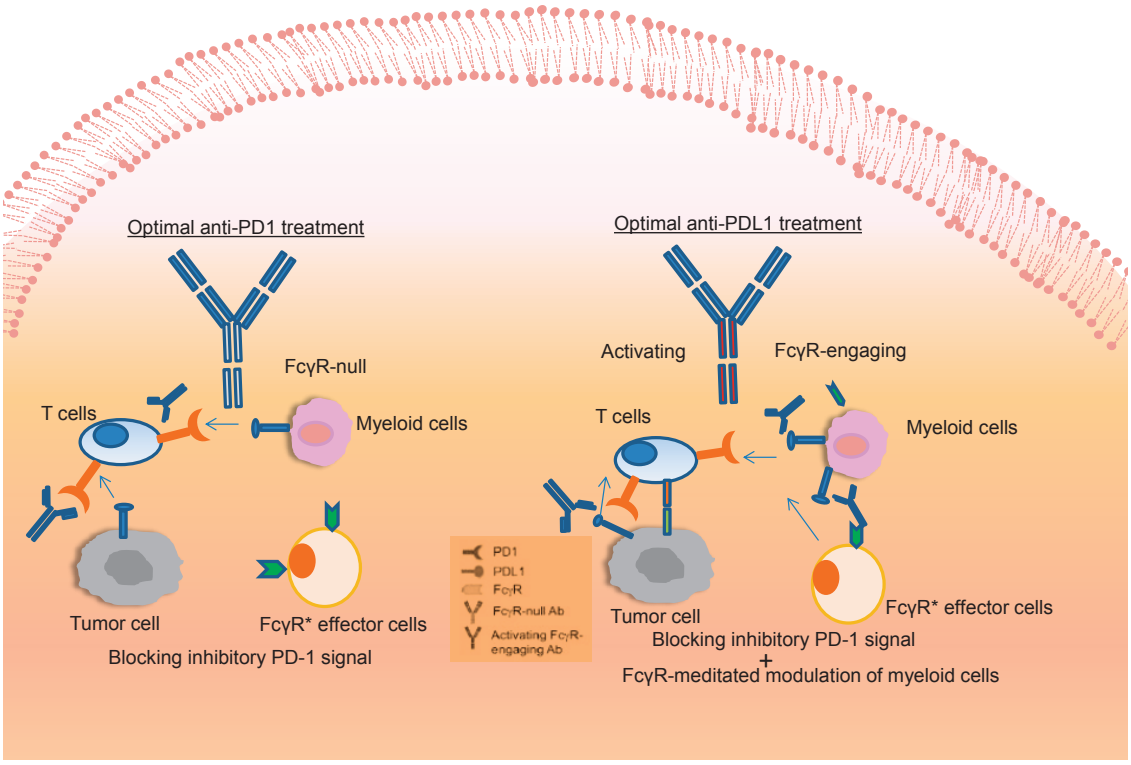
Candidates	Type	Target	Company	China Status	Subtypes	Global status
CD20						
M Gazyva (Obinutuzumab)	Biologics	CD20	Roche	Ph3	FL, DLBCL	Approved in US 2016, EU 2017; NDA in Japan
Anti-CD20 mab	Biologics	CD20	Shanghai Pharma	Ph1	CD20+ r/r B-cell lymphoma	-
MIL62	Biologics	CD20	Mabworks	Ph1	CD20+ r/r B-cell lymphoma	-
BTK						
BGB-3111	Chemical	BTK	BeiGene	Pivotal Ph2	MCL, CLL, WM	Pivotal Ph3: WM, 1L CLL
ICP-022	Chemical	BTK	Innocare	Ph1	SLL, MCL	-
SHR1459	Chemical	BTK	Hengrui	Ph1	BCL	-
CT-1530	Chemical	BTK	Centaurus	Ph1	B-NHL	-
DTRMWXHS-12	Chemical	BTK	Hisun	Ph1a	BCL	-
CD22,CD30,CD38						
M Adcetris (Brentuximab vedotin)	Biologics	CD30	Seattle Genetics	Ph2	HL, sALCL	Approved in US 2012, EU 2013, Japan 2014
M Darzalex (Daratumumab)	Biologics	CD38	J&J	Ph2	ENKTL, nasal type	Ph2 in US
SM03	Biologics	CD22	Longrui	Ph2	NHL	-
PI3K						
M Aliqopa (Copanlisib)	Chemical	PI3K	Bayer	Ph3	NHL	Approved in US 2017
HMPL-689	Chemical	PI3Kδ	Chi-Med	Ph1	B-cell lymphoma	-
BEBT-908	Chemical	PI3K / HDAC	Bebetter Med	Ph1	Lymphoma / Leukemia	-
EGFR						
Avitinib (AC0010)	Chemical	EGFR	ACEA Pharma	Ph1	DBCLC, MCL, SLL/CLL	-
PD-1/L1						
SHR 1210	Biologics	PD-1	Hengrui	NDA	cHL	-
				Ph2	r/r ENKL, nasal type	-
IBI308	Biologics	PD-1	Innovent	NDA	cHL	-
				Ph2	r/r ENKL, nasal type	-
BGB-A317	Biologics	PD-1	Beigene	Pivotal Ph2	r/r cHL	-
				Ph2	T /NK cell lymphoma	-
						-

Source: Insight database, FDA

Cancer immunotherapies (I/Os): Potential game changers

Cancer immunotherapy (or immuno-oncology [I/O]) has reached several milestones in the past few decades, with immune checkpoint inhibitors (PD-1/PD-L1 inhibitors) and CAR-T (chimeric antigen receptor T-cell therapy) as the two most prevailing breakthrough therapies for cancers, raising the prospects for cancers to be managed or even cured in future. As physician communities are well educated, cancer treatment in China could shift gradually from chemotherapies to targeted therapies and immunotherapies. We examine the I/O space in China to map the landscape of the PD-1/L-1 pipelines, and we expect the first regulatory approval of a PD-1/L1 agent in China at end-2018 or early 2019.

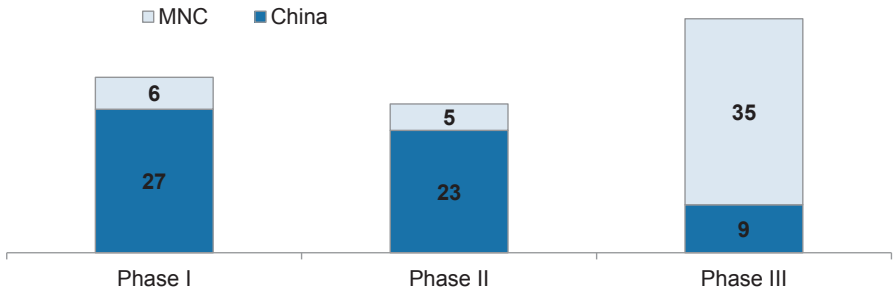
Exhibit 123: PD-1/PD-L1 mechanism of action



Source: Company data, Goldman Sachs Global Investment Research

- **20+ players working on 30 PD-1/L1 candidates:** There are a total of 18 PD-1/L1 mAbs in different phases of clinical trials, with 12 either having filed investigational new drug applications (INDs) or about to start trials. In addition to the five globally marketed PD-1/L1 agents (Opdivo, Keytruda, Imfinzi, Tecentriq and Bavencio), Novartis has brought its globally investigational anti-PD1 mAb into China. Over 100 trials are running on PD-1/L1 agents, with 40% at phase III and a few more at the pivotal phase II, covering more than 20 different cancer types.

Exhibit 124: Over 100 clinical trials on PD1/L1 agents in China
# of PD-1/L1 trials



Source: Insight database, chinadrugtrials.org.cn

- **Rolling NDA becomes official:** The CDE released new guidelines on data requirements for PD-1/L1-agent NDA submissions, specifically for data from single-arm trials (objective response rate, or "ORR" as primary endpoints) on refractory/recurrent advanced cancers without standard-of-care therapies (e.g., classic Hodgkin's lymphoma, cHL). The CDE also officially confirmed that a rolling NDA (i.e., initial submission without complete data set, which will be followed up during the review) will be accepted, implying a fast-track pathway for PD-1/L1 in China. For more details, see *CFDA to accept rolling NDA submission for PD-1/L1*, published on February 8, 2018.
- **5 PD-1 NDAs by April 2018; more expected in 2Q/3Q:** Five NDAs have been filed as of April 2018, including Bristol-Myer Squibb's Opdivo (niovlumab, for the indication of non-small-cell lung cancer), Merck's Keytruda (pembrolimumab, for melanoma), Junshi's JS001 (for melanoma), Innovent's IBI308 (likely for Hodgkin's lymphoma), and Hengrui's SHR-1210 (camrelizumab, likely for Hodgkin's lymphoma). All five NDAs have been granted priority review designations. We expect Beigene to potentially file its NDAs in 2Q/3Q2018.
- **CAR-T IND accelerated in 1Q18:** As of April 8, 2018, 13 INDs have been filed on CAR-T therapies from nine players, including JW Therapeutics (the joint venture set up by Juno and Wuxi AppTec) and eight domestic companies. A total of nine out of the 13 INDs were filed in 1Q18, and the acceleration was driven by government guidelines on cell therapy trials. We expect the timeline for NDA submission might still be two to three years away.

The I/Os space is beyond the scope of PD-1/L1 and CAR-T, and domestic frontrunners are also working on clinical trials on candidates targeting CTLA-4, IDO, TIM-3, LAG-3 and OX40. However, we are more focused on PD-1/L1 and CAR-T in this report, given: 1) proven clinical efficacy (vs. new targets that are not fully proven yet and might still be assets with high risk of development failure); and 2) proven commercial potentials with available global benchmark (five PD-1/L1 inhibitors approved by the US FDA contributed ~15% of total oncology drug sales in the US in 2017 with total sales of ~US$6bn).

Thresholds for regulatory approval: Case study of five FDA-approved PD-1/L1 agents

The CFDA's recent guidelines provided that rolling NDA for PD-1/L1 agents could be based on data from single-arm trial with objective response rate (ORR) as primary endpoints on refractory/recurrent advanced cancers without standard-of-care therapies, and noted that at least six months of follow-up data would need to be submitted during NDA review. All four of China's leading PD-1/L1 biopharmaceutical companies have developed clinical trials and NDA filing strategies based on the new guidelines, selecting melanoma (Junshi), Hodgkin's lymphoma (HL) (Hengrui/Innovent/Beigene) and bladder cancer (Beigene) as indications for pivotal phase II small-scale trials, saving time on patient enrollment.

To better understand the potential thresholds for regulatory approval of domestic PD-1/L1 agents, we analyzed the trial design and clinical results of all US FDA approved PD-1/L1 inhibitors on the three indications mentioned above:

- **Approval based on ORR from single-arm trial is common:** Out of the 30 US FDA indication approvals for five PD-1/L1 inhibitors (Keytruda, Opdivo, Tecentriq, Bavencio, and Imfinzi), 19 (or 64%) were based on trials with ORR as primary endpoints. In the approval for melanoma, HL and bladder cancer, nine out of 12 were based on ORR.
- **ORR benchmarks:** By focusing on single-arm trials only, our analysis suggests that the approvals granted to PD-1/L1 agents showed:
  - **Hodgkin's lymphoma:** ORR in the range of 66%-69% in second-line treatment, with duration of responses (DOR) either not reached or at 11 to 13 months.
  - **Bladder cancer (or urothelial carcinoma):** ORR of 23.5%-29% in first-line setting and 13.3%-19.6% in second line.
  - **Melanoma:** Only Keytruda was approved for second-line treatment based on ORR data, which was 23.6%-23.8% under different dosing strategy.

Exhibit 125: FDA approved PD-1/L1's ORR data as benchmark (single-arm trials are highlighted)
Trial design and results of FDA approved PD-1/L1 agents on Hodgkin's lymphoma, bladder cancer and melanoma

Drug	Line	Trial design	Primary endpoint	Secondary endpoint	Enrolled size
Hodgkin's lymphoma					
Opdivo	2L	Open label, single arm	ORR (66%, failed HSCT / Adcetris)	DOR (13.1m), TTR (2m)	95
		Open label, single arm	ORR (69%, failed HSCT)	DOR (not reached), TTR (2m)	258
Keytruda	2L	Open label, single arm	ORR (69%)	DOR (11.1m)	210
Bladder cancer					
Opdivo	2L	Open label, single arm	ORR (19.6%)	DOR (10.3m)	270
Keytruda	2L	Open label, parallel, randonmized	OS (10.3m vs. 7.4m for chemo), PFS 2.1m (vs. chemo 3.3m)	ORR (21% vs. 11% for chemo)	542
Keytruda	1L	Open label, single arm	ORR (29%)	DOR (not reached)	370
Tecentriq	2L	Open label, single arm	ORR (14.8%)	DOR (not reached)	310
Tecentriq	1L	Open label, single arm	ORR (23.5%)	DOR (not reached)	119
Bavencio	2L	Open label, single arm	ORR (13.3% at 13 wks; 16.1% at 6 wks)	DOR (not reached)	242
Imfinzi	2L	Open label, single arm	ORR (17%)	DOR (not reached)	182
Melanoma					
Opdivo	2L	Open label, parallel, randonmized	ORR (31.7% vs. 10.6% for chemo)	PFS (4.7m vs. 4.2m in investigator's choice group)	120
Keytruda	2L	Open label, single arm	ORR (23.6% for 2mg/kg, q3w vs. 23.8% for 10mg/kg, q3w)	DOR (not reached)	173
Keytruda	1L	Open label, parallel, randonmized	OS (Hazard ratio of 0.69 for q3w vs. 0.63 for q2w), PFS (4.1m for q3w vs. 5.5m for q2w vs. 2.8m for ipilimumab)	ORR (33% for q3w & 34% for q2w vs.12% for ipilimumab)	834
		Double blind, parallel, randomized	PFS (2.9m for 2mg/kg vs. 2.9m for 10mg/kg vs. 2.9m for chemo)	ORR (21% for 2mg/kg vs. 25% for 10mg/kg vs.4% for chemo)	540

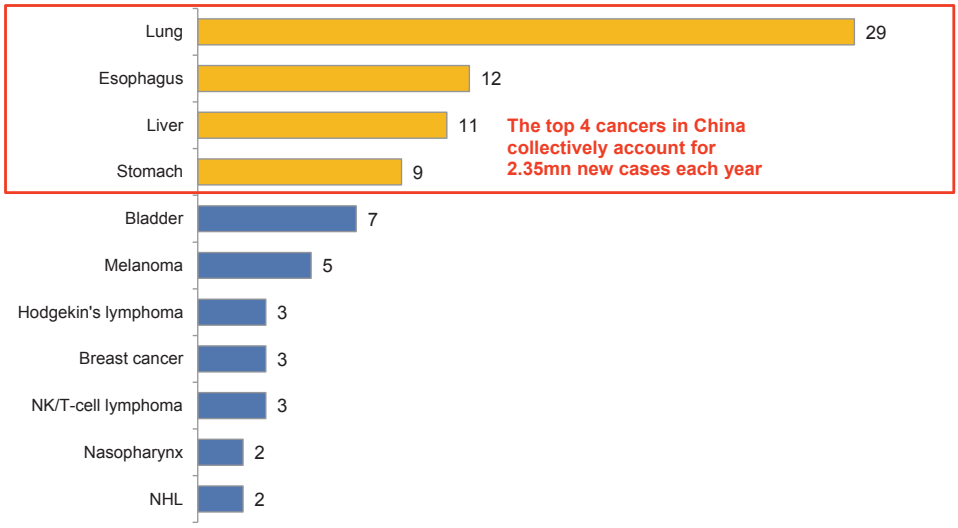
Source: FDA

Clinical development pathway: Hodgkin's lymphoma + off-label

Our analysis of the 100+ trials on PD-1/L1 agents indicates that clinical development strategies, particularly among frontrunners (e.g. Hengrui, Beigene), are similar:

- **NDA on rare cancers**: The above three companies are targeting NDA filings based on data from pivotal phase 2 trials on classic Hodgkin's lymphoma (cHL) and bladder cancer, both of which are rare cancers in China. There is a potential fast-track path to regulatory approval (Opdivo's cHL/bladder cancer indication was approved by the US FDA based on phase II data), given the priority review and smaller sample size to shorten the time for clinical trials (60 patients in Hengrui/Beigene's phase 2 on cHL and 90 in Innovent's, vs. 400+ for phase 3 trials).
- **Off-label targets most prevalent cancers**: However, we expect significant off-label sales after product launch, supported by extensive ongoing trials targeting major cancer types: over 50% of the trials target the four largest cancer types in China, i.e. lung, liver, esophagus and stomach cancer.

Exhibit 126: Clinical development strategy is locally tailored
Number of trials by cancer type as of March 2018



Source: Insight database

Long-term potential hinges on clinical excellence

Given the potential competition among PD1/L-1 agents, we expect the longer-term commercial value of the molecules would heavily rely on the evidence-based clinical data and safety profile. We analyzed the clinical data (mostly phase 1 data) released on the PD1 agents from Hengrui, Beigene and Junshi, including single-agent trials and those testing different PD-1 combos:

- The objective response rates for single-agent are in the range of 4%-33.3%, and some combos generate a higher response rate, e.g. Hengrui's SHR1210 + decitabine on refractory/recurrent cHL (63.2%) and Beigene's BGB-A317 + in-house BTK inhibitor BGB-3111 on lymphoma (40%).
- Some adverse events (AEs) were shared by all four candidates (fatigue, fever, and hypothyroidism), while the profiles differ on some AEs, implying differentiation among the four candidates. We highlight that Hengrui's SHR-1210 triggered a unique AE, with reactive capillary hemangiomas in 79.3% of patients in the trial, which has led to some market concerns on the candidate's safety profile. However, given that it was a grade 1/2 AE (i.e., mild side-effects), we believe the risk remains manageable based on currently available data, but pending more data for better assessment.

Exhibit 127: PD-(L)1 data at 2018 ASCO meeting

Phase	Indication	Regimen	# of pts	Efficacy	Safety
Hengrui - Camrelizumab (SHR-1210)					
I/II	r/r cHL	PD-1 + decitabine	57	Pd-1 only - CR 17% + PR 34% + SD 51% S+D, refractory to pd-1: CR 23%, PR 30%, SD 23% S+D, pd-1 naive: CR 67%, PR 22%, SD 11% PFS: 88% of PFS >24wks	Cherry hemangioma (75% in cohort 1 / 93% in cohort 2) Leukocytopenia (32% in cohort 2)
I/II	r/r primary mediastinal large B-cell lymphoma	PD-1 + decitabine + GVD (gemcitabine, virorelbine, doxorubicin)	18	Cohort 1 (PD-1 + GVD): CR 28.5%, PR 57%, SD 14% Cohort 2 (PD-1 + GVD + decitabine): CR 75%, PR 25%	<=grade 3 hematotoxicity
Ia/Ib	HCC/GC/EGJ	PD-1 + apatinib	42	All: ORR 30.6% (all in 125mg/250mg cohort), DCR 83.3% HCC: ORR 50%, DCR 85.7%, PFS not reached GC/EGJ (250mg cohort): ORR 20%, DCR 80%, PFS 3 months	>10% - hypertension, increased AST / ALT, 58% grade3+ AEs
Ib	NSCLC, 3L+	PD-1 + apatinib	27	ORR: 41.2% (30.8% in arm 1, 75% in arm2) DCR: 94.1% (92.8% in arm 1, 100% in arm2) RP2D: 250mg A + pd1	42% in arm 2(375mg A) needs dose reduction to 250mg, SAE 14.8%
I	Advanced solid tumors	PD-1	58	ORR 31%, DCR 46.5%, no CR PR 34.5% in ESCC, 37.5% in GC, 33.3% in NSCLC / NPC / HCC / CRC, 100% in bladder	Reactive capillary hemangiomas 79.3% (11% grade 2, 89% grade 1) Hypothyrodism: 29.3% Pruritus, elevated transaminase, increased bilirubin, fatigue fever (10-20%)
Innovent - Sintilimab (IBI308)					
II	r/r cHL	PD-1	96	ORR: 74% (CR 24%) DoR: 64 out of 71 still ongoing	Most common pyrexia 43.8%, most are grade 1-2
I	Advanced solid tumors	PD-1	12	ORR: 18.2% PR, no CR, 36.4% DCR DoR: 9.5m and 5.7 months RP2D: 200mg q3w	No DLT/MTD, most common are fever, thyroid dysfunction, bilirubin, pneumonitis, 1/3 grade 3+
Junshi - JS001					
II	Advanced melanoma	PD-1	121	ORR: 20.7% (CR 0.8%, PR 19.8%), DCR 60.3% ORR lower in acral (14.3%), mucosal (0%) subtypes, higher in CSD (chronically sun damaged 35.3%) and non-CSD (33.3%) mDoR not reached, most responses still ongoing	Most AEs were grade 1/2 (proteinuria, ALT increase, rash, hyperglycemia, over 20%), grade 3/4 AEs 18%
II	Bladder cancer, 2L+	PD-1	27	No CR, ORR 29.6% (all PR), DCR 77.8%	Grade 1/2 for most AEs
Ib/II	r/m ESCC	PD-1	34	ORR 23.5% (all PR, 20% in PDL1+, 25% in PDL1-), DCR 64.7%	Most grade 1/2
Ib/II	Gastric adenocarcinoma	PD-1	25	ORR 20% (all PR, 60% in PDL1+, 10% in PDL1-), DCR 60% (80% in PDL1+)	
Ib	Metastatic mucosal melanoma	PD1 + axitinib	24	ORR: ORR 50% (no CR, 50% PR), DCR 87.5%, 10 out of 12 PR stilling ongoing response	No DLTs, grade 1/2 common AE - hypertension, hand-foot skin reaction, oral ulcer, hypo-thyroidism and fever
I	Advanced or r/r alveolar soft part sarcoma	PD-1	12	25% (8% CR, 17% PR), response heterogeneity is common - In PD-L1+ pts, 50% ORR, 75% DCR Time to response: 5.7, 7.7, 23.9 weeks DoR: 48.3, 31.1+, 36+ weeks mPFS: 12.4 m	grade 1/2 , no DLT
I	Advanced melanoma	PD-1	32	ORR 22% (3% CR melanoma, 19% PR), DCR 53% - High tumor-infiltrating lymphocytes – 50% ORR - >1% PD-L1 – 46% ORR - Acral – 20% ORR, 53% DCR - Mucosal – 25% ORR, 50% DCR DoR: 6 out of 7 CR/PR still response	No DLT / MTD, grade ½, most common - hyper- or hypo-thyroidism (42%), rash (39%), fever (28%), leukopenia (22%), elevation of liver enzymes (19%), anorexia (17%), and fatigue (14%)
I	Cancers	PD-1	15	CR: 6.7%, PR 33.3% (ORR 40%), DCR 73.3%	No DLT, most grade 1/2, only 1 grade 3 (pneumonia)
I	TNBC	PD-1	20	0%, 35% DCR (40% in PD-L1+)	No DLT/MTD, grade 1/2, hypo-(25%) or hyper-(15%) thyroidism, AST increase (20%), ALT increase (20%), anemia (20%), hyperglycemia (15%),hypertriglyceridemia(15%), pruritus (10%), and fatigue (10%)
I	Cancers	PD-1	33	ORR 48.5% (CR 18.2%, PR 30.3%), DCR 70% mTTR: 10.6 wks mPFS 8.8m RP2D: 3mg/kg, q2w	No DLT/MTD, grade 1/2 for most AEs

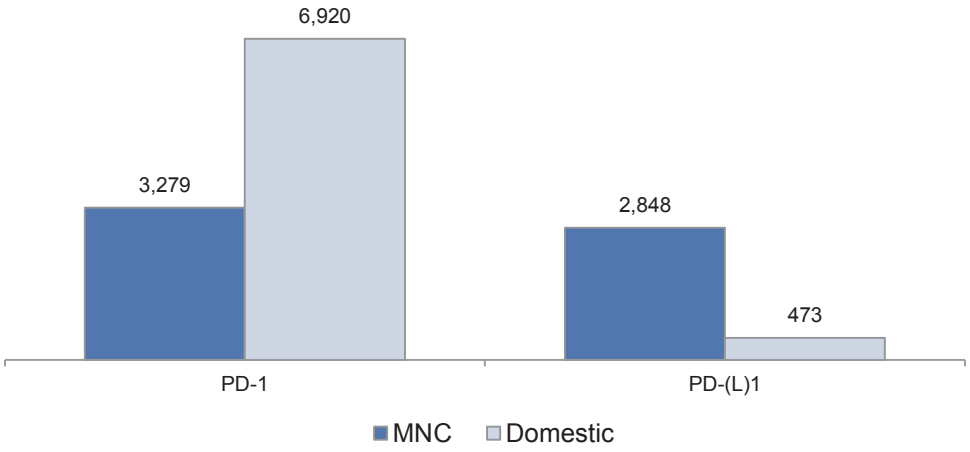
Source: ASCO 2018

Fast-evolving immunotherapies in China build on various advantages

The emerging development of I/Os in China over the past two years has been largely driven by:

- **Policies:** Breakthroughs in drug-approval policies, particularly the streamlined IND for innovative drugs, establishment of an accelerated review system (i.e., conditional approval of phase 2 data with priority review for breakthrough therapies) and clear guidelines on clinical trials for PD-1/L1 and cell therapies, which includes CAR-T.
- **Access to capital:** With Opdivo/Keytruda proven to be the next-generation blockbusters in cancer treatment, access to capital and government funding has become easier for I/Os projects/start-ups. Moreover, we view the proposed changes by HKEx on listing rules for pre-revenue biotech companies as the next catalyst in the space (potentially in mid-2018 per HKEx's proposed timeline).
- **Risk/reward-balanced R&D strategies:** Given the relative lack of sufficient novel drug development experience at most Chinese pharma companies, follow-on strategies to develop new molecules/therapies based on proven targets might be more feasible at the current stage. More importantly, given the affordability issue, a broad patient base (indication) is essential for meaningful commercial value. Accordingly, PD-1/L1 is probably an ideal target for the follow-on R&D strategies.
- **Well-educated physicians/patients:** Based on our calculation of trials with disclosed sample size, a total of over 13,500 patients have been or are planning to be enrolled in the ongoing 90+ clinical trials on PD-1/L1 mAbs, implying that awareness of PD-1/L1 therapies among cancer patients will likely be substantially higher than with most targeted therapies. Additionally, most pivotal trials are multi-center trials and each is conducted at an average of 10-50 sites (hospitals), suggesting physicians are being thoroughly educated on the efficacy and potential side-effects of PD-1/L1 mAbs, as well as clinical solutions for managing those AEs. In our view, the on-trial patient and physician education may pave the way for fast patient penetration at the initial stage of product launch for early movers.

Exhibit 128: Over 13,500 patients enrolled/to be enrolled in PD-1/L1 trials
Patient enrollment plan of all PD-1/L1 trials in China as of April 2018



Source: Insight database

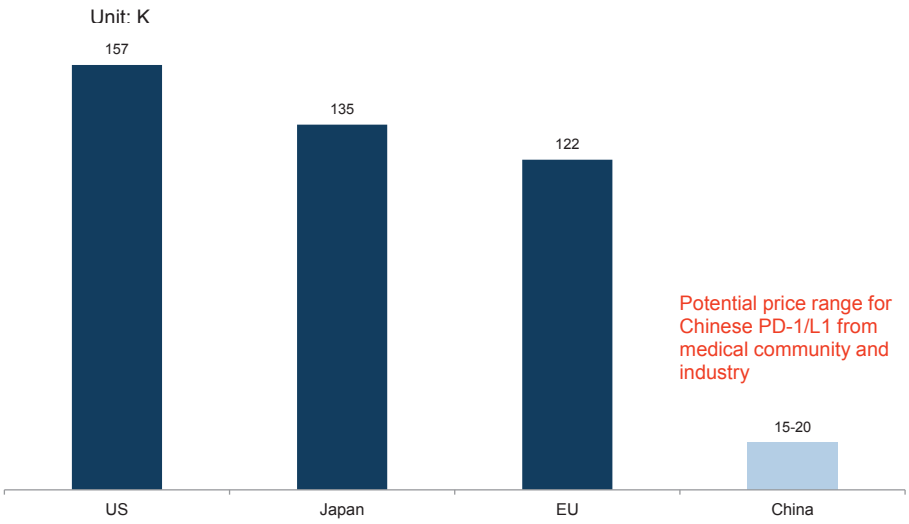
- **A stronger-than-ever talent pool**: The growing backflow to China of scientists trained at big US/EU pharma/biotech companies in the past decade and the emergence of Contract Research Organisation (CRO) platforms (e.g., Wuxi Pharma and Tigermed) are paving the way for the growth and development of I/Os in China.

China's I/Os may have a global impact at the commercial stage

While it might be too early to provide concrete estimates on China's potential market share in the global PD-1/L1 market, we see a few areas in which PD-1/L1 in China may have a global impact:

- **Likely lower pricing may alter competitive landscape:** While the efficacy of PD-1/L1 agents could be quite similar, the pricing in China might be substantially lower – though the pricing will not be finalized until the launch of the first domestic PD-1/L1 in China, the feedback from our discussions with the medical community in China suggest the consensus view for reasonable pricing for domestic PD-1/L1 could be in the range of US$15K-20K for annual treatment costs (vs. US$150K+ in the US and slightly lower in Japan/EU), and the price could further decline with the targeting of listing on reimbursement catalogs. If a lower pricing scenario were to become a reality, which we believe is possible given the government's emphasis on the affordability of domestic novel therapies, it could affect the product pricing strategies of MNCs in China. More importantly, it could potentially trigger medical tourism from overseas markets to China for cheaper yet quality-comparable I/Os treatment.

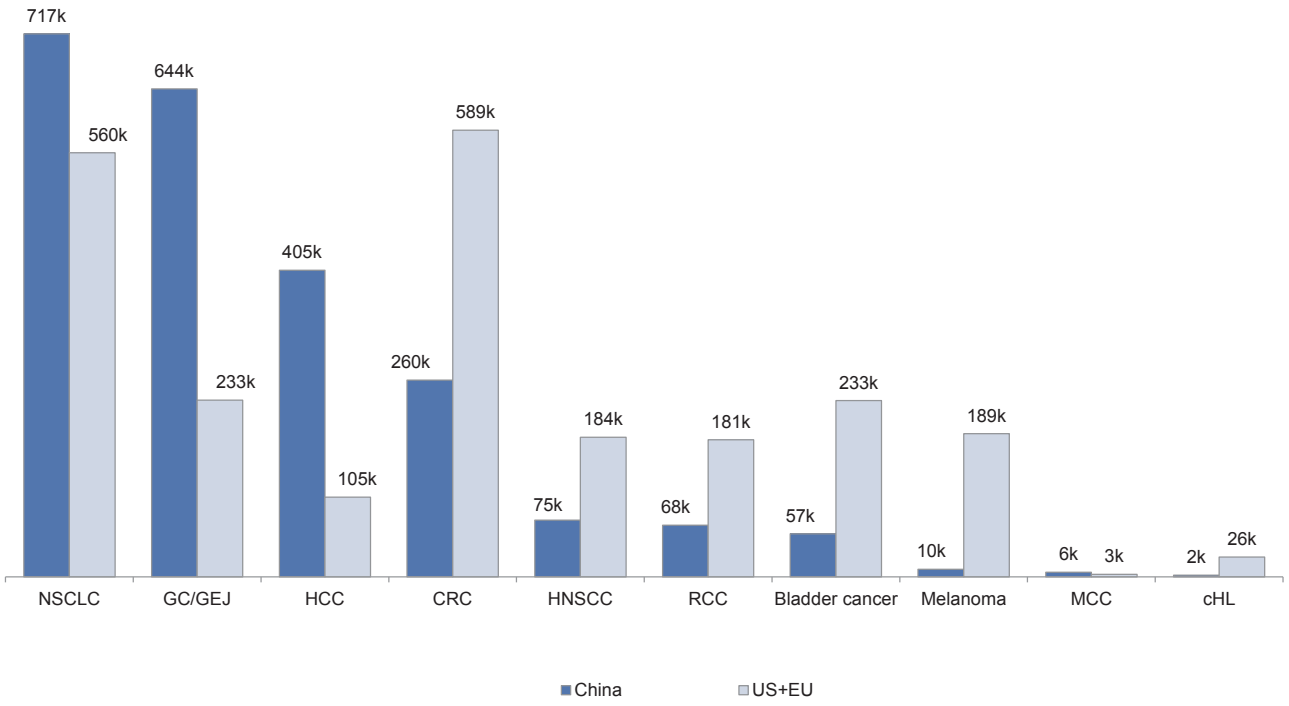
Exhibit 129: Pricing of Chinese PD-1/L1 may be lower
GS estimates



Source: Insight database, chinadrugtrials.org.cn, accc-iclio.org, fiercepharma.com, japantimes.co.jp, thesocialmedwork.com, company data, Goldman Sachs Global Investment Research

- **Large patient base with differentiated cancer demographics:** PD-1/L1 has been approved for treating more than 10 cancer types. For those approved indications, the addressable patient base in China is equivalent to that in the US plus the EU. More importantly, the cancer demographics in China are different from those in the US and the EU. For example, stomach and liver cancers are among the top-five most prevalent cancers in China while such incidences have been notably lower in the US. Meanwhile, a highly prevalent cancer in the US, melanoma, which is the first indication approved for Keytruda/Opdivo, is a relatively lower priority in China. These differences could expand global PD-1/L1's commercial value relative to specific cancers prevalent in China or East Asia.

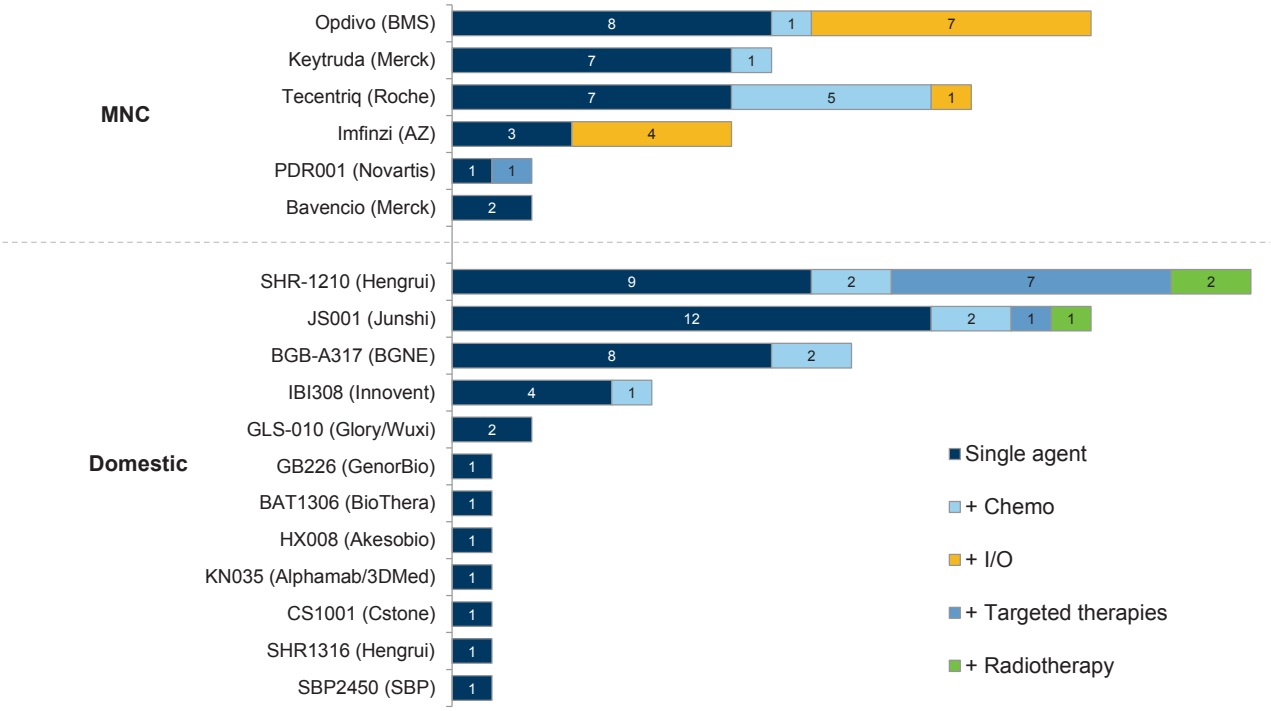
Exhibit 130: Larger patient base in key indications vs. EU/US
For globally approved indication for PD1/L1 as of March 2018



Source: Globalcan 2012, seer.cancer.gov

- **Undertreated patients for clinical development**: Given the lack of access to most advanced therapies and affordability issues without reimbursement coverage, the treatment rate for cancer patients in China remains low, particularly in terms of the penetration of targeted therapies and antibodies and third-line or later-line treatments. The undertreated patient base in China, most of which were I/Os treatment naive, is a significant resource for investigational new PD-1/L1 agents to tap. Moreover, Chinese I/Os developers could leverage the relatively lower costs for clinical trials in China to drive better returns on developing PD-1/L1 agents.
- **In-house resources for combo strategy**: Combo therapy is one factor that should allow PD-1/L1 development to further enhance response rates and expand into more indications. We believe an in-house combo strategy will be the most efficient way, given better control over clinical development strategy. Hengrui, with a large portfolio of standard-of-care chemo/apatinib and an in-depth pipeline of targeted therapies, enjoys the flexibility of a combo strategy, in our view. Beigene is also working on in-house combos (PD1+PARP, PD1+BTK) that are at phase I.

Exhibit 131: Single agent trials vs. combo - MNCs/domestic PD-1/L1 trials

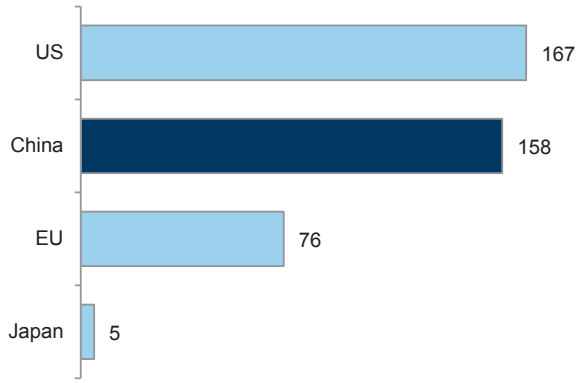


Source: Insight database

CAR-T development accelerates in China

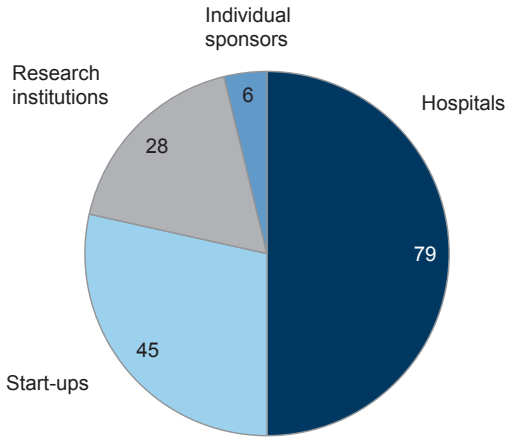
China is now the second-largest base for CAR-T trials worldwide: as of March 2018, a total of 158 CAR-T trials (or about one-third of global trials on CAR-T) are ongoing in China, more than the EU (76 trials) and Japan (5 trials) combined, and close to the US (167 trials). It is worth noting that more than 70% of the trials were initiated by hospitals and research institutes, while 28% were initiated by companies, which include biotech start-ups (operated independently or being acquired by larger healthcare companies) and MNCs and their JVs with local partners, e.g. Fosun Pharma - Kite Pharma JV and Juno - Wuxi AppTec JV (JW Therapeutics).

Exhibit 132: China is the second-largest base for CAR-T trials
# of ongoing CAR-T trials in key countries/regions



Source: Insight database

Exhibit 133: Hospitals positive for investigator-initiated studies
Breakdown of CAR-T clinical trials by type of sponsor



Source: clinicaltrials.gov

Key drivers for CAR-T research in China include:

- **Significant unmet medical needs in cancer patients:** There are over 80K new cases of lymphoma in China every year and the prevalence could be over 200-300K, without considering the potential of CAR-T in solid tumors. This significant demand is one of the key drivers for hospitals, most of which are government-owned public hospitals, to conduct physician-initiated CAR-T studies (over 60 of the sponsors/collaborators of CAR-T studies in China are hospitals).
- **Government's establishment of regulatory framework:** The CFDA released the first guidelines for development and evaluation of cell therapies on December 22, 2017, officially paving the way for CAR-T INDs. Since then, a total of nine Chinese companies have filed INDs with the CFDA for their CAR-T therapies in the past two months.
- **Collaboration with global partners:** The emergence of CAR-T in China has also triggered a growing interest in global biotech/pharma collaborations in the space, through license-in (e.g., Janssen Biotech signed a global 50:50 profit/cost sharing co-development agreement with GenScript for Nanjing Legend's CAR-T) and license-out to China (e.g., Fosun Pharma-Kite Pharma JV and Juno-Wuxi PharmaTech JV).

Exhibit 134: China's I/O overseas strategy - partnership with global big pharma and biotech giants

	Innovent		Beigene	Gloria / Wuxi Biologics	Legend Bio
Partner	Eli Lilly		Celgene	Arcus Bio	JnJ (Janssen)
Date	Mar, 2015	Oct, 2015	Jul, 2017	Aug, 2017	Dec, 2017
Candidates	CD20, PD-1, 3 anti-PD-1 bispecific mAbs	Up to 3 anti-PD-1 based bispecific antibodies	BGB-A317 (anti-PD-1)	GLS-010 (anti-PD-1) + 10 other products	LCAR-B38M Car-T
Scope	Ex-China	Ex-China	Ex-Asia + Japan rights, solid tumor	North America, EU, Japan and certain other territories	50/50 worldwide; 70 Legend)/30 (Janssen) in Greater China
Payment (upfront + milestones)	Upfront $56mn, milestone of $400mn+	$1bn+ & potential ex-China sales royalties	Upfront $263mn, Milestone up to $980mn, ex-China sales royalties	Upfront $18.5mn, milestone up to $422.5mn (regulatory) + $375mn (commercial)	Upfront $350m + milestones

Source: Company data

Selected CAR-T trials, despite the lack of clinical standards in China before end -2017, have shown promising preliminary results, e.g., Nanjing Legend (GenScript's subsidiary, not covered) presented early data of its CAR-T LCAR-B38M at the 2017 American Society of Clinical Oncology (ASCO) meeting, showing 100% ORR in 19 multiple myeloma patients and 74% CR after four-month follow-up. To facilitate the development of CAR-T therapies by domestic companies, the CFDA's first guidelines for development and evaluation of cell therapies was announced on December 22, 2017, officially paving the way for CAR-T INDs. Since then, 11 IND applications have been filed.

Exhibit 135: Juno, Kite's local JV/Novartis vs. domestic start-ups
Mapping of key CAR-T players in China

	Company	Target	Indication	Efficacy	China IND
MNCs	FosunKite	CD19 (KTE-C19)	B-cell lymphoma / leukemia	US data of Yescarta: ORR 76%, CR 50% (n=111, FAS)	Not yet
	JW Therapeutics (Juno – Wuxi AppTec JV)	CD19 (JWCAR029)	r/r DCBCL	-	Jan, 2018
Domestic CAR-T (9 companies filed China IND)	Legend (LCAR-B38M)	BCMA	MM	ORR 100% (n=33)	Dec, 2017 (US IND targets 2Q18)
	Marino / Galaxy Bio	CD19	Lymphoma	ORR 70%, CR 55% (n=25)	Dec, 2017
	HRAIN Biotech	CD19	ALL, NHL	ALL: CR 87.5% (n=40); NHL: ORR 59%, CR 41% (n=17); MM ORR 75% (n=4)	2 INDs - Dec, 2017 / Feb, 2018
	CARsgen (series of CAR-T agents)	GPC3, Claudin 18.2, CD19, BCMA, EGFR/EGFRvIII	Solid tumors (liver, lung, pancreatic, gastric, glioma), B-cell lymphoma, MM	CAR-GPC3-T in HCC: PR 20%, SD 40% (n=5)	Dec, 2017
	AnkeBio / PersonGen	CD19	ALL, NHL	ORR 100% (n=19)	Jan, 2018
	Unicar	CD19, CD269	NHL, MM	-	4 INDs in 2017/2018 for 3 CAR-T

Source: Insight, Company data

Other major diseases and their treatment

In addition to cancer, there are a number of other major diseases affecting patients in China. Fortunately, there is also a wide variety of treatments in use and under development.

- Diabetes - potential treatment regimen shifts to new-gen therapies
- Autoimmune diseases - focus on penetration of biologics
- CNS (central nervous system) diseases - an emerging burden in China
- Age-related macular degeneration (AMD) - niche but promising market
- Hepatitis C: Direct-acting anti-viral agents to emerge

Other major diseases and their treatment

Diabetes: Potential treatment regimen shifts to new-gen therapies

Diabetes In China

107Mn Total patient base **9.85%** Prevalence rate **36.7%** Diagnosis rate **85.5%** Treatment rate

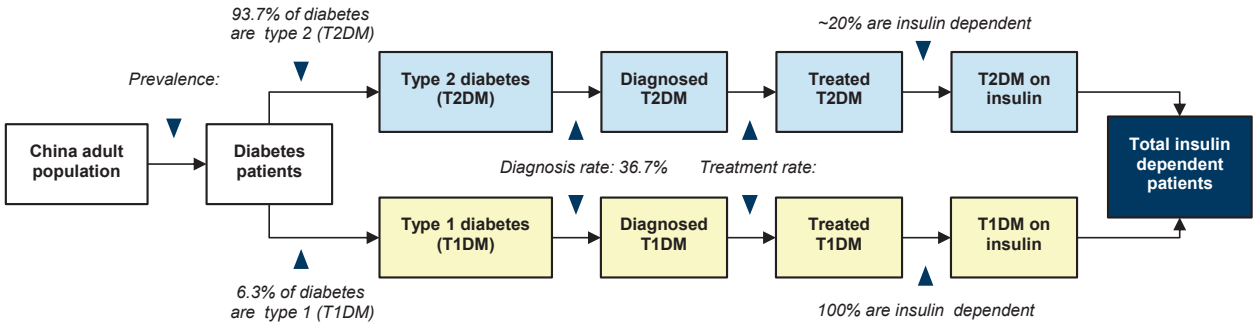
Most common type: Type 1 diabetes (6.3%), Type 2 diabetes (93.7%)
Major treatment regimens: Insulin, oral drugs (biguanide, a-glucosidase inhibitor, Sulfonylurea, Glitazone, Glinides, GLP-1, DPP-4, SGLT-2)

Diabetes, or diabetes mellitus, is a metabolism disorder in which the patient's blood sugar (blood glucose) level is above a reasonable range. The high blood glucose level is either due to: 1) the production of insulin, a hormone made by the pancreas to convert glucose to energy, being inadequate (Type 1 diabetes, T1DM, ~10% of all diabetes); or 2) the cells do not respond properly to insulin (Type 2 diabetes, T2DM). Type 1 diabetes is typically diagnosed in children, while Type 2 diabetes is more frequently diagnosed in adults. Patients with a high level of blood glucose can develop serious complications including cardiovascular diseases, kidney disease (diabetes is a leading cause of kidney failure globally), diabetic foot (pain, ulcer and foot infection) and blindness (diabetic macular edema, DME).

Disease prevalence

Recent national surveys suggest the diabetes afflicts 10%-11% of Chinese adults, implying over 100mn patients, among which about 8-9mn patients are insulin dependent. Diabetes has become one of the major diseases in China, and the government listed it as one of the major chronic diseases in the "Heath China 2030 Plan" to improve prevention and treatment penetration.

Exhibit 136: Diabetes in China: 107mn patients with 8.4mn insulin dependent
Diagram of diabetes prevalence, diagnosis and treatment



Source: National Bureau of Statistics, Goldman Sachs Global Investment Research

Exhibit 137: China's insulin market model

	Unit	2010A	2011A	2012A	2013A	2014A	2015A	2016A	2017A	2018E	2019E	2020E
DIABETES PATIENT BASE												
Diabetes patients	mn	98.9	100.3	101.8	103.3	104.8	106.3	107.8	109.2	110.7	112.2	113.7
Prevalence among adults	%	*9.7%*	*9.7%*	*9.8%*	*9.8%*	*9.9%*	*9.9%*	*10.0%*	*10.0%*	*10.1%*	*10.1%*	*10.2%*
- Type 1 diabetes (T1DM)	mn	6.2	6.3	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2
as % of total	%	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*	*6.3%*
- Type 2 diabetes (T2DM)	mn	92.6	94.0	95.4	96.8	98.2	99.6	101.0	102.4	103.7	105.1	106.5
as % of total	%	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*	*93.7%*
Diagnosed diabetes patients	mn	32.6	34.5	36.4	38.3	40.2	42.2	44.2	46.7	49.5	52.4	55.6
Diagnosis rate	%	*33.0%*	*34.4%*	*35.8%*	*37.1%*	*38.4%*	*39.7%*	*41.1%*	*42.8%*	*44.7%*	*46.7%*	*48.9%*
- Diagnosed T1DM	mn	2.1	2.2	2.3	2.4	2.5	2.7	2.8	2.9	3.1	3.3	3.5
- Diagnosed T2DM	mn	30.6	32.4	34.1	35.9	37.7	39.6	41.4	43.8	46.3	49.1	52.1
Treated diabetes patients	mn	27.8	29.4	31.0	32.6	34.2	35.9	37.6	39.7	42.1	44.6	47.3
as % of total patients	%	*25.8%*	*29.3%*	*30.4%*	*31.6%*	*32.7%*	*33.8%*	*34.9%*	*36.4%*	*38.0%*	*39.7%*	*41.6%*
as % of diagnosed patients	%	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*	*85.0%*
- Treated T1DM	mn	1.7	1.8	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.8	3.0
- Treated T2DM	mn	26.0	27.5	29.0	30.5	32.1	33.6	35.2	37.2	39.4	41.8	44.3
INSULIN DEPENDENT PATIENTS												
# of patients on insulin / insulin analog	mn	3.7	4.0	4.7	5.5	6.3	6.9	7.9	8.6	9.9	11.4	13.1
as % of diabetes patients treated	%	*13.3%*	*13.7%*	*15.0%*	*16.9%*	*18.4%*	*19.3%*	*20.9%*	*21.6%*	*23.6%*	*25.6%*	*27.6%*
- T1DM on insulin		1.7	1.8	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.8	3.0
- T2DM on insulin		1.9	2.2	2.7	3.4	4.2	4.7	5.5	6.1	7.3	8.6	10.1
Total insulin market - volume	mn vial	**134.8**	**146.7**	**169.7**	**200.6**	**230.5**	**253.2**	**286.7**	**313.9**	**362.9**	**417.0**	**476.8**
Total insulin market - sales	Rmb m	**6,876**	**8,054**	**9,622**	**11,394**	**13,270**	**14,767**	**17,316**	**18,559**	**21,459**	**24,496**	**27,869**
INSULIN ANALOG (3rd-genenration)												
Total patients on insulin analog	mn	1.0	1.2	1.6	2.1	2.6	3.0	3.7	4.2	5.0	5.9	7.0
Average daily dose = ~30UI												
Total insulin analog volume	mn	35.6	45.1	59.4	78.3	96.0	109.7	134.9	153.2	183.3	216.9	254.2
Total insulin analog sales	Rmb m	**2,761**	**3,724**	**4,910**	**6,202**	**7,633**	**8,801**	**10,872**	**11,939**	**14,107**	**16,359**	**18,883**
HUMAN INSULIN / ANIMAL INSULIN (2nd/1st generation)												
Total patients on insulin	mn	2.7	2.8	3.0	3.4	3.7	3.9	4.2	4.4	4.9	5.5	6.1
Average daily dose = ~30UI												
Total human / animal insulin volun	mn	**99.2**	**101.6**	**110.4**	**122.3**	**134.4**	**143.4**	**151.8**	**160.6**	**179.5**	**200.1**	**222.5**
Total human / animal insulin sales	Rmb m	**4,115**	**4,331**	**4,712**	**5,192**	**5,637**	**5,965**	**6,443**	**6,620**	**7,352**	**8,137**	**8,985**

Source: Goldman Sachs Global Investment Research

Treatment paradigm for diabetes in China

The most updated type 2 diabetes treatment and prevention guidelines were finalized in 2017 and officially released in March 2018. The key changes to the guidelines were:

- Replacement "1st-line, 2nd-line, 3rd-line and 4th-line" concept with "monotherapy, dual therapy, triple therapy and multiple insulin injection", highlighting the importance of combo therapies for diabetes patients that failed single-agent treatment with metformin (as first choice for most patients).
- More flexibility in drug combos.
- Encourage earlier use of insulin and GLP-1 receptor agonist (choices for dual therapy in new edition, vs. 3rd-line/4th-line in previous version).

Exhibit 138: Type 2 diabetes treatment guidelines in China (2017 edition)

Monotherapy	Metformin	α-glucosidase inhibitor / SU / glinides
Dual Therapy	Metformin +	
	Oral SU / glinides / α-glucosidase inhibitor / DPP-4i / TZD / SGLT-2i	***Injection*** Insulin (1-2 injection / day) / GLP-1 RA
Triple Therapy	Metformin +	
	Two of above listed therapies with different machanism	
Multiple insulin injection	Metformin +	
	Basal insulin + Prandial insulin	Premixed insulin multiple times daily

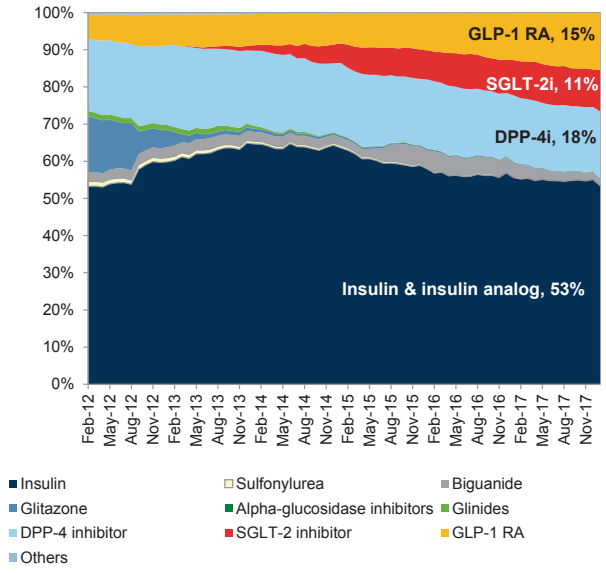
Source: Chinese Diabetes Society

Reimbursement coverage to drive growth of newer-generation anti-diabetes medicines

Insulin products, including human insulin (second-generation insulin) and insulin analog (third-generation), accounted for over 40% of the anti-diabetic market in China in 2017 (vs. over 50% in the US). In non-insulin anti-diabetic medicines, the prescription in China is highly different from that in US as it is still dominated by older-generation drugs:

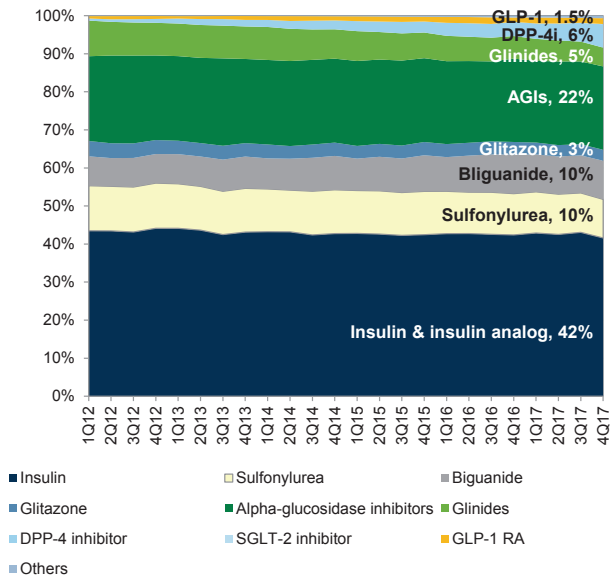
- GLP-1 receptor agonist, DPP-4 inhibitors and SGLT-2 inhibitor only accounted for <8% of market share in China or 13.2% of non-insulin anti-diabetic medicine sales vs. 95% in the US; with DPP-4 inhibitor and Victoza listed in the new 2017 national reimbursement list, we expect the market share of newer-generation non-insulin products to improve in the coming years.

Exhibit 139: Newer-generation therapies dominate US diabetes market
US diabetes market by key categories of therapies



Source: IMS database

Exhibit 140: Old-generation drugs as key treatment in Chinese anti-diabetic drug market
Chinese diabetes market by key categories of therapies



Source: PDB database

- The most widely used oral anti-diabetic drugs (OADs) in China are acarbose (32% of all OADs in 1Q18) and meformin (17% of all OADs); both were still dominated by off-patent originator drugs (i.e., Glucophage and Glucobay).

Exhibit 141: Metformin and acarbose as major OADs in China
CFDA approved major oral anti-diabetic drugs (including GLP-1 RAs)

Drugs		Market share	Reimbursement	# of players	Lead Products (market share)	Monthly cost of lead product*	Domestic generics leaders
Biguanide							
Metformin	二甲双胍	16.9%	'09 & '17 NRDL	50+	Glucophage (BMS, 75%)	Rmb71	Conquer No.1 <5% market share
Alpha-glucosidase inhibitors							
Acarbose	阿卡波糖	32.0%	'09 & '17 NRDL	3	Glucobay (Bayer, 66%)	Rmb187	Huadong Medicine 29%, Luye 4%
Voglibose	伏格列波糖	3.5%	'09 & '17 NRDL	10+	Basen (51%)	Rmb135	Jiangsu Chenpai 32%
Miglitol	米格列醇	0.9%	'17 NRDL	3 (all generics)	Aodiping (Weiao, 42%)	Rmb166	Weigao 42%, Zhejiang Medicine 38%
DPP-4 inhibitors							
Sitagliptin	西格列汀	5.4%	'17 NRDL	1	Januvia (Merck, 100%)	Rmb228	All exclusive products, no generics available
Saxagliptin	沙格列汀	2.9%	'17 NRDL	1	Onglyza (BMS, 100%)	Rmb249	
Vildagliptin	维格列汀	1.9%	Not covered	1	Galvus (Novartis, 100%)	Rmb259	
Linagliptin	利格列汀	0.9%	'17 NRDL	1	Trajenta (Boehringer Ingelheim, 100%)	Rmb254	
Alogliptin	阿格列汀	0.4%	'17 NRDL	1	Nesina (100%)	Rmb254	
Meglitinide (Glides)							
Repaglinide	瑞格列奈	7.3%	'09 & '17 NRDL	5	NovoNorm (Novo Nordisk, 81%)	Rmb177	Hansoh 17%
Nateglinide	那格列奈	0.7%	'09 & '17 NRDL	8	Starlix (Novartis, 81%)	Rmb215	Jiangsu Deyuan 15%
Mitiglinide	米格列奈	0.1%	'17 NRDL	5	Fadi (Sino Biopharm, 75%)	Rmb219	Sino Biopharm as dominant player
GLP-1 RA							
Liraglutide	利拉鲁肽	2.4%	'17 NRDL	1	Victoza (Novo Nordisk, 100%)	Rmb1,230	All exclusive products, no generics available
Exenatide	艾塞那肽	0.6%	Not covered	1	Byetta / Bydureon (3SBio/AZ, 100%)	Rmb1,609	
Benaglutide	贝那鲁肽	0.0%	Not covered	1	Yishengtai (Benemae, 100%)	Rmb1,814	
Thiazolidinedione (TZD)							
Pioglitazone	吡格列酮	3.0%	'09 & '17 NRDL	15+	Actos (31%)	Rmb181	Jiangsu Deyuan 16%, Luye 16%
Rosiglitazone	罗格列酮	1.6%	'09 & '17 NRDL	9	Tailuo (Taiji Group, 91%)	Rmb131	Taiji as dominant player
Sulfonylurea (SU)							
Glimerpiride	格列美脲	8.7%	'09 & '17 NRDL	14	Amaryl (Sanofi, 83%)	Rmb131	Wanbang No.1 <5% market share
Glipizide	格列齐特	5.7%	'09 & '17 NRDL	30+	Diamicron (Sevier, 94%)	Rmb156	Tianjin Huajin <5%
Gliclazide	格列吡嗪	1.5%	'09 & '17 NRDL	20+	Glucotrol (Pfizer, 73%)	Rmb199	Zibo Wanjie 9%, Yangtze River 5%
Gliquidone	格列喹酮	1.2%	'09 & '17 NRDL	6	Tangshiping (Double Crane, 94%)	Rmb130	Double Crane as dominant player
Glibenclamide	格列本脲	0.0%	'09 & '17 NRDL	6	Glibenclamide (Succhi, 45%)	Rmb04	Yunpeng Pharma 34%
SGLT-2 inhibitor							
Dapagliflozin	达格列净	0.2%	Not covered	1	Forxiga (AstraZeneca, 100%)	Rmb488	All exclusive products, no generics available
Empagliflozin	恩格列净	0.0%	Not covered	1	Jardiance (Boehringer Ingelheim, 100%)	Rmb458	

**: both market share and monthly costs based on PDB sample hospital 1Q18 data*

Source: CFDA, PDB database, Company data

Pipeline of non-insulin anti-diabetic drugs

Newer-generation classes, such as GLP-1, DPP-4 and SGLT-2 are the key focus in developing anti-diabetic medicines in China. The three leading players in the space (Tonghua Dongbao, Huadong Medicine, and United Labs) aim to expand their product portfolio in the area to leverage their established commercial infrastructure. Meanwhile, new players are entering, e.g. Hengrui, who have also positioned diabetes as one of the key therapeutic areas to build a future competitive edge.

- **GLP-1:** Three candidates are at the late-stage of development in China, including domestic novel GLP-1 RA PEG-loxenatide from Hansoh (NDA filed) and two from global players (Semaglutide from Novo Nordisk and Dulaglutide from Eli Lilly, both at Phase III). All of those three are once-weekly formulation (similar to 3SBio's recently launched Bydureon). More so, there are growing number of players focusing on developing Victoza biosimilar, with Huadong Medicine's subsidiary Jiuyuan Gene currently at the lead position.
- **DPP-4:** DPP-4 is an even more crowded space vs. GLP-1, with five CFDA approved drugs being marketed, 15 upcoming new molecules from domestic and MNC players (four at late-stage, including Hengrui's retagliptin, which is at a new phase III trial after the NDA withdrawal in 2016), and over 20 generics in pipeline.

- **SGLT-2:** Two of the three globally approved SGLT-2 have already been approved by CFDA in China, e.g. AstraZeneca's dapagliflozin (approved in March 2017) and BI's Empagliflozin (approved in September 2017), while Merck's ertulgiflozin is at phase III trial. Late-stage pipeline for SGLT-2 inhibitors also include Hengrui's henagliflozin at phase III.
- **New targets:** Glucokinase activator is the new class of anti-diabetic drug with differentiated mechanism of action, aiming to restore the impaired blood glucose sensor function, and thereby address the underlying cause of Type 2 diabetes. Hua Medicine's GKA HMS5222 (Dorzagliatin), which was licensed from Roche, is at phase III trial.

Exhibit 142: Non-insulin anti-diabetic drug pipeline

Candidates	Company	China Status	
GLP-1			
Loxenatide	Hansoh; Hansen	NDA filed	
M Semaglutide (Ozempic)	Novo Nordisk	Ph3	Approved in 2017 in US
M Dulaglutide (Trulicity)	Eli Lilly	Ph3	Approved in 2014 in US
Albenatide	Changshan	Ph2	
PEG exenatide	Pegbio	Ph1	
Glutazumab (GLP-1R antibody)	Gmax Bio	IND filed	
Supaglutede	Innogenpharm; Yinnuo	IND filed	
M Soliqua 100/33 (Lixisenatide / Insulin glargine)	Sanofi	IND filed	Approved in the US 2016
Victoza biosimilar			
Jiuyuan Gene at Ph1, Hybio's approved for clinical trials, 10 filed IND (incl. Tonghua Dongbao, United Labs, Fosun Pharma, HEC and Sino Biopharm)			
Byetta biosimilar			
4 NDAs, 1 Ph3, 5+ approved for clinical trials, 2 INDs			
DPP-4			
M Teneligliptin (Tenelia)	Mitsubishi	Ph3	Approved in Japan in 2012
Retagliptin	Hengrui	Ph3	Withdrew NDA in 2016, new ph3
M Trelagliptin (Zafatek)	Kelun Pharma*	Ph3	Origniator drug was approved in Japan in 2015
Fotagliptin	Salubris	Ph2	Licensed from Fosun Pharma
Evogliptin	Luye	Ph1	Licensed from Dong-A (Korea)
Imigliptin	Xuanzhu Pharma	Ph1	
Youge-liptin	Easton Biopharma	Ph1	
Cetagliptin	CGene Tech	Ph1	
Besigliptin	Hansoh	IND approved	
Dutogliptin (HD118)	Huadong Medicine	IND approved	
Anagliptin	Domestic generics	IND approved	
M Gemigliptin (Zemiglo)	LG life Science / CR Double Crane	IND approved	Approved in South Korea in 2012,
M Omarigliptin (MK-3102, Marizev)	Merck	IND approved	Approved in Japan in 2015, project ceased in US/EU
Augliptin	Nanjing Changao	IND approved	
SGLT-2			
M Steglatro (Ertugliflozin)	Merck	Ph3	Approved in the US in 2017
Henagliflozin	Hengrui	Ph3	
HEC-44616	HEC Pharma	Ph1	
Janagliflozin	Xuanzhu	Ph1	
M Synjardy (Empagliflozin / Metformin)	Boehringer Ingelheim	Ph1	Approved in the US in 2015
Tofogliflozin	Huawe	IND approved	
Tianagliflozin	TIPR	IND approved	
M Ipragliflozin	Astellas	IND approved	Approved in Japan in 2014
M Sotagliflozin	Sanofi	IND filed	Ph3 in the US
SBM-TFC-039	Fosun Pharma (Wangbang)	IND filed	Licensed from Sirona Bioichem in 2014
Glucokinase activator (GKA)			
Dorzagliatin (HMS5552)	Hua Medicine	Ph3	Licensed from Roche
GPR40 agonist			
Fuglifam	Hengrui	Ph1	

M *Products from multinational biotech / pharma companies. TIPR: Tianjin Institute of Pharmaceutical Research*

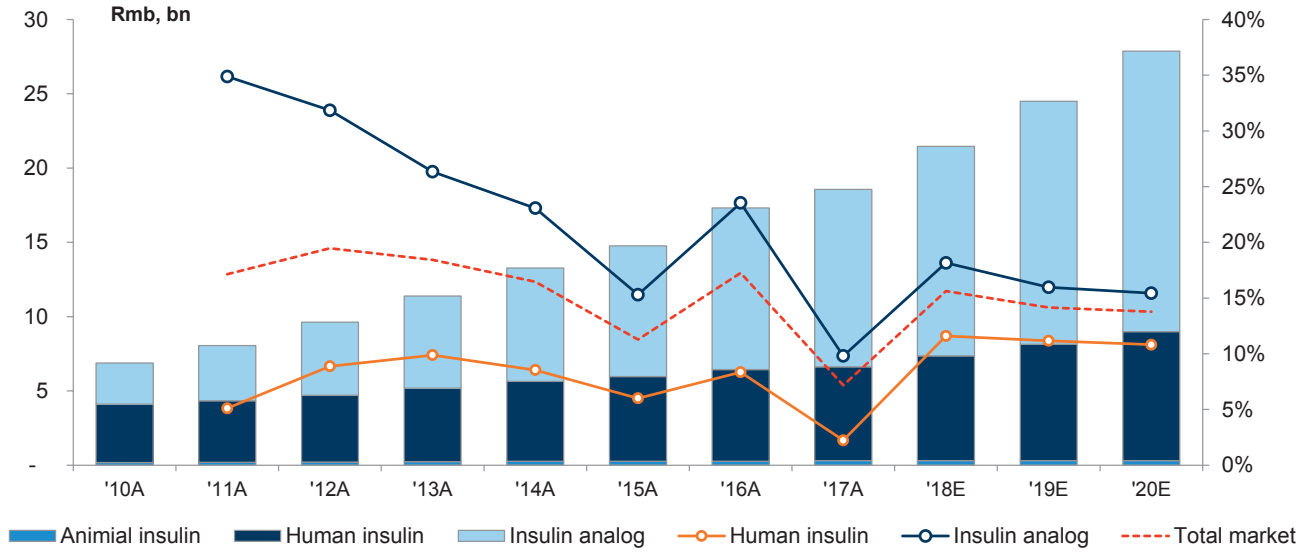
**: lead generic among 20+ generic versions*

Source: Insight database

Insulin market in China - competition to shift to insulin analog

The Chinese insulin market in 2017 was valued at ~Rmb18.6bn, with Rmb11.9bn from insulin analog and Rmb6.6mn from human/animal insulin. We see insulin analog as a major growth driver for the market over the next few years.

Exhibit 143: Insulin analog to drive growth of the Chinese insulin market
Sales trend of three generations of insulin products in China (2010-2020E)

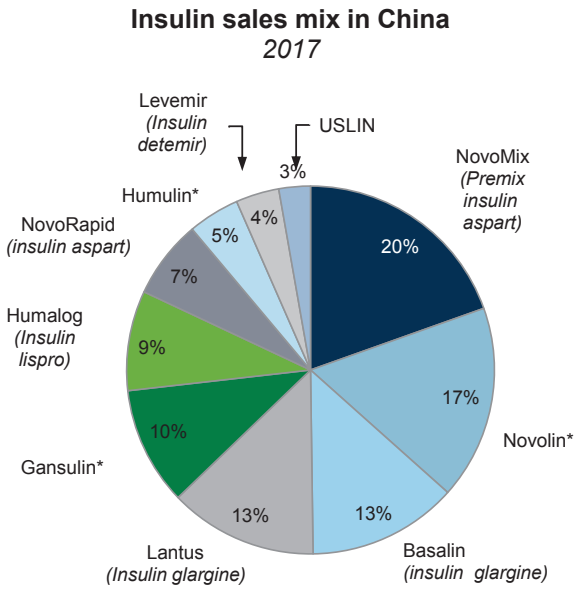


Source: Company data, Goldman Sachs Global Investment Research

Key insulin products in China

Compared with the US market, where human insulin only accounted for <10% of total insulin sales in 2017, human insulin in China-+ contributed ~35% of total insulin sales, and ~50% in volume. For insulin analog, insulin aspart, insulin glargine and insulin lispro are most widely prescribed in China.

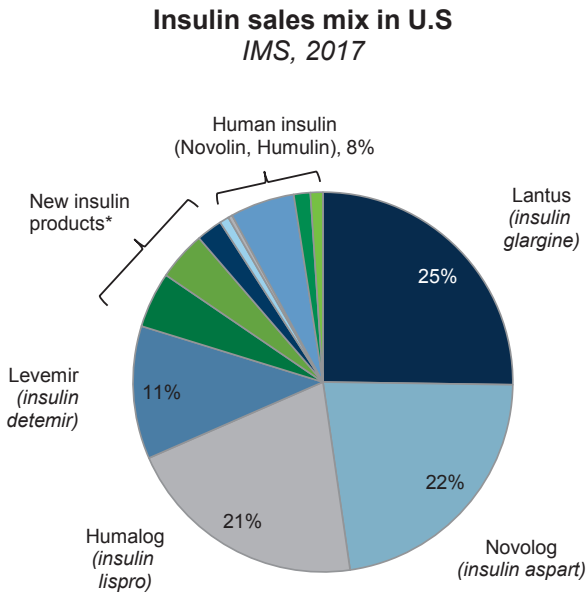
Exhibit 144: Insulin mix in China



*: Novolin, Humulin, Gansulin are human insulin

Source: Company data

Exhibit 145: Insulin sales mix in the US



*: Tresiba, Toujeo, Basaglar, Apidra, Soliqua, Xultophy, and Afrezza

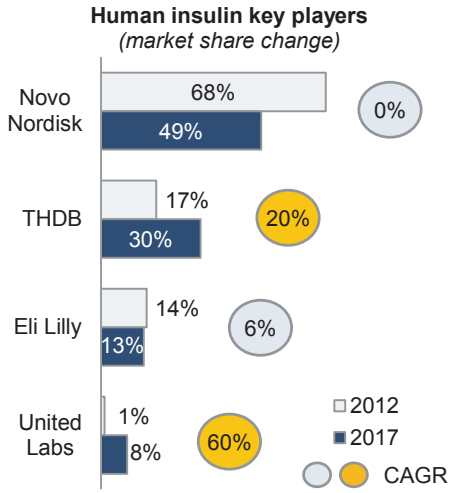
Source: IMS database

Key insulin players in China

In the human insulin market, Novo Nordisk (Novolin) and Tonghua Dongbao (Gansulin) are the top two players, seized 49% and 30% market share in 2017, respectively. Eli Lilly has licensed out its human insulin product (Humulin)'s China rights to 3SBio in 2017. United Labs launched human insulin product USLIN in 2011, focusing on lower-tier cities.

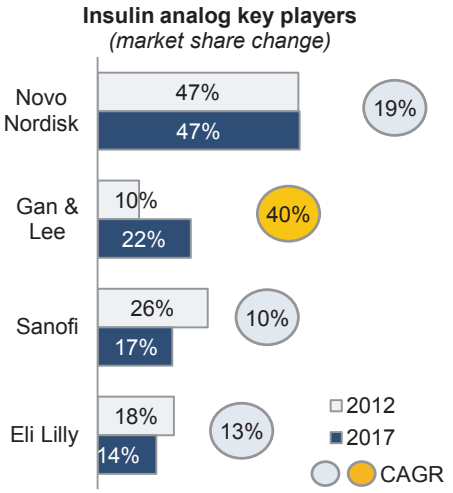
In the insulin analog market, three MNCs are dominating - Novo Nordisk captured 47% market share (NovoRapid, NovoMix and Levemir), followed by Sanofi (Lantus) 17% and Eli Lilly (Humalog) 14%. Gan & Lee is the first domestic company to enter this market, ramped up in the past decade with market share of 22% in 2017 (the No. 2 player in China's insulin analog market). United Labs also launched a insulin glargine in 2017.

Exhibit 146: Change of market shares in major insulin manufacturers



Source: Company data

Exhibit 147: Insulin analog of key players



Source: Company data

Insulin pipeline on the horizon - potential more new players

We expect the accessibility of insulin products in China to further improve in the coming years with existing players expanding the insulin product portfolio, particularly in insulin analogs, and more new players entering the market.

Exhibit 148: Mapping the key insulin players in the Chinese insulin market
Approved insulin products and products in pipeline in China; as of April 30, 2018

Insulin type	Ultra short acting	Short acting	Intermediate acting	Long acting (basal insulin)	Ultra long acting	Premixed human insulin	Premixed insulin analog	Co-formulation
Onset	10-20 min	~30 min	1~2 hr	30-90 mins	30-90 mins	30 mins	10-20 mins	14 min
Peak	0.5-3 hr	1.5-4 hr	4-12 hr	w/o peak	w/o peak	2-12 hr	0.5-4 hrs	72 min
Duration	3-5 hr	4-8 hr	18-24 hr	> 24 hr	up to 42 hr	10-24 hr	14-24 hr	up to 42 hr
Novo Nordisk	NovoRapid 诺和锐 (insulin aspart)	Novolin R 诺和灵 R (regular insulin)	Novolin N 诺和灵 N (NPH insulin)	Levemir 诺和平 (insulin detemir)	Tresiba 诺和达 (insulin degludec)	Novolin 30R, 50R (30%, 50% regular insulin)	NovoMix 30, 50 (30%, 50% insulin aspart)	Ryzodeg 70/30 (insulin degludec/aspart) at phase 3
Eli Lilly	Humalog 优泌乐 (insulin lispro)	Humulin R 优泌林 R (regular insulin)	Humulin N 优泌林 N (NPH insulin)	Basaglar (insulin glargine) passed IND		Humulin 70/30 (30% regular insulin)	Humalog 25 / 50 (25%, 50% insulin lispro)	
Sanofi	Apidra 艾倍得 (insulin glulisine)			Lantus 来得时 (insulin glargine)				
Gan & Lee Pharma	Prandilin 速秀霖 (insulin lispro)			Basalin 长秀霖 (insulin glargine)		Human insulin 30R NDA filed	Prandilin 25R 速秀霖 25 (25% Insulin lispro)	
							Insulin aspart 30 NDA filed	
	Insulin aspart NDA						Insulin lispro 50R IND filed	
Tonghua Dongbao	Insulin aspart completed phase 3	Gansulin R 甘舒霖 R (regular insulin)	Gansulin N 甘舒霖 N (NPH insulin)	Insulin glargine NDA filed		Gansulin 30R, 40R, 50R (30%, 40%, 50% regular insulin)	Insulin aspart 30, 50 at phase 3	
	Insulin lispro IND filed			Insulin detemir passed IND			Insulin lispro 25R and 50R IND	
United Labs	Insulin aspart NDA	USLIN R 优思灵 R (regular insulin)	USLIN N 优思灵 N (NPH insulin)	USLEN 优乐灵 (insulin glargine)	Insulin degludec at preclinical		Insulin aspart 30 NDA	
				Insulin detemir passed IND			Insulin aspart 50 at preclinical	
HEC Pharma		Human insulin at phase 3	NPH insulin passed IND	Insulin glargine at phase 3		Human insulin 30R passed IND	Insulin aspart 30 approved for clinical trials	
Hisun Pharma	Insulin aspart (HS005) at phase 3	Human insulin at phase 1		Insulin glargine (HS004) at phase 3	Insulin degludec passed IND	Human insulin 30/70 at phase 3		
Fosun Pharma - Wanbang		Human insulin at phase 3		Insulin glargine at phase 3			Insulin lispro 25R and 50R passed IND	
Hefei Tianmai Biotech			NPH insulin NDA			Human insulin 30/70 NDA		
Liaoning BoAo Biopharm				Insulin glargine at phase 3			Insulin aspart 30 IND filed	
SL Pharma	Insulin aspart IND filed						Insulin aspart 30, 50 IND filed	
Huadong Medicine	Insulin aspart at preclinical			Insulin detemir IND filed	Insulin degludec at preclinical			

Recombinant human insulin (2nd-gen) | Insulin analog (3rd-gen) | Pipeline (China): Preclinical studies
Pipeline (China): NDA | Pipeline (China): IND / clinical trials

Source: Company data, CFDA

Autoimmune diseases: Focus on penetration of biologics

Autoimmune[1] In China

11.2Mn Total patient base **0.81%** Prevalence rate

Most common type: Rheumatoid arthritis (44%), Ankylosing spondylitis (32%), Psoriasis (24%)
Emerging therapies in China: Targets includes TNF-a, RANKL, JAK, IL-6, CTLA4 and CD20. Binding to TNF-a and CD20 candidates make up 70% of total pipelines

1 - Listed in "most common type"

Disease demographics

Autoimmune disorders occur when a patient's immune system performs abnormally and attacks the patient's body instead of protecting it. The mainstream treatment aim is to suppress the immune system response. Common autoimmune diseases include rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriasis (Ps).

Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease that primarily affects joints. The cause of RA is unknown, but it is believed that RA may relate to inciting antigen gaining access to joints, which can trigger immune responses. If untreated, RA can cause permanent joint damage. Therefore, early and aggressive treatment plays an important role. RA usually strikes persons that are 20-50 years of age, and affects women three times as often as men. Treatments can include either oral or injectable medications that suppress the immune system. About 4.4mn-5mn people have RA in China, corresponding to a prevalence rate of 0.32%~0.36%.

There are a number of other auto-immune diseases with pathologies similar to RA's. Patients with such diseases may be eligible for RA therapies, expanding RA's potential market size.

Ankylosing spondylitis (AS) is a form of arthritis that primarily causes inflammation of the spinal joints. The main differences between RA and AS are the patient ages and sites at onset. AS appears in the tendons and ligaments surrounding the joints. It primarily affects patients in their 20s, and males are three times more likely to be afflicted with the disease. There is no known cure for AS, but there are treatments available to reduce its symptoms and manage the pain. It has a prevalence rate of 0.26%, resulting in a 3.6mn patient base in China.

Psoriasis (Ps) causes the immune system to be overactive and attack the skin, leading to scales and red patches that can be itchy and painful. In addition to skin lesions, Ps patients also suffer from inflammatory arthritis, which results in joint deformations and disability. Similar to AS, the main purpose of available treatment methods is symptom management. A combination of topical and systemic therapies as well as phototherapy are used over a patient's lifetime. Approximately 2.6mn patients in China are affected.

The prevalence rates of the major auto-immune diseases in Western countries are generally higher than in Asia. There are about 7.9mn patients living with RA, AS, or Ps in China compared to 8mn in the US and 0.8mn in Japan.

Exhibit 149: Prevalence of autoimmune diseases across different countries

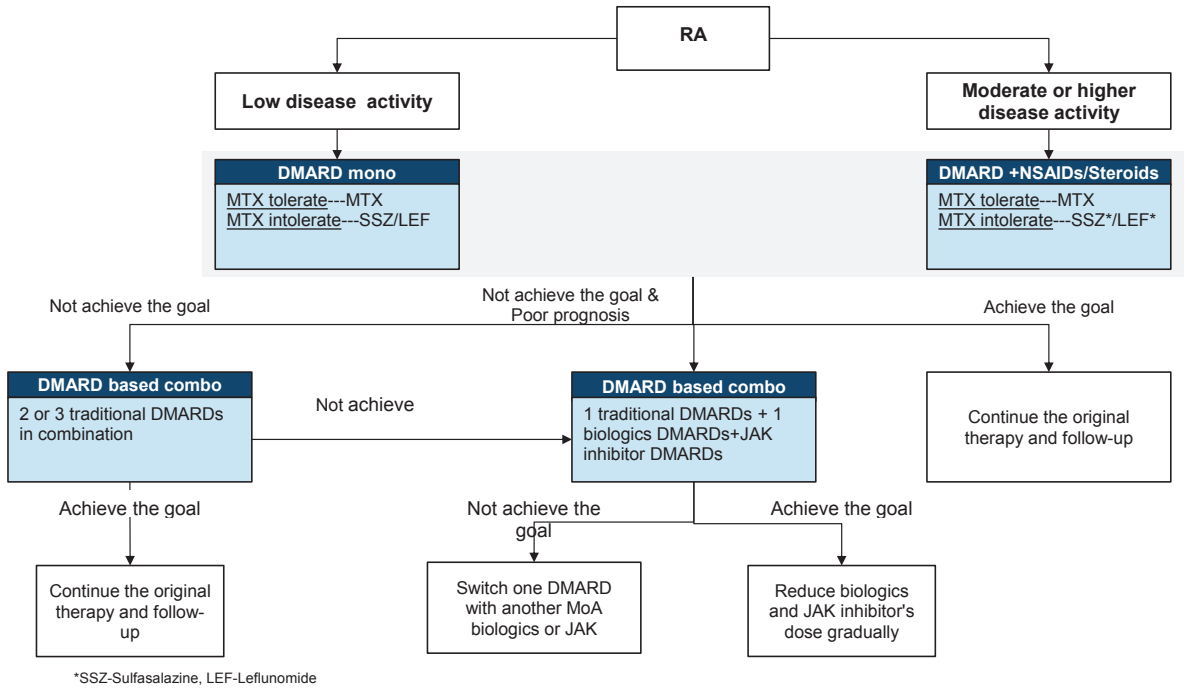
	Unit	China	US	EU	Japan
Population	mn	1381	327	508	126
Prevalence (%)					
- Rheumatoid arthritis (RA)	%	0.36%	1.07%	0.70%	0.17%
- Ankylosing spondylitis (AS)	%	0.26%	0.32%	0.24%	0.01%
- Psoriasis (Ps)	%	0.19%	1.06%	1.87%	0.44%
Total patient base	**mn**	**11.2**	**8.0**	**14.3**	**0.8**

Source: Rheumatology

Treatment

Currently, there is no cure for auto-immune diseases. The goals of RA treatment are to stop inflammation, relieve symptoms, prevent organ damage and improve overall well-being. Medication includes non-steroidal anti-inflammatory drugs (NSAID), disease-modifying anti-rheumatic drugs (DMARD), steroids and phytomedicines. For patients without obvious effect and response to medicine, surgeries and autologous peripheral blood stem cell transplantation (ABSCT) can be regarded as a supplemental choice.

Exhibit 150: Treatment paradigm



Source: China treatment consensus

For symptom management

- **NSAID.** NSAIDs include ibuprofen, naproxen and others. However, they may cause severe gastrointestinal toxicity and nephrotoxicity. For patients likely to suffer stomach ulcers, second-generation NSAIDs like celecoxib (also known as COX-2 inhibitor) are preferred due to their better safety profile for the stomach.
- **Steroids-used in various stages of RA.** Steroids are widely used as quick-acting and potent anti-inflammatory medications. Due to the side-effects of steroids, short-term and low-dose usage are adopted in clinical practice.

For slowing disease activity

DMARD can be grouped in the following categories: Immuno-suppressants, biologics – second or third line, and JAK inhibitors.

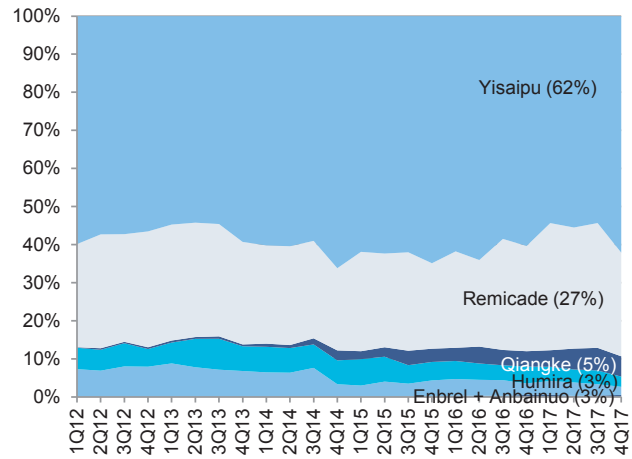
- **Traditional DMARD** include methotrexate, hydroxycholorquine, Sulfasalazine, Leflunomide, Azathioprine, cyclosporin, cyclophosphamide, etc. They are used in the first-line treatment. An individual therapy is emphasized on drug selection and dose adjustment. **Biologics** may act more rapidly than traditional DMARD. Without specific targets in the inflammatory process, biologics do not suppress the entire immune response as other RA treatments do. **JAK inhibitors** are a new subcategory of DMARD. It targets the Janus kinase or JAK pathways found in immune response. Xeljanz (Tofacitinib Citrate) was approved by the CFDA in March 2017 and included into the China treatment consensus in April 2018.
- In China, combinations of methotrexate (MTX) and phytomedicines (such as triptolide, sinomenine and total glucosides from paeony) are also considered to be DMARD therapies. Despite the long history of prescribing phytomedicines (since 1969), a lack of safety and efficacy data limited its application, and more data from large-scale clinical trials are needed. Currently, they can not be prescribed to expectant mothers.

Targeted therapies to highlight

There are six targeted therapies approved for the treatment of RA.

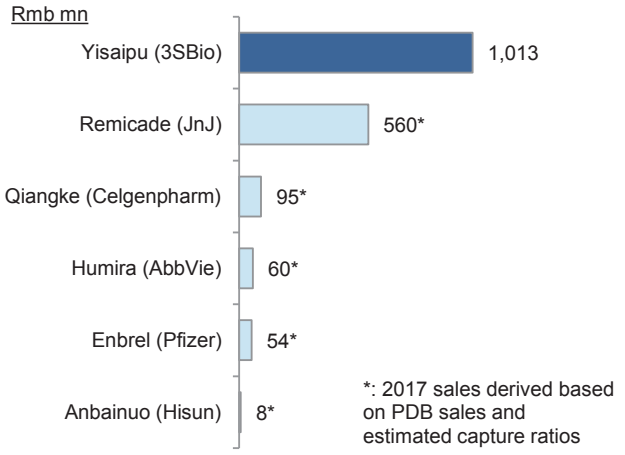
Yisaipu (3SBio): 2017 sales in China were Rmb1bn, more than the sum of sales of the other approved drugs for RA, due to: 1) first-to-market advantage (CFDA approval for the treatment of RA in 2005, and AS and Ps in 2007); 2) a lower annual treatment cost (~Rmb73k) than the three originator drugs; and 3) inclusion into the 2017 NRDL has helped penetration into more new patients. We expect Rmb2bn in sales of Yisaipu by 2020 with further volume ramp-up.

Exhibit 151: Market share change of various targeted therapies for RA



Source: PDB database

Exhibit 152: 2017 sales of six approved targeted therapies for RA



Source: PDB database, Goldman Sachs Global Investment Research

Remicade (Infliximab, Johnson & Johnson): Remicade, a chimeric antibody against TNF, was approved by the CFDA for the treatment of RA, AS, and Crohn's disease in 2006, and Ps in 2013. As of April 2018, Remicade is the only targeted therapy available for Crohn's disease. It was withdrawn from national reimbursement negotiation in 2017 for the treatment of Crohn's disease, while the pricing (annual treatment cost of ~Rmb82k) is still competitive vs. Humira and Enbrel. It is worth noting that Remicade is administered via intravenous injection vs. self-administered subcutaneous injection for other RA drugs, which may be a decisive factor for patients that are afraid of self-injection.

Humira (Adalimumab, AbbVie): Humira is a humanized anti-TNF antibody, and AbbVie received the CFDA's approval for RA in 2010, AS in 2013, and Ps in 2017. Despite global 2017 sales of US$18bn, the globally largest drug was not as popular in China. According to our estimates based on the sample hospital database, Humira's 2017 sales in China were Rmb60 mn, or US$8.7 mn, or 6% of sales of Yisaipu. One advantage of Humira is its less-frequent dosing (once biweekly).

Enbrel (Etanercept, Pfizer) and its biosimilars: Like Yisaipu, Enbrel is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the TNF receptor linked to the Fc portion of a human antibody IgG1. Enbrel is fully human, and therefore does not have a high incidence of infusion reactions. Enbrel was approved by the CFDA for the treatment of RA and AS in 2010 with no indication expansion since then. There are two biosimilars of Enbrel, i.e. Celgenpharm's Qiangke (approved in 2011) and Hisun's Anbainuo (approved in 2015).

Exhibit 153: Comparison of targeted therapies for RA

	Yisaipu	Enbrel (Etanercept)	Humira (Adalimumab)	Remicade (Infliximab)
Marketer in China	CPGJ (3SBio)	Pfizer	AbbVie	J&J
Launch in China	2005, Jan	2010, Jan	2010, Jan	2006, Jan
Sales performance				
PDB '17 sales (Rmb mn)	Rmb 302.7 mn	Rmb 16.3 mn	Rmb 17.9 mn	Rmb 167.4 mn
Growth in '17	*5.5%*	*-11.7%*	*-11.5%*	*35.3%*
3-year CAGR	*5.0%*	*0.6%*	*-15.6%*	*24.3%*
Pricing, costs and reimbursement				
Dosing (for RA)	25mg, twice weekly	50mg, once weekly	40mg, once biweekly	3-5mg/kg (2-3 vials) every 8 weeks
Administration route	Subcutaneous (s.c.) injection	Subcutaneous (s.c.) injection	Subcutaneous (s.c.) injection	Intravenous (i.v.) injection
Annual treatment cost	Rmb 72,900	Rmb 219,672	Rmb 206,442	Rmb 82,185
Yisaipu's discount	*-*	*-66.8%*	*-64.7%*	*-11.3%*
Reimbursement list	2017 NRDL	Ningxia and Tibet PRDL	None	Gansu and Tibet 2017 PRDL
Patient Assistance Program				
- Initiation	2015, Nov	2014, Apr	2012, Jul	2012, Mar
- Partners	Beijing Bethune Charity Foundation	Shared partner: China Primary Health Care Foundation (CPHCF)		
- Programs	Patients receive social welfare support: up to 48 doses; Low-income patients: up to 12 for free	Patients receive social welfare support: up to 48 doses; Low-income patients: up to 12 for free	Regular: buy 5 get 5 for free; Low-income: up to 10 free doses	6 doses for low-income patients and 2 for other qualified patients for each application
PK data				
Half-life	74 ± 4 hours	102 ± 30 hours	2 weeks (10-20 days)	7.7 to 9.5 days
Cmax	3.0±0.2μg/mL	2.4 ± 1.0 mcg/mL (n=23)	4.7 ± 1.6 μg/mL (40mg)	n.a. (median: 0.5 to 6 mcg/mL)
Tmax	53 ± 6 hours	69 ± 34 hours	131 ± 56 hour (40mg)	-
Efficacy / safety data				
Rheutomaid Arthritis (RA)				
- ACR20	2 weeks: 35.59%; 12 weeks: 66.10%; 24 weeks: 80.39%	3 months: 62%; 6 months: 65%; 12 months: 72%	6 months: 53%	54 weeks: 66%
Psoriatic Arthritis (PA)				
- PASI (Psoriasis Area and Severity Index)	After 12 weeks - PASI 50: 93.33%; PASI 70: 83.33%; PASI 90: 56.67%	After 3 months - PASI 50: 71%; PASI 75: 47%	after 16 weeks - PASI 75: 71%	After 6 months - PASI 75: 60%; PASI 90: 39%
Ankylosing Spondylitis (AS)				
- ASAS (Assessment in Ankylosing Spondylitis)	ASAS20: 55.07% / 68.12% / 78.26% after 2 / 6 / 12 weeks	ASAS 20 / 50 /70: 60% / 45% / 29% after 12 weeks	ASAS 20 / 50 /70: 58% / 38% / 23% after 12 weeks	ASAS 20 / 50 /70: 60% / 44% / 28% after 24 weeks
Side effects	Injection site reactions, rash, ALT elevation, infection	(Incidence > 5%): Infections and injection site reactions	(Incidence > 10%): infections, injection site reactions, headache and rash	(Incidence > 10%): infections, infusion-related reactions, headache, abdominal pain

Source: Company data

A patient with autoimmune diseases may have an immune system out of control and damage the body mistakenly. Hence, it is necessary to reduce inflammation and suppress immune response simultaneously. The treatment principle makes the targeted therapy effective by binding a specific target and blocks the pathway.

The market of autoimmune diseases is dominated by MNCs, which own 8 out of 10 in-market products. However, the future sales growth may not be optimistic due to limited efficacy, R&D obstacles, and insufficient awareness of the affordability issues in China. We expect MNCs to invest more sources into this area, and find a few new MoA (mechanism of action) which can be added to the pipeline. We also note that the majority of local companies become potential threats to originators and make the competition even more intense with their on-going biosimilar research. Now around 15 of 70 candidates have almost reached the later stages of the clinical development, phase III or NDA submission. The major targets in progress are TNF-a, RANKL, JAK, IL-6, CTLA4 and CD20. Binding to TNF-a and CD20 candidates make up 70% of total pipelines.

Key candidates in pipeline for AMD

They include:

- **Anti TNF-a biosimilar**: As a TNF-a inhibitor, Remicade (J&J, 2007), Enbrel (Pfizer, 2010) and Humira (AbbVie, 2011) are followed by local companies and they have 3, 4 and 26 potential generics, respectively. We expect competition to become more complex and fierce for Humira considering its five potential competitors at phase III, including Fosun Pharma. For Remicade and Enbrel, the threat is from Genor Biopharma and Qilu Pharma's phase III candidates.
- **Anti-CD20 biosimilar**: MabThera (Roche, 2000) is only indicated for patients with FL and DLBCL lymphoma in China. However, it was also approved by the CFDA for CLL, RA, granulomatosis with polyangiitis (GPA), and microscopic polyangiitis. More research still continues to explore its efficacy in other immune diseases. Given the success of anti-CD20 antibody-mediated B cell depletion therapy, 16 local companies are conducting clinical trials of MabThera's biosimilar. Among them, Fosun Pharma has already submitted an NDA and Innoven is at phase III , which means they could field the first go-to-market Rituxan biosimilar.
- **Anti-JAK biosimilar**: XELJANZ (Pfizer, 2017) has been in the market for only one year, but it will have to face upcoming competition from Kelun and Sinobiopharm, which have both already submitted NDAs and are awaiting the next action.
- **Anti-RANKL biosimilar**: Xgeva (GSK, phase III) is proved in the US for patients with osteoporosis. Currently, there are seven local companies engaged in this market, but they are still only at the very beginning of clinical trials.
- **Originators' progress**: In the pipeline, UCB (Cimzia -TNF a), BMS (Orencia – CTLA4) and Eli Lilly (Olumiant – JAK) have progressed to phase III and are expected to provide additional options to patients in the short term.

Exhibit 154: Pipelines of autoimmune therapies

Candidates	Type	Target	Company	China Status
CD20				
BAT4306F	Biologics	CD20	Bio-Thera	IND filed
TNF-α				
M Cimzia (Certolizumab pegol)	Biologics	TNF-α	UCB	III
RANKL				
M Xgeva / Prolia (Denosumab)	Biologics	RANKL	GSK	III
JAK				
M Olumiant (Baricitinib)	Chemical	JAK	Eli Lilly	III
SHR0302	Chemical	JAK	Hengrui	II
M ASP015K (Peficitinib)	Chemical	JAK	Astellas	IND passed
DTRMHS-07	Chemical	JAK	Hisun	IND passed
M Fedratinib	Chemical	JAK	Celgene / Sanofi	IND passed
KL130008	Chemical	JAK	Kelun	IND filed
IL-6				
Gerilimzumab (GB224)	Biologics	IL-6	Genor Biopharma	I
M Sirukumab	Biologics	IL-6	Johnson & Johnson	IND passed
M Sarilumab (SAR153191)	Biologics	IL-6	Sanofi	IND passed
CTLA-4				
M Orencia (Abatacept)	Biologics	CLTA-4	BMS	III
M *Products from multinational biotech / pharma companies*				
BTK				
M AC0058TA	Chemical	BTK	ACEA Biosciences	IND passed
WXFL10230486	Chemical	BTK	Humanwell	IND passed

Source: Insight database

CNS[1] In China

238Mn Total patient base **17.5%** Prevalence rate **20%** Awareness rate[2]
20% Diagnosis rate[2]

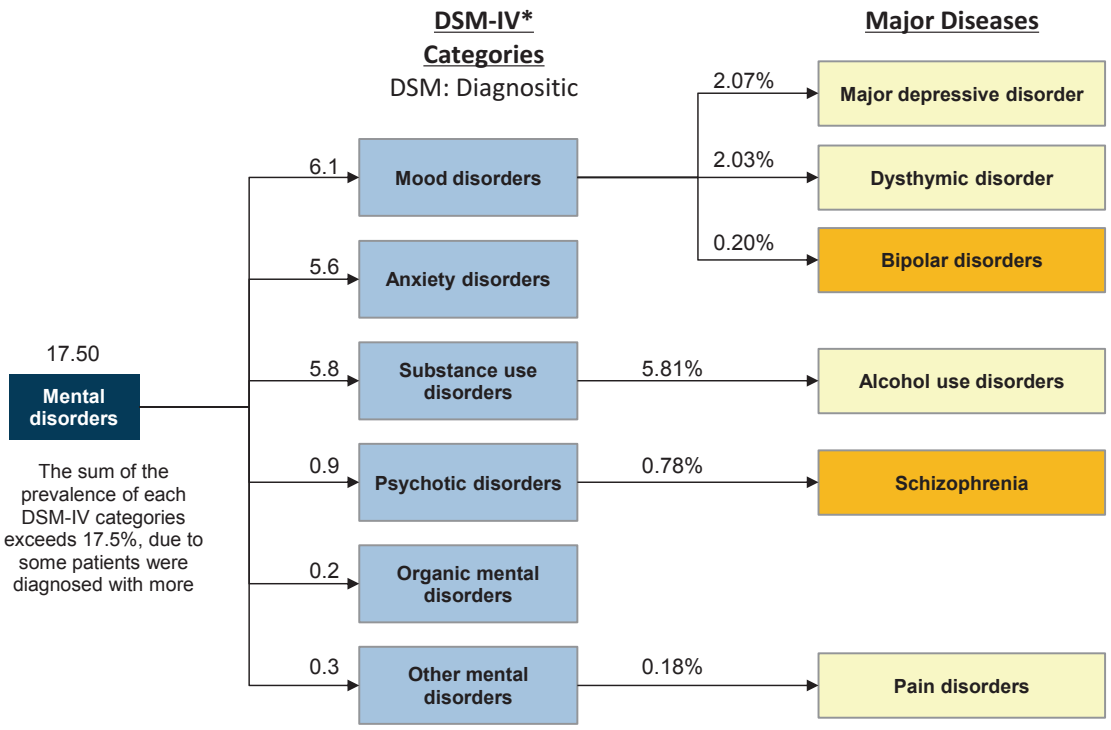
Most common type: Schizophrenia (4.5%) , Depression (12%) , Parkinson's diseases (1%) and Epilepsy (1%)
Major therapies in China: Typical antipsychotics (Sulpiride), Atypical Antipsychotic (Olanzapine, Quetiapine, etc), Escitalopram, Sertraline, Levodopa, Pramipexole

1 - Listed in "most common type" ; 2 – Depression for example

CNS diseases overview

Central nervous system (CNS) diseases are emerging in China and around one in five Chinese suffers from mental or neurological disorders at some point in his/her life. There are about 268mn people experiencing CNS diseases across the country, making mental disorders one of the leading causes of ill-health and disability in China. CNS diseases can be categorized into several groups: depression, bipolar affective disorder, schizophrenia, Parkinson's diseases, Alzheimer's diseases, epilepsy and a few more. These diseases are generally characterized by mix of symptoms like abnormal thoughts, perceptions, emotions, behavior and relationships with others.

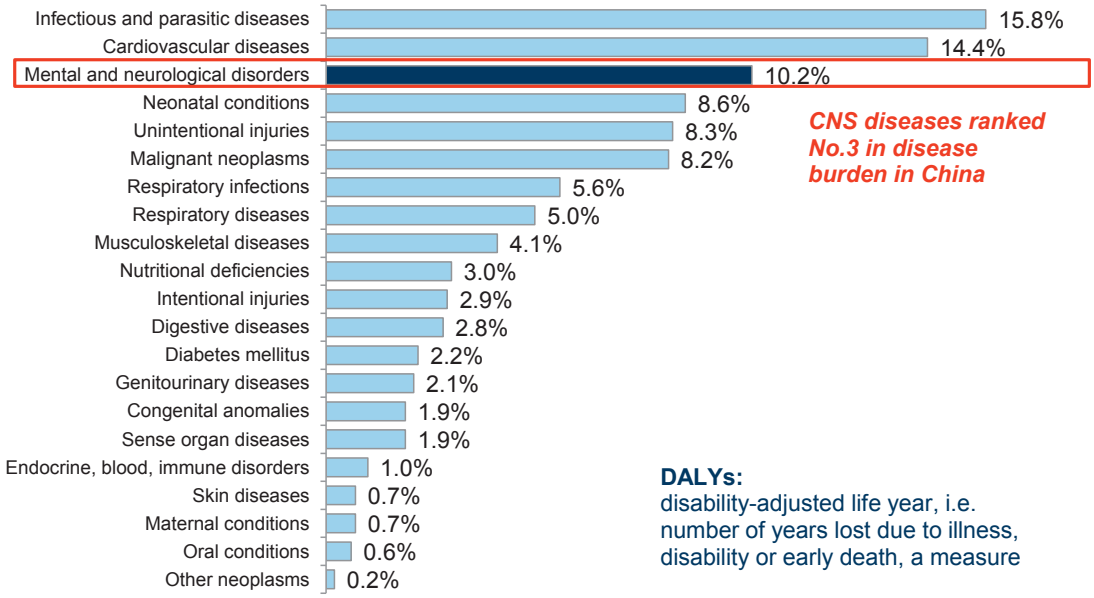
Exhibit 155: Prevalence of CNS disease and subgroups



Source: Prevalence treatment and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey

In addition to the large patient base, CNS diseases can significantly lower patients' quality of life, and may incur further economic loss due to the poor mental health conditions associated with CNS diseases. According to a 2011 study conduct by World Economic Forum and Harvard School of Public Health, the cumulative economic impact of mental disorders in China can amount to a US$4.5 trn loss in 2012-2030.

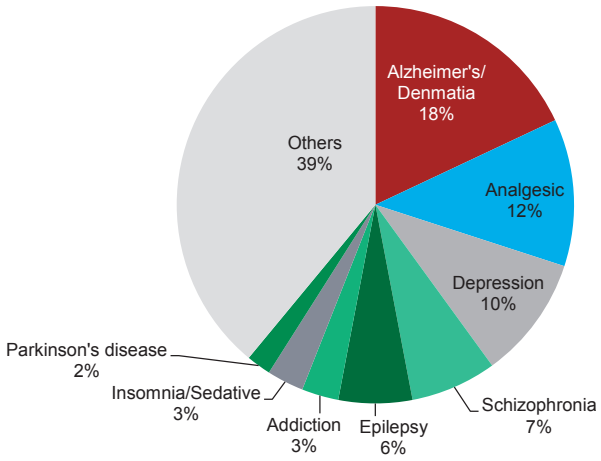
Exhibit 156: CNS diseases can lead to long periods with bad health conditions



Source: WHO

The CNS drugs market is broken down by subgroups in Exhibit 157. The overall CNS drugs market is relatively fragmented with the top 8 subgroups accounting for ~60% of the market share.

Exhibit 157: Breakdown of CNS/Mental Drug Market



Source: PDB database

Major diseases categories in CNS

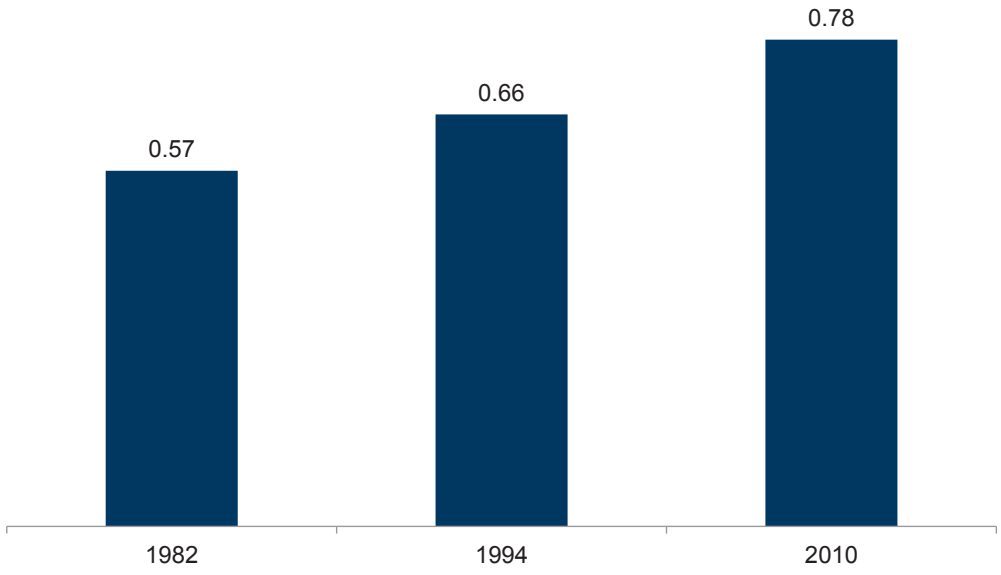
1. Summary of schizophrenia

Schizophrenia is among the most common and serious CNS diseases globally. It accounted for ~50% of the patients housed in mental specialty hospitals in China and is mostly prevalent among the youth. This psychotic disorder is marked by severely impaired thinking, emotions and behaviors, and ~50% of the patients bear permanent damage to their mental functions.

1) Epidemiology

The prevalence of schizophrenia in Chinese patients has grown considerably from 0.57% in 1982 to 0.78% in 2010. The increase in prevalence of schizophrenia may be associated with fast industrialization and urbanization in China. However, the direct cause of schizophrenia remains an open question in academia.

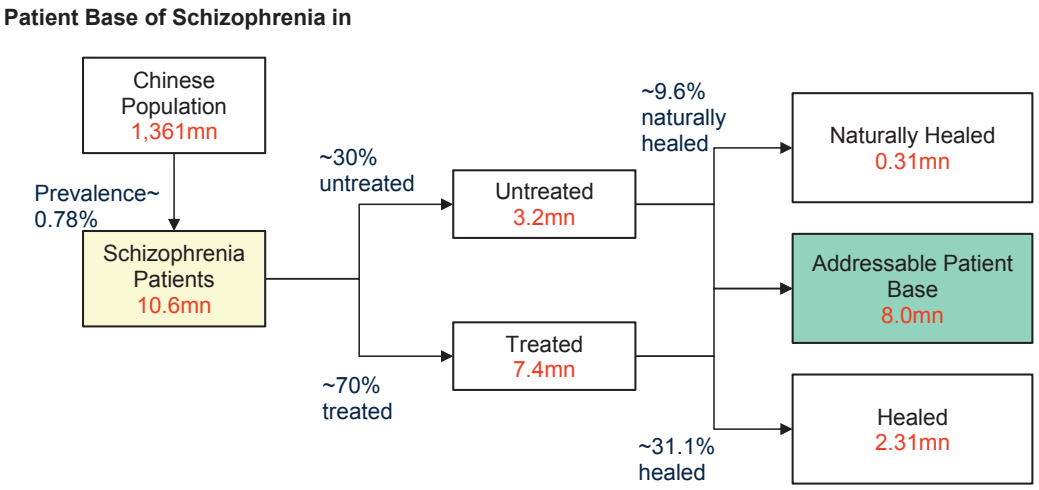
Exhibit 158: Prevalence of schizophrenia in different period



Source: Insight database

As illustrated in Exhibit 159, the total Chinese patient base of schizophrenia is ~10.6mn with ~8mn addressable by anti-schizophrenia medicines.

Exhibit 159: Chinese schizophrenia patient base analysis



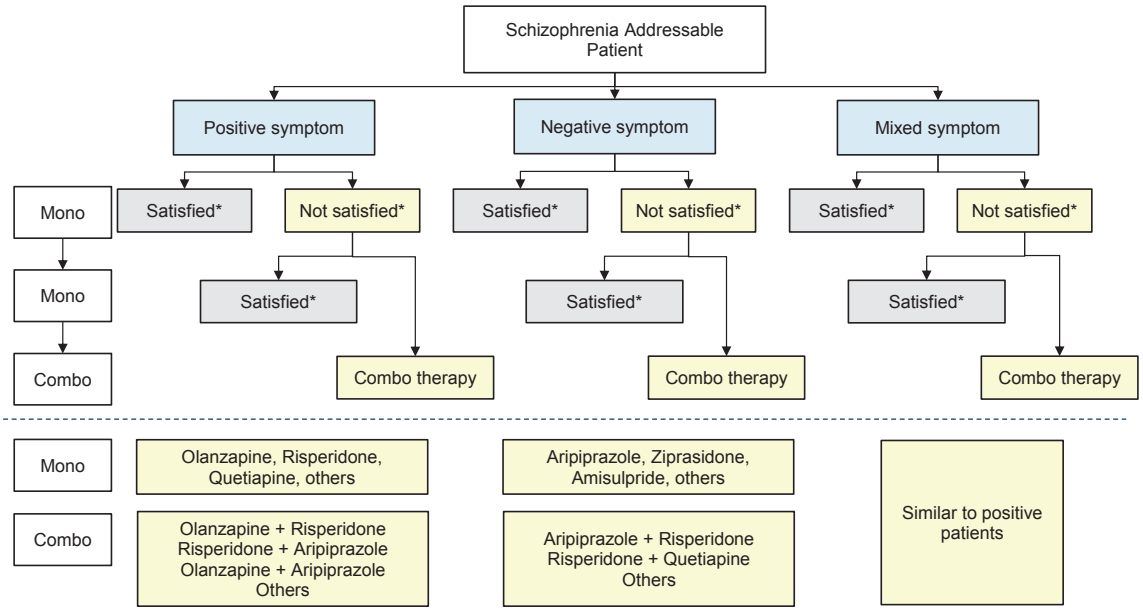
Source: Goldman Sachs Global Investment Research

2) Treatment

Generally, physicians classify patients with schizophrenia into positive symptoms, negative symptoms and mix symptoms based on their clinical manifestation. This classification is used to make further treatment and prescribing decisions.

Schizophrenia usually requires lifelong treatment, which according to the Chinese clinical treatment guidelines of schizophrenia, includes an acute phase, a stabilization phase, and a maintenance phase. During the acute phase, the treatment objectives are to prevent the patient from suffering injuries and control disordered behaviors. Moving to the stabilization phase, treatment may aim to reduce the stress of the patient and consolidate the remission of symptoms. During the final maintenance phase, the patient may show no symptoms, such as tension, irritability, depression, negative symptoms and cognitive deterioration, while the treatment should continue to manage relapses and improve quality of life.

Exhibit 160: Treatment flow for schizophrenia



Source: Chinese clinical guidelines for schizophrenia

There are two major types of antipsychotic medication:

1) Typical ("conventional") antipsychotics effectively control the "positive" symptoms such as hallucinations, delusions, and confusion of schizophrenia.

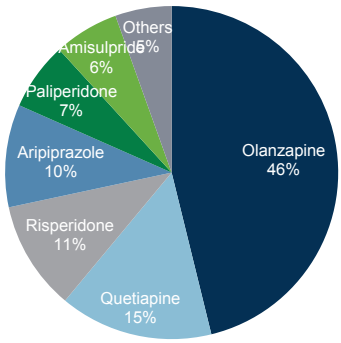
2) Atypical ("new generation") antipsychotics treat both positive and negative symptoms of schizophrenia, often with fewer side effects.

Exhibit 161: Treatment Paradigm for Schizophrenia in China

	Typical Antipsychotic 1st-generation	Atypical Antipsychotic 2nd-generation
First Developed Block Target	1950s -Dopamine receptor D2	1960s -Dopamine receptor D2 -5-HT receptor 2 -Other pathways
Lead Drugs (Recommended in 2015 China guideline for schizophrenia)	Chorpromazine (氯丙嗪) Perphenazine (奋乃静) Haloperidol （氟哌啶醇） Sulpiride (舒必利) Top 4 drugs (collectively ~82% market share)	Risperidone（利培酮） Olanzapine （奥氮平） Quetiapine（喹硫平） Aripiprazole (阿立哌唑) Ziprazidone (齐拉西酮) Clozapine (氯氮平) Sertindole (舍吲哚)
Recommend	Still used as 1st line therapy in some regions in China	1st-line: US/EU/WPA and also in China
Serious Side Effects	EPS(extrapyramidal system is sue) and TD (tardive	Less side effects

Source: Chinese clinical treatment guideline for schizophrenia

Exhibit 162: Market shares of the most common antipsychotics in 2017



Source: PDB database

The treatment paradigm for schizophrenia has shifted from the first-generation typical antipsychotic drugs to second-generation atypical antipsychotic drugs due to: 1) better efficacy, particularly in recovering impaired cognitive functions; 2) less side effects, including extrapyramidal symptoms (inability to initiate movement and remain motionless) and tardive dyskinesia (involuntary repetitive body movements, e.g. grimacing and excessive eye blinking) as induced by the typical antipsychotic drugs. Atypical antipsychotics are currently the standard medication for schizophrenia. Specifically, olanzapine, risperidone and ouetiapine are mostly used for patients with positive symptoms, while aripiprazole and ziprasidone are used for those with negative symptoms.

Mono drug is recommended by treatment guideline as the first-line treatment as most patients have a satisfactory response to mono antipsychotics at the beginning of their treatment. Olanzapine, paliperidone and amisulpride are known to both have good efficacy and a broad spectrum. If a mono therapy is ineffective, a different antipsychotics drug or a combo therapy will be considered.

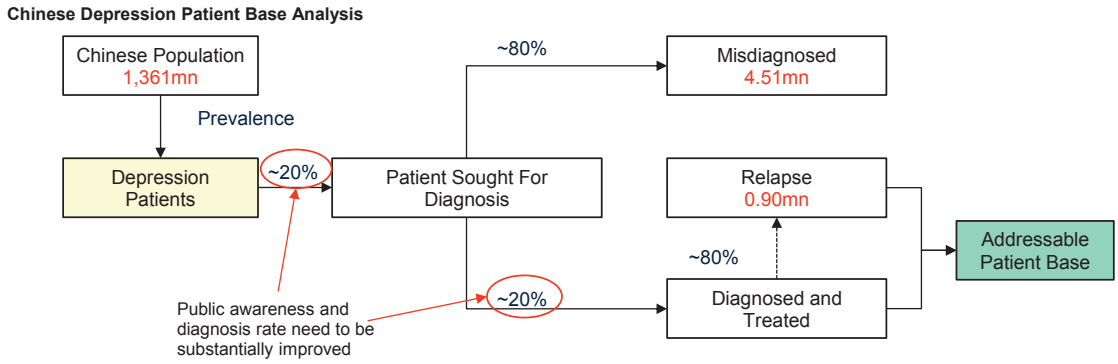
The market shares of schizophrenia drugs are relatively stable over the past five years with olanzapine accounting for ~46% market share.

Summary of depression

1) Epidemiology

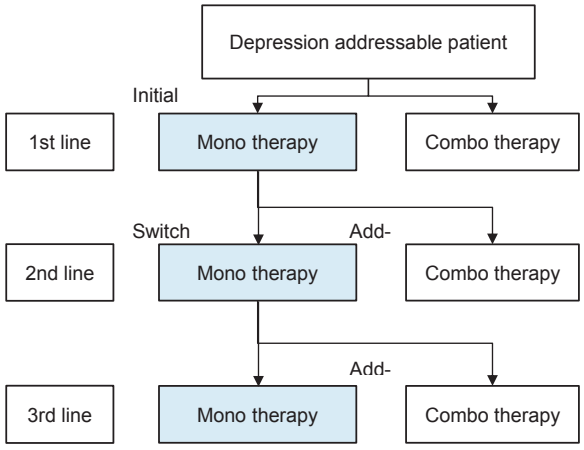
There are about 28mn patients suffering depression in China, corresponding to a prevalence rate of ~2.07% vs. only ~0.76% in 1982. Despite the notable growth in the patient base, depression remains under-treated in China. The addressable patient base for anti-depressants might be <20% of the total patient base, even considering the high recurrence rate (~80%), largely due to: 1) low public awareness of depression as a serious mental disease; and 2) the inability of Chinese physicians to diagnose the disease given their lack of sufficient training. The diagnosis rate is less than 20% in China for patients visiting hospitals for diagnosis, vs. an average of ~55.6% in 15 countries/regions in a survey conducted by WHO since 1998.

Exhibit 163: Chinese depression patient base analysis



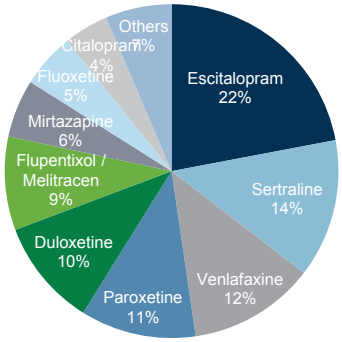
Source: Goldman Sachs Global Investment Research

Exhibit 164: Treatment flow for depression



Source: Chinese clinical guidelines for depression

Exhibit 165: Market share of major anti-depressants in 2017



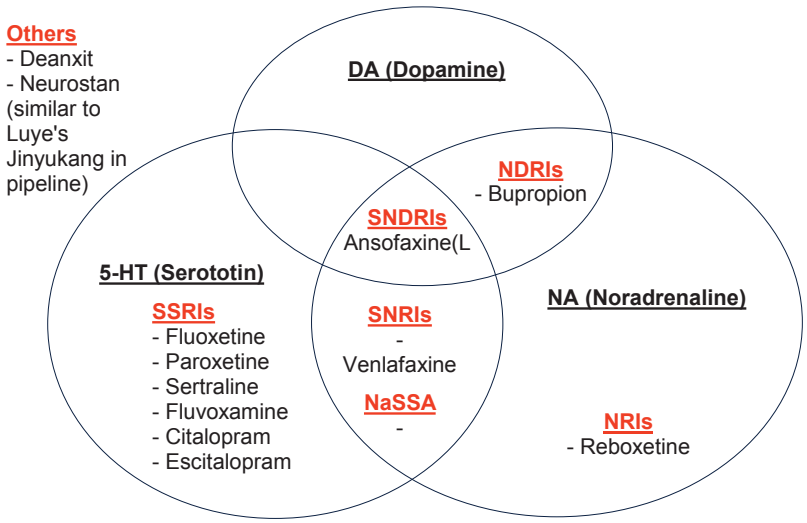
Source: PDB database

2) Treatment and major drugs' performance

The goal for depression treatment is to achieve and sustain a full remission. Medication plays a key role in the treatment and other therapies may include psychotherapy and somatic therapy. Monotherapy is recommended as the first and second line treatment by the Chinese clinical treatment guidelines of depression. Patients with depression may show drastically different onset of action of various antidepressants. If it takes too long for a drug to become effective, the patient would be recommended to combine more than one antidepressant or switch medicines.

Dependent on various mechanism of actions, current anti-depressants can be classified as selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSA), selective noradrenaline re-uptake inhibitors (NRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs) and others. Initial choice of medication should be made by considering the clinical features such as the severity and types of symptoms, the previous therapy and the presence of co-occurring disorders.

Exhibit 166: Types of anti-depressants



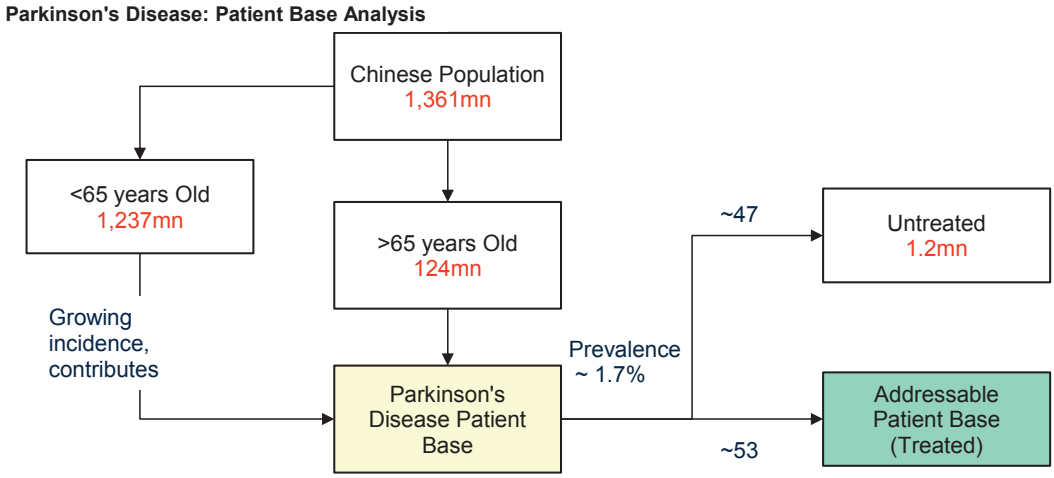
Source: Chinese Guideline for Depression (China Medical Association)

The market shares of major anti-depressants are shown in Exhibit 165. As reported in a 2018 Lancet article by Cipriani et al., escitalopram (an SSRI, originator drug Lexapro by Lundbeck was launched in 2005 and 9 generics have been approved by the CFDA since 2013) was among the most effective anti-depressants in head-to-head studies, and it has gained market share from ~10% in 2012 to ~22% in 2017 due to the launch of multiple generics.

Summary of Parkinson's diseases

Parkinson's disease (PD) is a progressive chronic disease that affects the motor system. The most well-know symptoms of PD include slowness, tremors, stiffness and postural instability.PD is more prevalent in elderly people (aged 65 years old or above). Similar to other age-related diseases, the rapid growth of the patient base for PD was primarily driven by China's aging population, although the incidence rate in the younger population is also climbing. According to a 2005 Lancet article by Zhang et al., the prevalence of PD in Chinese people aged >65 is 1.7%, or a patient base of ~2mn. Adding the extra ~500K from the younger population, we estimate the total Chinese PD patient base to be ~2.5mn, while only ~50% receive treatment. We expect further acceleration in the growth of the incidence rate of PD with the improving life expectancy in China.

Exhibit 167: Chinese Parkinson's diseases patient base analysis



Source: Goldman Sachs Global Investment Research

Exhibit 168: First-line therapies for Parkinson's disease in China

1st-line Drugs	一线用药	Lead Brand / Manufacturer
Levodopa	复方左旋多巴	Madopar (Roche)
Dopamine receptor (DR) agonist		
Pramipexole	普拉克索	Sifrol (Boehringer Ingelheim)
Rotigotine*	罗替戈汀	Neupro (UCB)
Piribedil	吡贝地尔	Trivastal Retard (Servier)
Bromocriptine	溴隐亭	Gideon Richter
MAO-B Inhibitor		
Selegiline	司来吉兰	Bdepryl (Orion)
COMT inhibitor compound		
Entacapone	恩他卡朋	COMTan (Novartis)
Tolcapone	托卡朋	Sendening (Huakang Pharma)
For patients with tremors as major symptoms		
Amantadine	金刚烷胺	Jangsu Pengyao Pharma
Trihexyphenidyl	苯海索	Kangpu Pharma

* Not marketed in China yet

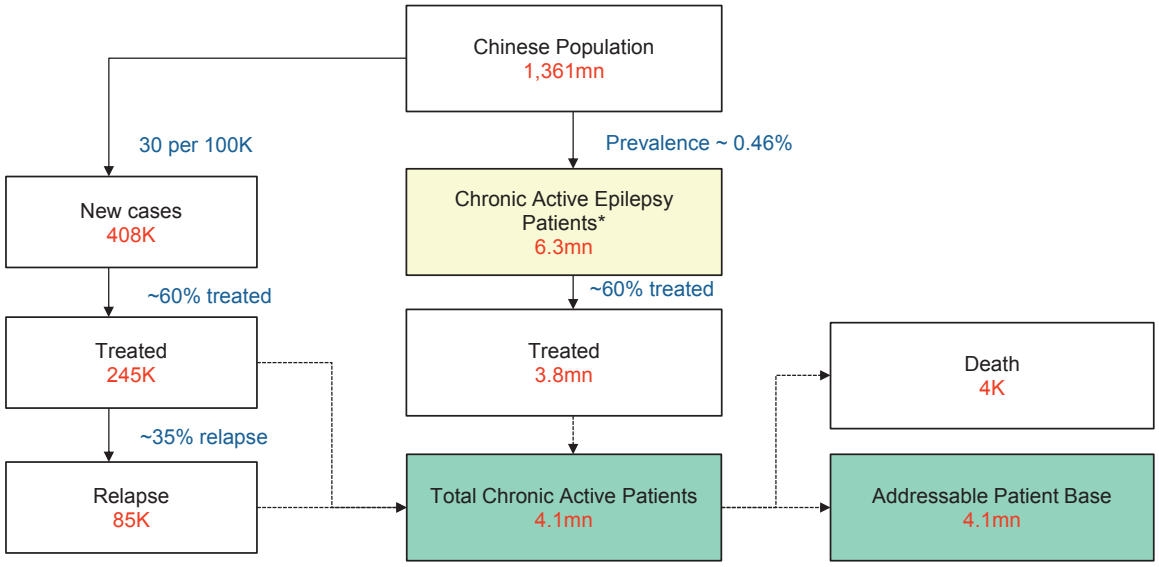
Mostly Recommended

Source: Insight database

Summary of epilepsy

Epilepsy cannot be cured, but the seizures, which are the major symptom of epilepsy, could be controlled in ~70% of patients with appropriate medications. There are ~9mn epilepsy patients in China, with ~6mn as active (on medicine or had seizures during the past three months). Considering the low treatment rate (~40%) and high relapse rate (>35%) for new epilepsy cases, we estimate the total addressable patient base for antiepileptic drugs is ~4mn in China.

Exhibit 169: Chinese epilepsy patient base analysis



Source: Goldman Sachs Global Investment Research

The key growth driver for the market could be the improving treatment rate for epilepsy patients, supported by:

- Educational projects initiated by the government: The former Ministry of Health started the prevention and management of epilepsy in rural areas in 2000, and the phase two project was started in 2006, focusing on training rural doctors for diagnosis and treatment of epilepsy. Besides, a growing number of "epilepsy centers" were set up in Class 2/3 hospitals.
- Improving government funding to epilepsy treatment: The former Ministry of Health set up a dedicated charity fund for epilepsy treatment in 2013 with initial fund size of Rmb10 mn. Though the fund size remains small, it might signal potentially more resources down the road for epilepsy.
- Major disease insurance to enhance reimbursement: Epilepsy was included into the major disease insurance catalog in 2012, and we expect the reimbursement rate for epilepsy to gradually improve, with the expansion of the major disease insurance trials in the coming years (government targets to cover all province by end-June 2014).

Pipeline analysis

Despite the substantial impact of mental disorders on modern societies, there is still much room for R&D into CNS diseases by Chinese pharma companies. For example, the standard treatment of schizophrenia has been the use of antipsychotic medications since the mid-1950s. However, only second-generation antipsychotics (atypical antipsychotics) were introduced in the 1990s and since then no breakthrough therapies can be found in this area. There are many challenges to develop new mechanisms of action in medications to treat CNS diseases, including the complexity of the human brain, a lack of animal models and drug approval threshold as well as relatively lower return compared to other therapeutic areas given the same amount of R&D investment. Current clinical trials summarized below are mostly at the IND stage. Only a few candidates are at phase III and they are not fundamentally different from state-of-the-art drugs.

Exhibit 170: Pipeline of CNS disease drugs

Candidates	Company	Type	China Status	Global Status
Schizophrenia / Bipolar Disorder				
Iloperidone	CSPC	Chemical	NDA filed	US FDA approved Vanda's Fanapt in 2009
Latuda (Lurasidone)	Dainippon Sumitomo	Chemical	NDA filed	US FDA approved in 2010
Olanzapine / Fluoxetine	PharmaMax	Chemical	NDA filed	US FDA approved Eli Lilly's Symbyax in 2003
Risperidone microspheres (LY03004)	Luye	Chemical	Ph3	US FDA approved JNJ's Risperdal Consta in 2003
Vraylar (Cariprazine)	Allergan	Chemical	IND approved	US FDA approved in 2015
DSP-5423P (Blonanserin)	Dainippon Sumitomo	Chemical	IND approved	Japan PMDA approved in 2008
TPN672	SIMM	Chemical	IND approved	-
Asenapine	Kelun	Chemical	IND approved	US FDA approved Allergan's Saphris in 2009
Depression				
Desvenlafaxine	Hansoh	Chemical	NDA filed	US FDA approved Pfizer's Pristiq in 2008
Vilazodone	Hansoh	Chemical	Ph3	US FDA approved Allergan's Viibryd in 2011
Ansofaxine	Luye	Chemical	Ph2	-
Haloperidone (HHT-101)	Huahai	Chemical	Ph2	-
Ammuxetine	CSPC	Chemical	Ph1	-
Esketamine	JNJ	Chemical	IND approved	NDA filed in 2018
Levomilnacipran	Huahai	Chemical	IND approved	US FDA approved Allergan's Fetzima in 2013
Rexulti (Brexpiprazole)	Otsuka / Lundbeck	Chemical	IND filed	US FDA approved in 2015
Parkinson's disease				
Neupro (Rotigotine)	UCB	Chemical	NDA filed	EU EMEA approved in 2006
Rotigotine microspheres (LY03003)	Luye	Chemical	Ph2	-
FLA	IMM, CAMS&PUMC	Chemical	Ph1	-
Istradefylline	Hengrui	Chemical	IND approved	Japan PMDA approved Kyowa Hakko Kirin's Nouriast in 2013
Safinamide	Sino Biopharm	Chemical	IND approved	EU EMEA approved Pfizer's Xadago in 2015
Alzheimer's disease				
Octahydroaminoacridine	Huayang Hightech	Chemical	Ph3	-
AZD-3293 (Lanabecestat)	Eli Lilly	Chemical	Ph3	Ph3 in the US
Oligo-Mannurarate	Greenvalley	Chemical	Ph3	-
Phenchlobenpyrrone	Shipurui	Chemical	Ph2	-
L-Clausenamide	Huanghai	Chemical	Ph2	-
AD-35	Hisun	Chemical	Ph1	-
AD16	SCCIP	Chemical	IND approved	-
Donepezil / Memantine (Extended release)	Hansoh	Chemical	IND approved	US FDA approved Actavis's Namzaric in 2014
Gantenerumab	Roche	Biological	IND filed	Ph3 in the US
Crenezumab	Roche	Biological	IND filed	Ph3 in the US
CNP520	Novartis / Amgen	Chemical	IND filed	Ph3 in the US
HHT-201	Huahai	Chemical	IND filed	-
Epilepsy				
Divalproex	PKU Healthcare	Chemical	NDA filed	US FDA approved Abbott's Depakote in 1996
Vimpat (Lacosamide)	UCB	Chemical	NDA filed	US FDA approved in 2008
Stiripentol	SSY	Chemical	Ph1	EU EMEA approved Biocodex's Diacomit in 2007
DP-VPA	Nhwa	Chemical	Ph1	-
Fycompa (Perampanel)	Eisai	Chemical	Ph3	EU EMEA approved in 2012
Levaoxiracetam	Medisan	Chemical	IND approved	-
Clobazam	Kehui	Chemical	IND approved	US FDA approved Lundbeck's Onfi in 2011
Valproic Acid	Sanofi	Chemical	IND approved	US FDA approved AbbVie's Depakene in 1978
Fosphenytoin	Aosaikang	Chemical	IND approved	US FDA approved Parke Davis's Cerebyx in 1996
Tiagabine	Haiwangfu	Chemical	IND approved	US FDA approved Cephalon's Gabitril in 1997
Rufinamide	CR Pharma	Chemical	IND approved	US FDA approved Eisai's Banzel in 2008
Briviact (Brivaracetam)	UCB	Chemical	IND approved	US FDA approved in 2008
Eslicarbazepine	Shanghai Pharma	Chemical	IND approved	EU EMEA approved Eisai's Zebinix in 2007

SCCIP: The South China Center for Innovative Pharmaceuticals
IMM, CAMS&PUMC: The Institute of Materia Medica at Chinese Academy of Medical Sciences and Peking Union Medical College
SIMM: Shanghai Institute of Materia Medica

Source: FDA, Insight database

AMD In China

4.4Mn Total patient base **9.7%** Prevalence rate[1] **6.8%** Awareness rate

Most common type: dry AMD (85%~90%) , wet AMD (15%-20%)
Targeted therapies in China Lang Mu (Conbercept) , Lucentis (Ranibizumab) , Eylea (Aflibercept) , Avastin (Bevavcizumab)

1 – Among population aged over 50

Disease demographics

Age-related macular degeneration (AMD) refers to the loss of function in the macula (the central portion of the retina), partially due to aging. As the AMD incidence rate rises, AMD is expected to become one of the major factors leading to blindness among people that are over 50 years old. In China, there are over 40mn Chinese patients with AMD, corresponding to a prevalence rate of ~10% and about 3mn new cases per year. The prevalence rates vary significantly across countries: ~17% in the US and ~23% in Japan.

AMD is diagnosed by imaging the eyes after injections of dyes, such as fluorescein or indocyanine green, or through optical coherence tomography (OCT). These techniques can let retinal specialists assess the location and pattern of the new blood vessel growth and assist in laser photocoagulation if needed.

There are two types of AMD: 1) dry AMD, which accounts for 85%~90% of AMD, is caused by waste build-up beneath the retina, with 10%-20% progressing to wet AMD, 15%-20% becoming blind, and no therapy currently approved for dry AMD; 2) wet AMD (wAMD), or exudative AMD, accounts for the remaining 10%-15%, which occurs when waste blocks the nutrients supplied to the retina and new blood vessels grow under the retina. wAMD can progress relatively rapidly, with 80%-90% of patients ultimately becoming blind. In China, there are about 4.5mn wAMD patients and 450k new cases each year.

Exhibit 171: ~77k patients on anti-VEGF therapies in China
AMD disease model

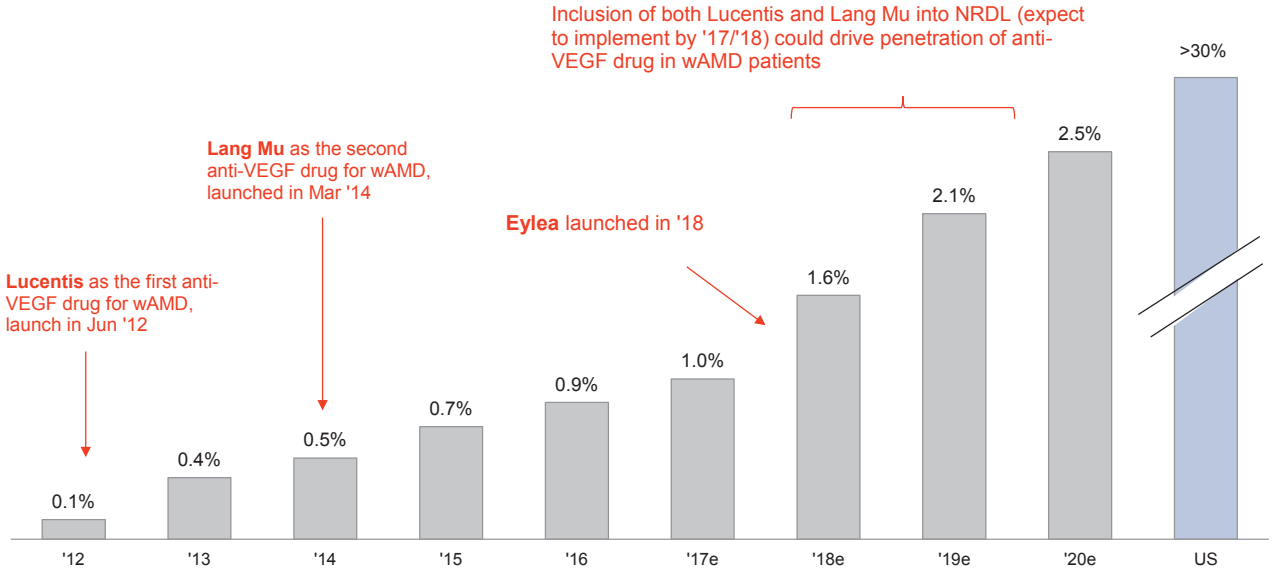
	Unit	2012A	2013A	2014A	2015A	2016A	2017E	2018E	2019E	2020E
AMD (Age-related macular degeneration)										
Total AMD patients	million	27	29	31	34	37	41	44	48	52
Prevalence	*%*	*7.6%*	*8.0%*	*8.4%*	*8.8%*	*9.3%*	*9.7%*	*10.2%*	*10.7%*	*11.3%*
Total wet AMD (exudative) patients	**'000**	**2,614**	**2,892**	**3,204**	**3,556**	**3,948**	**4,388**	**4,878**	**5,415**	**5,999**
Prevalence	*%*	*0.7%*	*0.8%*	*0.9%*	*0.9%*	*1.0%*	*1.1%*	*1.1%*	*1.2%*	*1.3%*
as % of total AMD	*%*	*9.8%*	*10.0%*	*10.2%*	*10.4%*	*10.6%*	*10.8%*	*11.0%*	*11.3%*	*11.5%*
New wet AMD patients	**'000**	**248**	**277**	**312**	**352**	**391**	**440**	**490**	**538**	**584**
Total patients on anti-VEGF therapies	**#**	**3,343**	**11,570**	**16,922**	**26,011**	**35,120**	**45,667**	**77,329**	**114,515**	**151,008**
Penetration rate	*%*	*0.1%*	*0.4%*	*0.5%*	*0.7%*	*0.9%*	*1.0%*	*1.6%*	*2.1%*	*2.5%*
- Anti-VEGF therapy naive patients	#	3,343	10,567	13,451	20,934	27,317	35,131	63,629	91,316	116,653
% of patients on anti-VEGF	*%*	*100.0%*	*91.3%*	*79.5%*	*80.5%*	*77.8%*	*76.9%*	*82.3%*	*79.7%*	*77.2%*
Penetration in new wet AMD patients	*%*	*1.3%*	*3.8%*	*4.3%*	*5.9%*	*7.0%*	*8.0%*	*13.0%*	*17.0%*	*20.0%*
- Treated patients	#	-	1,003	3,471	5,077	7,803	10,536	13,700	23,199	34,354
% of patients on anti-VEGF		*0.0%*	*8.7%*	*20.5%*	*19.5%*	*22.2%*	*23.1%*	*17.7%*	*20.3%*	*22.8%*
% of previous year treated patients stayed on trea		*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*	*30.0%*
Market share - by # of patients										
- Conbercept (Lang Mu)	#	-	-	3,245	9,919	17,516	24,283	41,275	59,061	75,014
Market share %	*%*	*0.0%*	*0.0%*	*19.2%*	*38.1%*	*49.9%*	*53.2%*	*53.4%*	*51.6%*	*49.7%*
- Ranibizumab (Lucentis)	#	3,176	11,108	13,170	15,572	17,077	20,835	32,961	45,376	55,306
Market share %	*%*	*95.0%*	*96.0%*	*77.8%*	*59.9%*	*48.6%*	*45.6%*	*42.6%*	*39.6%*	*36.6%*
- Bevacizumab (Avastin) - off label	#	167	463	508	520	527	548	773	916	1,057
Market share %	*%*	*5.0%*	*4.0%*	*3.0%*	*2.0%*	*1.5%*	*1.2%*	*1.0%*	*0.8%*	*0.7%*
- Aflibercept (Eylea) - approved in Feb 201	#							2,320	9,161	19,631
Market share %	*%*							*3.0%*	*8.0%*	*13.0%*

Source: Goldman Sachs Global Investment Research

The treatment method is dependent on the progression of the disease. 1) Early AMD, as characterized by multiple intermediate drusen (yellow deposits under the retina, which are 63-124 μm in diameter), or mild RPE (retinal pigment epithelium) abnormalities (such as hypopigmentation or hyperpigmentation): the recommended treatment is regular observation with no medical or surgical therapies; 2) Intermediate AMD, as characterized by numerous intermediate drusen, or at least one large drusen (with >125 μm in diameter), or geographic atrophy (not in the center of the fovea): the recommended treatment is antioxidant vitamins + minerals; 3) advanced AMD, as characterized by geographic atrophy in the center of the fovea: the recommended treatment is VEGF (vascular endothelial growth factor) therapy as the first-line treatment, and combination treatment of VEGF therapy with photodynamic therapy (PDT) as the second-line treatment.

Our estimate of anti-VEGF drugs in the treatment of AMD shows that the general penetration rate has kept growing with the launch of Lucentis, Lang Mu and Eylea in 2012, 2014, and 2018, respectively. The inclusion of Lucentis and Lang Mu into the NRDL could further boost the penetration of the anti-VEGF drugs. However, the current penetration level in the Chinese market (<2%) is notably smaller than that in the US market (>30%), which implies room for a further ramp-up in volume.

Exhibit 172: Still room for higher penetration vs. US
Anti-VEGF drug penetration level in 2012-2020E



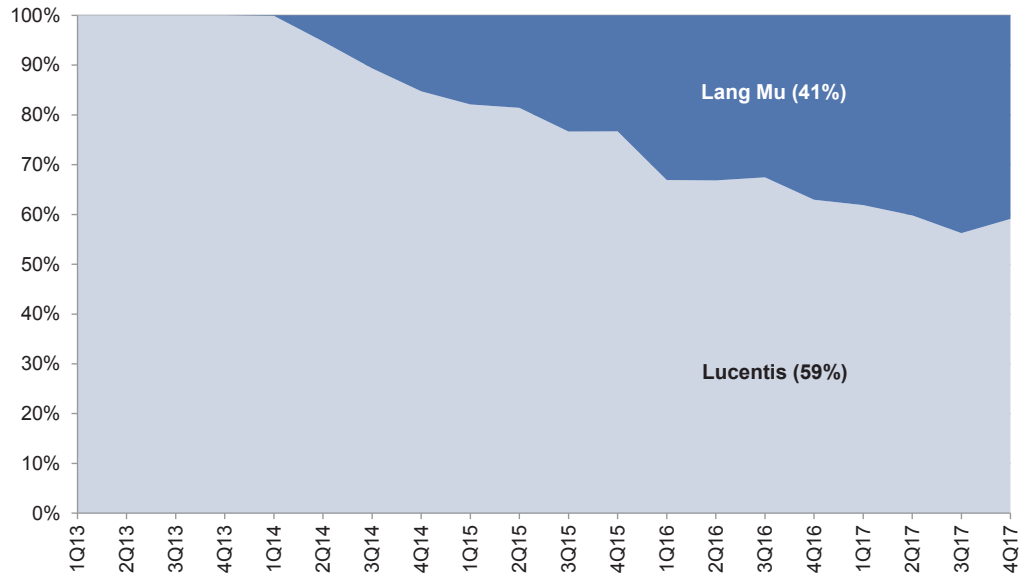
Source: Goldman Sachs Global Investment Research

Targeted therapies to highlight

There are four targeted drugs available for Chinese patients with AMD:

- **Lang Mu (Conbercept) from Kanghong:** Lang Mu, approved for wAMD in 2013 and pathological myopia choroidal neovascularization (pmCNV) in 2017, is the first AMD drug developed by a domestic Chinese company. It is included in the 2017 NRDL, and the resulting annual treatment cost is ~Rmb34k, which is around 50% less expensive than Lucentis. Lang Mu has been gaining market share from Lucentis since its launch in 2014, and it accounted for over 40% of the market share as of 2017. We expect Lang Mu to further gain market share with potential indication expansion.
- **Lucentis (Ranibizumab) from Novartis:** Lucentis's first approval by US FDA was in 2006 and five indications have been approved since, including wAMD, macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), and mCNV. It was the first CFDA-approved drug in the Chinese AMD market. We expect Lucentis's market share to further decline with faster indication expansion by Lang Mu and new market entrant Eylea.

Exhibit 173: Since its launch in 2017, Lang Mu has quickly taken market share from Lucentis
Market shares of Lang Mu and Lucentis since 2012



Source: PDB database

- **Eylea (Aflibercept) from Regeneron/Bayer:** Eylea is a fusion protein indicated in the US for wAMD, and macular edema following RVO, DME, and DR. CFDA approved Eylea for the treatment of DME in 2018, which makes Elyea the only approved drug for DME in China. The future clinical development strategy for Elyea in China is likely to seek approval for macular edema following RVO and DR ahead of its competitors.
- **Avastin (Bevavcizumab) from Roche for off-label use**: Avastin has been approved for CRC and NSCLC by CFDA, while this drug is also prevalent in the off-label treatment of wAMD. As reported in a 2011 study by NIH in the US, Avastin is equally as effective in treating AMD compared with Lucentis. The proven efficacy and attractive pricing (4% of annual treatment cost of Lang Mu) outweigh the infection risks during repackaging of Avastin into small dosages, but we expect the off-label use of Avastin to remain at a relatively low level with more indications approved for the other AMD drugs.

Exhibit 174: Comparison of available targeted therapies for wAMD

Molecule Trade name	Conbercept Lang Mu	Ranibizumab Lucentis	Aflibercept Eylea	Bevacizumab Avastin
Molecular structure	Fusion protein with domain 2 of VEGFR-1 and domains 3 and 4 of VEGFR-2 fused with IgG1 Fc	Monoclonal IgG antibody fragment (Fab)	Fusion protein with domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused with IgG1 Fc	Monoclonal IgG antibody
Molecular weight	143 kDa	48 kDa	115 kDa	149 kDa
Marketer in China	Kanghong Pharma	Novartis (licensed from Roche)	Bayer (licensed from Regeneron)	Roche
Launch				
- China	Mar 2014	Jun 2012	Feb 2018	2010
- US	Approved for Ph3 in Oct 2016	2006	2011	2004
Approved indication				
- China	wAMD (2013), pmCNV (2017)	wAMD (2012)	DME (2018)	mCRC, NSCLC, wAMD (off-label)
- US	-	pmCNV, RVO-ME, DME, DR	wAMD, pmCNV, RVO-ME, DME, DR	mCRC, NSCLC, mBC, GBM, mRCC, wAMD (off-label)
Mechanism of action and pharmacodynamics profile				
- Binding target	All isoforms of VEGF-A, VEGF-B, VEGF-C, and PlGF	All isoforms of VEGF-A	All isoforms of VEGF-A, VEGF-B, and PlGF	All isoforms of VEGF-A
- VEGF-A binding affinity	0.5pM	46pM	0.5pM	58pM
- Half-life in vitreous	4.2 days (rabbit)	2.9 days (rabbit)	4.8 days (rabbit)	5.5 days (rabbit), 6.7 days (human)
- Safety concern	Generally mild and transient adverse effects e.g. conjunctival hemorrhage and eye pain	Generally mild and transient adverse effects e.g. conjunctival hemorrhage and eye pain	Generally mild and transient adverse effects e.g. conjunctival hemorrhage and eye pain	FDA warns risk of infection due to repackaging of Avastin vials into smaller doses for wAMD treatment
Annual sales for retinal disease indications in '17				*off-label use for wAMD
China market	Rmb618mn (GSe)	Rmb1,046mn (GSe)	-	minimal due to concern on infection risk
Worldwide	US$90mn (China only)	US$1,888mn	US$5,929mn	US$140mn
Market share (by sales) for retinal disease indications in '17				
- China	41%	59%	-	minimal due to concern on infection risk
- Worldwide	minimal	23.7%	74.3%	c. 2%
Treatment cost				*off-label use for wAMD
- Wholesale price (per vial)	Rmb5,721 (0.2ml:10mg)	Rmb5,779 (0.2ml:10mg)	n/a	Rmb2,123 (4ml:100mg)
- Dosing	1 vial per month for first 3 months, then 1 vial every three months	1 vial per month	1 vial per month for first 3 months, then 1 vial every two months	Typically repackaged into 20 doses (0.05mL:1.25mg) and 1 dose per month for wAMD treatment
- Annual dosage	6.0 vials	12.0 vials	7.5 vials	0.6 vials
- Annual cost	Rmb34,329	Rmb69,351	n/a	Rmb1,274
vs. Lang Mu cost		202%	n/a	4%
- Reimbursement list	'17 NRDL (prev. Sichuan only)	'17 NRDL (prev. no reimbursement)	n/a	No reimbursement for wAMD

Glossary: wAMD: wet age-related macular degeneration; mCRC: metastatic colorectal cancer; NSCLC: non-squamous non-small cell lung cancer; mBC: metastatic breast cancer; GBM: glioblastoma multiforme; BCVA: best corrected visual acuity;

Source: Company data, Goldman Sachs Global Investment Research

Key candidates in pipeline for AMD

There are six targeted drugs in various clinical development stages for the treatment of AMD and six more just passed or have filed an IND application. All candidates are anti-VEGFR targeted therapies.

- **Lang Mu (Conbercept) from Kanghong:** As of April 2018, Kanghong expects three potential indications of Lang Mu to expand, including DME (NDA filed), BRVO (branch retinal vein occlusion, in Phase 3), and CRVO (central retinal vein occlusion, in Phase 3). It is worth noting that Lang Mu's BRVO and CRVO could be the first-to-market indications once approved. More so, the drug is currently in phase 3 clinical trials in the US.
- **Lucentis biosimilars from Qilu (QL1205), Eastern Biotech (JY025), and Huadong:** Given Lucentis's proven efficacy, several domestic companies are developing Lucentis biosimilars and attempting to enter the AMD market with minimized risk profiles. Qilu's QL1205 is the front-runner of Lucentis biosimilars and is currently under investigation in a phase 1 trial for wAMD. Eastern Biotech filed an IND application for JY025 in March 2018, and Huadong's Lucentis biosimilar is still at the preclinical stage.

- **Other potential drugs:** CM082 in Phase 1 trial from Betta is the only small molecule in the pipeline. TAB014's China rights are licensed out to Lee's pharma. Several companies filed INDs for their Avastin biosimilars with the AMD indication, including 3Sbio (601A), Eastern Biotech (JY28), and Fosun Pharma (HLX04).

Exhibit 175: Pipeline for wAMD drugs in China

Candidate	Phase	Indication	Company	Notes
Conbercept	NDA filed	DME	Kanghong	Indication expansion
	III	BRVO (branch retinal vein occlusion)		
	III	CRVO (central retinal vein occlusion)		
	III	wAMD		In the US
QL1205	I	wAMD	Qilu	Lucentis biosimilar
HB002.1M	I	wAMD	Huahai	Fc protein, Anti-VEGF antibody
TK001	I	wAMD	T-mab Biopharma	Anti-VEGF antibody
CM082 (Vorolanib)	I	wAMD	Betta	Oral drug
TAB014	I	wAMD	TOT Biopharm	Avastin biosimilar; Out-lisensed to Lee's Pharma
601A	IND passed	wAMD	3SBio	Avastin biosimilar
JY028	IND passed	wAMD	Eastern Biotech	Avastin biosimilar
JY025	IND filed	wAMD	Eastern Biotech	Lucentis biosimilar
BAT5906	IND filed	wAMD	Bio-Thera	Anti-VEGF antibody
HLX04	IND filed	wAMD	Fosun / Henlius	Avastin biosimilar
hPV19	IND filed	wAMD, DME	Stainwei	Anti-VEGF antibody
Lucentis biosimilar	Preclinical	wAMD	Huadong	Anti-VEGF antibody

Source: Insight database, Company data

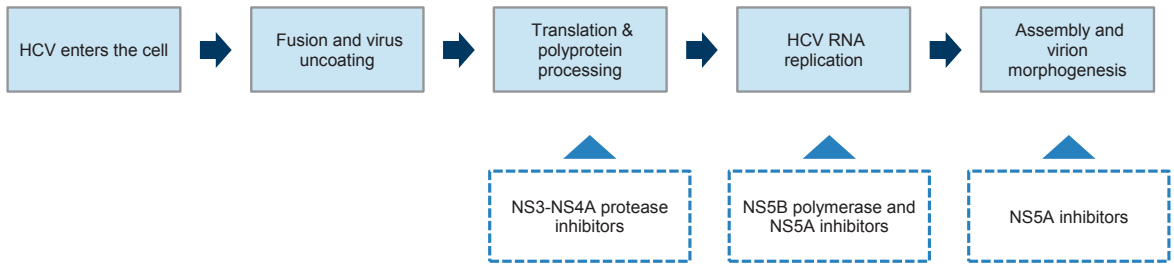
Hepatitis C In China

95.2Mn Total patient base **7%** Prevalence rate **24.7%** Awareness rate

Most common genotype: Genotype 1 (58.2%) , Genotype 2 (15.4%) , Genotype 3 (8.7%) , Genotype 6 (6.3%)
Major treatment regimens : PEGylation interferon plus ribavirin, Direct-acting anti-viral agents plus PR, Direct-acting anti-viral agents combination

Chronic hepatitis C is a disease caused by the hepatitis C virus (HCV). HCV, a kind of RNA virus, has extremely high mutation rates resulting in large variations in its nucleotide sequences. Therefore, an effective vaccine against HCV has not been discovered yet. Nevertheless, a structural gene's C region and non-structural gene's NS3, NS4 and NS5 regions are relatively conserved and play an important role in HCV replication of its life cycle, which form the basis for the development of DAA (direct-acting antiviral agents) drugs.

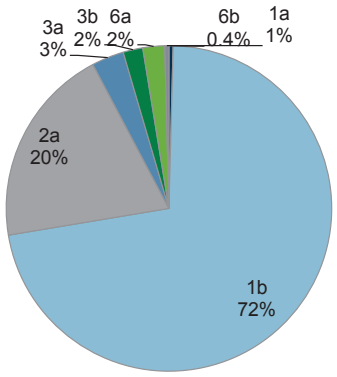
Exhibit 176: HCV life cycle and targets of DAAs



Source: Insight database

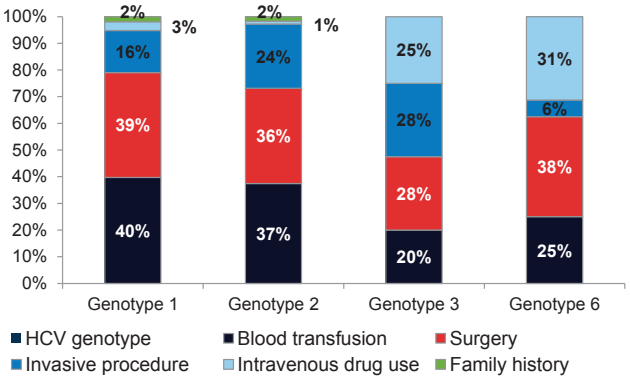
Four genotypes and seven subtypes of HCV have been detected while Subtypes 1b and 2a are still the most prevalent HCV subtypes in China. HCV genotype and subtype are related to disease progression and response to antiviral therapy. Genotypes 2, 3 and 6 have a better response to antiviral treatment while genotypes 1 and 4 have poorer responses.

Exhibit 177: Distribution of genotypes



Source: Hepatitis C virus genotype and subtype distribution in Chinese chronic hepatitis C patients: nationwide spread of HCV genotypes 3 and 6

Exhibit 178: HCV transmission cause distribution



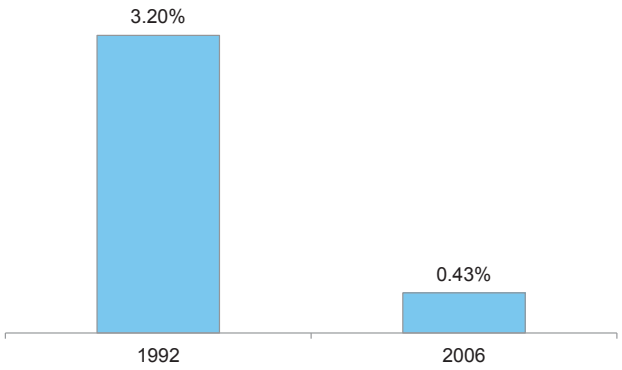
Source: Hepatitis C virus genotype and subtype distribution in Chinese chronic hepatitis C patients: nationwide spread of HCV genotypes 3 and 6

Genotypes 1 and 2 are nationally widespread, and a greater proportion of patients diagnosed with these genotypes have undergone blood transfusions and surgery. For genotypes 3 and 6, intravenous drug users account for a large portion of the patient population, and they are mostly located in the southern and southwestern areas of the country. Therefore, high-risk groups should include: Paid blood donors, transfusion and dialysis receivers, patients of unclean invasive operations and drug users from the late 1980s and early 1990s.

In the early stages, chronic infection typically has no symptoms. Over many years, complications such as liver failure and liver cancer (the main causes of death for HCV patients) come into play. Testing for HCV antibody is relatively widespread, while HCV RNA testing is mainly concentrated in the epidemiology or liver disease departments of large hospitals.

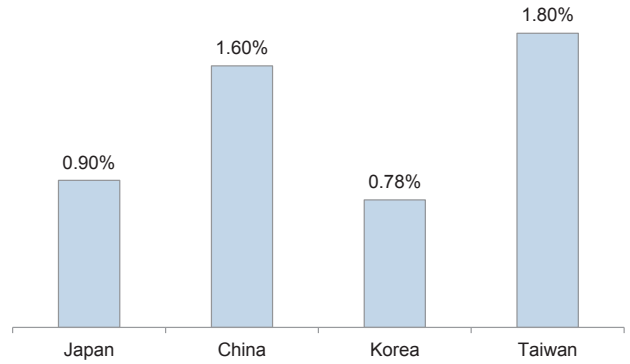
The peak of HCV infection in China came in the early 1990s. After reinforcements to the screening of blood donors and improved control of transmission originating from medical practices, the HCV infection rate has fallen significantly. The latest large-scale study of the chronic HCV infection rate in China puts it at 0.43%.

Exhibit 179: Prevalence of HCV in China in 1992 vs. 2006



Source: Treatment guideline

Exhibit 180: Prevalence among major Asian countries



Source: Hepatitis C Burden in the Asia-Pacific Region

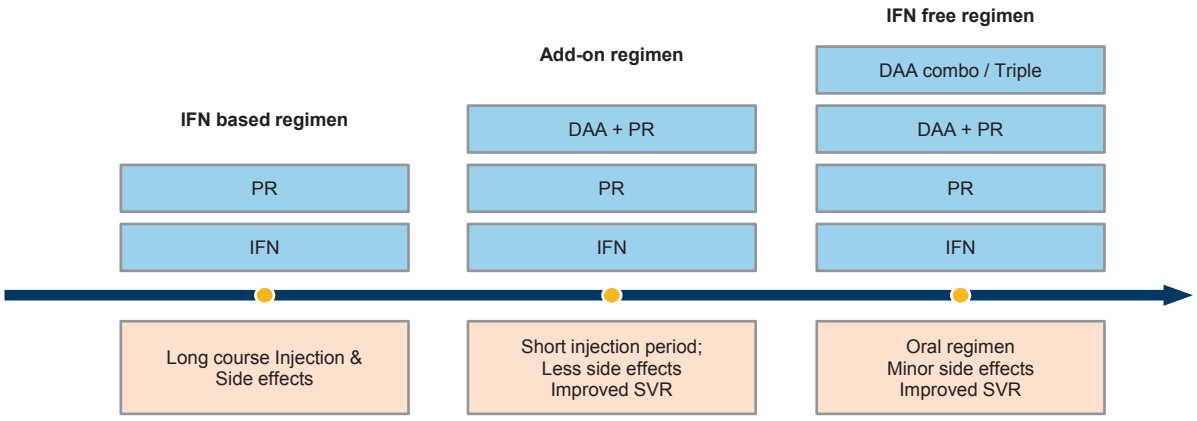
HCV prevalence varies substantially across Asian countries due to differences in nationwide medical conditions and attention from healthcare organizations.

Due to better control of transmission routes, mandatory implementation of HCV screening and an increasing cure rate, we believe there is potential for the number of HCV patients in China to trend downward.

Treatment

The standard treatment regimen is pegylated interferon combined with ribavirin. In addition, a combination of ordinary interferon and ribavirin or peginterferon monotherapy are also used. The disadvantages of standard treatment is its long duration and side-effects. In particular, some patients can not benefit from the standard therapy because of toxicity and therefore remain uncured. With more and more DAAs available in the market, we expect DAAs (including the non-interferon dependent DAA drug regimens) to meet patient needs due to their fewer side-effects and higher effective rate.

Exhibit 181: Treatment evolution after launch of DAA



Source: Insights

So far, there have been five HCV DAAs approved in mainland China: BMS's Asunaprevir soft capsule and Daclatasvir Dihydrochloride Tablets combined therapy, J&J's Simeprevir, Gilead's Sovaldi, AbbVie's ombitasvir-paritaprevir-ritonavir and Dasabuvir combined therapy of the same kind were approved for marketing by CFDA in the last year, while MSD's zepatier was just approved this year.

Exhibit 182: Current HCV nationwide therapy

Drug	Target	Company	Genotype	Duration	Efficacy	FDA approval	CFDA approval
PR (PegIFN / Ribavirin)	Traditional therapy	Roche	All	24-72w (48 avg)	50%	-	-
Simeprevir	NS3/4+PR	J&J	1	24-48w	80%	2013	8/28/2017
Sofosbuvir	NS5B+PR	Gilead	1, 2,3,4	12-24w	90%	2013	9/21/2017
Harvoni	NS5B+NS5A	Gilead	1	12-24w	90%+	2014	-
VIEKIRA PAK	NS3/4+NS5B+ NS5A+/-R	Abbive	1	12-24w	90%+	2014	9/21/2017
Dactasvir + Sofosbuvir	NS5B+NS5A+/-R	BMS/Gilead	1,3	12w	90%+	2014 (Japan, Europe)	-
Asunaprevir + Daclatasvir	NS3+NS5A	BMS	1b	24w	80%-90%	2014 (Japan, Europe)	-
Zepatier	NS3_NS5A+/-R	Merck	1,4	12-16w	90%+	2016	5/2/2018
Epclusa	NS5B+NS5A+/-R	Gilead	All	12w	90%+	2016	-
VIEKIRA XR	NS3/4+NS5B+ NS5A+/-R	Abbive	1	12-24w	90%+	2016	9/21/2017

Source: Insights

Pipeline

DAA is the main focus of HCV antiviral drug R&D. Different types of DAA drugs have different price-efficacy relationships and different drug resistance profiles.

There are three types of targets: NS3/4A, NS5B and NS5A. The only NS5B inhibitor in the market, Gilead's Solvadi, has achieved satisfying sustained virologic response (SVR). NS5A inhibitor has a resistance issue. Other disadvantages include the fact that they must be used in combination with other DAAs and can not be added to PR regimen. Of these, the NS5B inhibitor category has the greatest potential, and globally there is no second NS5B inhibitor in addition to Gilead's (due to the high barriers of development and production technology). So far, sofosbuvir's generic has not made any progress, but became the focus of local companies. As Gilead's patent is expected to expire in 2024, we believe local companies may begin to actively target this.

For NS3/4 inhibitors, Gingko Pharma is the first local company to make an IND application. However, Ascletis's ASC08 (licensed from Roche and Presidio Pharmaceuticals) has made fast progress in clinical trials and has already completed phase III trials – though it needs to be combined with Ritonavir (Abbvie) to increase the plasma concentration. Another candidate, ASC16 (an NS5A inhibitor) must be combined with Ribavirin (due to this kind of target's high rate of resistance) in order to achieve a satisfactory SVR. Hecpharm's candidate is licensed from Taiwan's Taigen Biotechnology and is still in the early stages of development.

For NS5A inhibitors, there are four local companies remaining in the clinical trial stage. ASC16 was licensed from Presidio of the US while both Beijing Kaiyin and Changzhou

Yinsheng Pharm have been authorized by Wuxi Apptec. A clinical study has found that NS5A inhibitor's unique structure can easily lead to high levels of resistance. In order to reduce the risk of resistance selection, NS5A inhibitors can be used in combination with other DAAs.

Exhibit 183: MNC development of DAAs

Company	China status	Target	Administration
Gilead Sciences	Marketed	NS5 inhibitors	PO
Merck & Co	Marketed	NS5+NS3/4 inhibitors	PO
Gilead Sciences	Marketed	NS5 inhibitors	PO
Medivir	Marketed	NS3/4 inhibitors	PO
Abbvie	Marketed	NS5+NS3/4 inhibitors	PO
AbbVie / Enanta Pharmaceuticals	Marketed	NS5+NS3/4 inhibitors HIV protease inhibitors	PO
AbbVie	Marketed	NS5 inhibitors	PO
Bristol-Myers Squibb	Marketed	NS5 inhibitors	PO
Roche	Phase III	NS3/4 inhibitors	PO
Beijing Kawin Technology	Phase III	Immunostimulants	SC

Source: Insights

Exhibit 184: Local clinical trials progress

Target	Drug	Company	China status
NS3/4 inhibitor	Seraprevir	Ginkgopharma	Phase II / III
	TP-168	Shanghai Tangrun Pharm	Phase I
	Kangdaprevir	HEC Pharm	Phase I
NS5A	Yimitasvir	HEC Pharm	Phase II
	KW-136	Beijing KaiYin Pharm	Phase III
	ASC16	Ascletis	Phase II
	福比他韦	WuXi Apptec	Phase II

Source: Insights

Appendix

- Valuation methodologies for biotech companies
- HK listing rule changes for pre-revenue biotech companies
- Pipeline by company
- Pipeline by target
- Glossary

Valuation methodologies for biotech companies

Valuation methodologies for biotech companies

Stock performance of biotech companies can change dramatically when these companies successfully launch their products from pipeline, or fail critical/pivotal clinical trials, making investing in biotech companies a rather risky proposition. Therefore, it is crucial for investors to understand how a biotech company can be valued, and thus make prudent decisions. Valuing a biotech company can be complex, as we need to account for expected revenue from existing products and the return from multiple R&D projects, while the company under consideration may be thinking about commencing an investigation into new platform technology, forming a strategic alliance, or entering into licensing agreements. However, traditional valuation metrics can be difficult to apply when valuing biotech companies, particularly those at the pre-commercial stage without marketed products to generate revenue and profit in the short term. Below we discuss several valuation matrices that could be considered in assessing Chinese biotech companies at different stages.

Risk-adjusted discounted cash flow (DCF)

Risk-adjusted DCF is one of the most widely used valuation methodologies for biotech companies, particularly for companies at the pre-revenue/loss making stage as they cannot be valued by applying earnings/revenue based market comparable multiples (e.g., P/E, PEG, P/S). While sharing the basis of traditional DCF (i.e., discounts the value of future free cash flows back to the present), risk-adjusted DCF incorporates: 1) the sales forecast of the products still in the pipeline; 2) estimated time for product launch and 3) the probability of the drug candidates in the pipeline being approved (i.e., the risk factor to be reflected in valuation).

Future free cash flow estimates are based on an understanding of the sales potential of drugs in the pipeline, profitability, capex and potential financing activities:

- **Sales forecasts:** In most cases, we only evaluate the sales potential of drug candidates that have already entered the clinical development stages, given that the risk for preclinical candidates is still too high and they may not enter in-human trials. The sales potential of a drug candidate is assessed by examining the addressable patient base, penetration, competition and treatment costs:
  - **Addressable patient base:** Using disease epidemiology data (prevalence, i.e. total existing patient base; incidence, i.e. new cases per annum; diagnosis rate) from published surveys and feedback from physicians, we can derive a total patient base. We can then narrow down the number to a more accurate addressable patient base following the indication that the investigational drug is targeting, e.g. icotinib, the first-line EGFR TKIs, only applies to a subgroup of lung cancer patients, i.e. non small cell type (85% of total lung cancer), EGFR mutated (30%-40%) and advanced/metastatic stage (~50%).

- **Penetration rate:** Defined by treatment rate and the competition from alternative therapies. Affordability (cost and reimbursement) and clinical outcome (efficacy and safety) affects the penetration rate. The penetration rate of similar products in China and the overseas market could be benchmarked.
- **Treatment cost:** Calculated using single dose price, dosing frequency and average treatment duration. The pricing of new therapies is likely to be comparable to the current standard-of-care treatment. For Chinese biotech companies, which strive to provide more affordable therapies to Chinese patients, their products, if approved, are likely to be priced at a discount to MNC competitors in China. We would like to remind investors that the price tags of drugs usually show the retail price in most cases. Considering the "zero drug mark-up" policy implemented at hospitals (i.e., the hospital purchase price is the same as the retail price), value-added tax (3% for biologics and oncology drugs, 16% for the rest) and distributor mark-ups (in the high single digits to low teens) need to be deducted when estimating the ex-factory price.
- **Patents:** We also would like to highlight that sales forecasts will also be affected by the protection period covered by the patent. Patent expiry will trigger potential entry of lower-priced generics into the market, leading to market share loss of the originator drug.

- **Margin estimates:** Biotech drugs are high-margin products that can potentially generate net margin above 30%.
  - **Gross margin:** Could be over 85%: Kanghong's conbercept, anti-VEGFR antibody at 88% in 2017; 3SBio's Yisaipu, fusion protein, at over 90%; Betta Pharma's novel anti-cancer drug icotinib at 95%. However, the gross margin could be lower in first 1-2 years before the capacity utilization picked up, and the it could take longer for biologics manufacturing to reach a stable status.
  - **SG&A expenses ex. R&D:** A direct sales model is likely to be the mainstream model for biotech companies, as academic-based marketing needs to be conducted to drive the patient penetration and physicians' recognition of the novel therapies. Selling expenses as a percentage of sales under a direct sales model in China could be in the range of 35%-45%, with G&A as 5%-10% of sales.
  - **R&D:** R&D expenses highly relate to: 1) the number of ongoing projects; 2) the development stages of those projects, i.e., the later the stage (e.g. phase III trials), the higher the cost; 3) targeted disease and sample size, trials on oncology drugs are probably the most expensive ones.
  - **Tax rate:** Biotech companies that are designated as high-tech companies qualify for a 15% tax rate, which can be further reduced/exempted for a period of time due to favorable policies from local government to facilitate the development of the biotech industry across China.

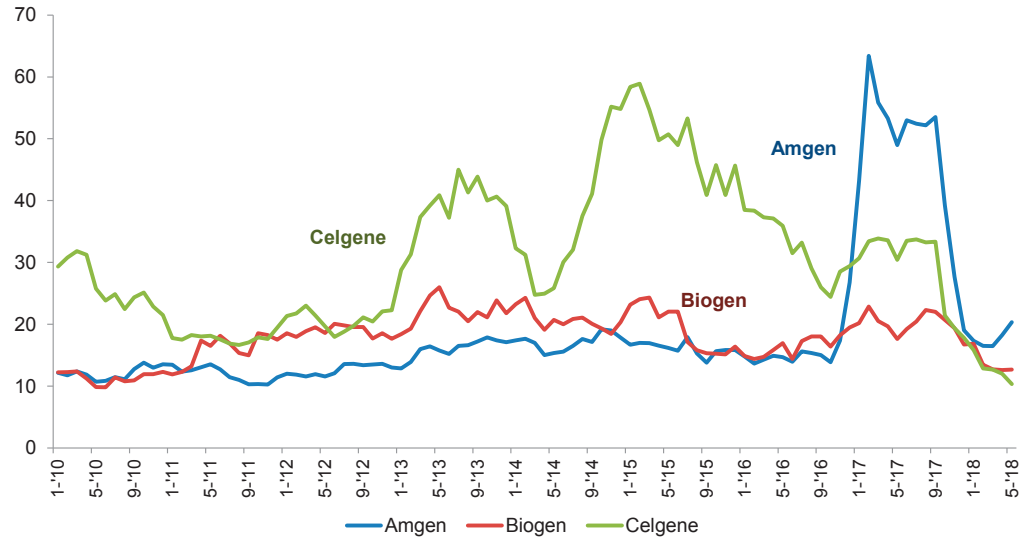
- **Risk factor (probability of success):** In general, the earlier the development stage, the higher the risk the drug candidate will fail. Historical success rate for novel therapies in different therapeutic areas or in different modalities (e.g., antibodies, small molecules) can be used as benchmarks, while data from clinical trials are key to assessing risk.
- **Discount factor and terminal growth:** Discount factor of 10%-15% and terminal growth of 1%-3% could be applied to derive a reasonable valuation range.

Despite a wide application of risk-adjusted DCF for biotech valuation, there are limitations: 1) the DCF method usually yields negative results for early-stage projects, which may not reflect the correct value of these projects; 2) the parameters in DCF (discount rates, success rates, peak sales, etc.) can be questionable and subject to many assumptions; 3) a thorough discussion of key assumptions (sensitivity analysis) can lead to a set of numbers that may vary significantly in terms of values; and 4) the results may refuse comparison among different companies.

P/E and PEG

Relatively mature and profitable biotech companies can be valued using multiples, such as P/E and PEG. Large-cap biotech companies in the US, such as Amgen, Biogen and Celgene, are trading at 10X~20X P/E multiples and -0.3X~0.3X PEG multiples, vs. 14X P/E and 0.1X PEG for the S&P 500. The comparison suggests the valuation of big biotech companies is quite aligned with large-cap companies in other sectors from the standpoint of P/E and PEG multiples.

Exhibit 185: Forward P/E change since 2010 for major US biotech companies



Source: Bloomberg

P/S or multiples of sales

There are other possible approaches for valuation of biotech companies. Sales multiples could be a "back-of-the-envelope" assessment for biotech companies, based on: 1) the estimated peak sales of core products in pipeline; and 2) a sales multiple (1-year forward) of 3X-10X, which is the range of P/S for HK-listed pharma/biotech names in the past three years (3Sbio, CSPC, Sino Biopharm, Luye, Livzon, Fosun Pharma, SSY, HEC Pharma, Lee's Pharm).

HK listing rule changes for pre-revenue biotech companies

On February 23, the Hong Kong Exchange (HKEX) released a consultation paper on the listing regime for companies in emerging and innovative sectors, highlighting pre-revenue biotech as one of the key focus areas in the new proposal to enhance listing rules in Hong Kong. The new rules became effective on May 1, opening the doors for pre-revenue Chinese biotech companies, i.e. R&D-driven biotech start-ups without commercialized products but with only one or a few products in pipeline, to be listed in Hong Kong. Prior to the advent of these new rules, a Nasdaq listing in the US was probably the best option for those companies (e.g., BGNE and ZLAB). We believe this new listing framework could result in the cultivation of a new biotech segment in the Hong Kong-listed healthcare space, thereby opening a new chapter for investment in China's healthcare sector.

Exhibit 186: New HKEx listing framework paves way for pre-revenue biotech IPOs
Key Hong Kong listing requirements for pre-revenue biotech

Core Products & R&D	*Investors, IPO & Financials*
● Core product beyond concept stage # *Novel small molecule drugs / biologics*: phase I trial(s) completed, no objection from regulators to commerce phase II # *505(b)(2) products* / biosimilar / class II/III medical device (incl. diagnostics)*: at least one in-human trial ● Regulated by competent authority: FDA (US), CFDA (China), EMA (EU), case-by-case for others ● Patented IP ● >12 months R&D of core products (in current line of business for > 2 years)	● Market cap ≥ 1.5bn (~US$190mn) ● Meaningful investment from sophisticated investors for at least 6 months before IPO (must remain at IPO) ● Working capital (post-money) ≥ 125% of group's cost for next 12 months ● IPO purpose: raise capital for R&D to bring the core product(s) to commercialization ● Risk management: acclerated de-listing process, stock marker "B", etc.

*: 505(b)(2) - a special FDA approval pathway for innovative formulations

Source: HKEx

Pipeline by company

Exhibit 187: Pipeline by company - part 1

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress
	Hengrui (600276.SS)					
B	PEG-G-CSF (19K)	Injections	Bone marrow stimulation	CIN	CN	Refiled, PR
	Retagliptin (SP2086)	Tablets	DPP-4 inhibitor	Type II diabetes	CN	To refile; + metformin
	Remimazolam (HR7056)	Injections	GABA(A) receptor agonist	Sedation+anesthesia	CN	
B	Camrelizumab (SHR-1210)	Injections	PD-1 mAb	cHL	CN	
				HCC		2L
				NSCLC		1L/2L
				ESCC		2L
				ED-SCLC		2L
				PLC		2L
				ENKL, nasal type		2L
				NPC		1st-line, +GP
	Pyrotinib (SHR1258)	Tablets	Irreversible pan-ErbB (HER) inhibitor	HER2+ m BC	CN	+ cap vs. placebo
				HER2+ m BC		+ cap. vs. lapatinib+cap.
				HER2+ NSCLC		3rd+ line
				HER2+ m BC		
				HER2+ m BC		+ capecitabine
				HER2+ gastric cancer		mono+combo+docetaxel
				HER2+ solid tumors		US Ph 1
	Famitinib (SHR1020)	Capsules	c-Kit + VEGFR2 + PDGFR + VEGFR3	CRC	CN	3rd-line
				NSCLC		+ docetaxel
						3rd/4th-line
				GIST		2nd-line
				GEP-NETs		1st/2nd-line
				RCC		1st/2nd-line, vs. sunitinib
				NPC		3rd+ line
				Pulmonary fibrosis (IPF)		
	Henagliflozin (SHR3824)	Tablets	SGLT-2 inhibitor	Type II diabetes	CN	
				Type II diabetes		+ metformin
	Hetrombopag Olamine	Injections	c-mpl (TpoR)	Chronic ITP	CN	
	SHR3680	Tablets	2nd-gen AR antagonist	mCPRC	CN	
				mCPRC		Ph1/2, Australia
B	BP102	Injection	VEGF (Avastin biosimilar)	NSCLC	CN	
	SHR-4640	Tablets	URAT 1 inhibitor	Gout, hyperuricemia	CN	
	SHR0302	Tablets	JAK inhibitor	RA	CN	Placebo-controlled
	SHR6390	Tablets	Selective CDK4/6 inhibitor	HR+ / HER- advanced BC	CN	PhIb/II, combo + letrozole
				Advanced melanoma		
				Solid tumor		
	SHR3162	Tablets	PARP inhibitor	Solid tumors	CN	Australia
	Huanmidegib (SHR1539)	Tablets	Hedgehog pathway	Cancers (likely BCC)	CN	
B	Vunakizumab (SHR-1314)	Injections	IL17 mAb	Psoriasis	CN	
	SHR7390	Tablets	Selective MEK1/2 inhibitor	MM, CRC, NSCLC	CN	
	Fuglifam	Tablets	GRP40 agonist	Type II diabetes	CN	
	HAO472	Injections	AML1-ETO oncoprotein	M2b type AML	CN	
	M6G	Injections	μ-opioid receptor agonist	post-surgery analgesic	CN	
B	SHR-1316	Injections	PD-L1 mAb	Cancers	CN	Ph 1, Australia (Atridia)

Source: Insight database

Exhibit 188: Pipeline by company - part 2

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress
	Hengrui (600276.SS)					
	SHR-1459	Oral	BTK inhibitor	B-cell lymphoma+RA	CN	Ph 1, China
B	SHR-A1201 (T-DM1)	Injections	HER2 ADC	HER2+ BC	CN	CTA/IND obtained in Aug 2016
B	SHR-1309	Injections	Anti-HER2	Cancers	CN	CTA obtained in Feb 2017
B	SHR-A1403	Injections	cMet ADC	Liver+gastric+NSCLC	CN	US FDA IND obtained in Jan 2017
	SHR-8554	Injections	MOR (μ-opioid receptors)	Pain management	CN	US IND in Apr 2017; CTA in Nov 2017
	SHR-9146	Tablets	IDO1/TDO	Cancers	CN	US IND in May 2017, CTA in Nov 2017
	SHR-0532	Tablets	ROMK inhibitor	Hypertension	CN	CTA obtained in Dec 2017
	SHR-2042	Injections	Undisclosed	Diabetes, obese	CN	
	SHR-7280	Tablets	GnRH	Endometriosis	CN	CTA obtained in May 2018
B	SHR-1501	Injections	IL-15 mAb	Cancers	CN	
B	INS068	Injections	Basel insulin	Diabetes	CN	US FDA IND obtained in Jan 2018
B	SHR-1603	Injections			CN	IND filed Feb 2018
B	SHR 1701	Injections			CN	IND filed Feb 2018
	SHR2554	Tablets			CN	CTA obtained in May 2018
	SHR-9549	Tablets	ER, HER2	BC	CN	Jan. 2018
B	SHR-0814	Injections	Relaxin	Heart failure	CN	
B	SHR-1209	Injections	PCSK9	Hypercholesterolemia	CN	
	Fosun Pharma (2196 HK / 600196.SS)					
	Henlius - Biologics+Biosimilar					
B	Rituxan biosimilar (HLX01)	Injection	CD20	NHL (DCBCL)	CN	Priority review
				Rheumatoid arthritis	CN	
B	Herceptin biosimilar (HLX02)	Injection	HER2	BC	CN	
				Gastric cancer	CN	
B	Humira biosimilar (HLX03)	Injection	TNFα	Psoriasis	CN	
				Rheumatoid arthritis	CN	
B	Avastin biosimilar (HLX04)	Injection	VEGF	mCRC	CN	
				NSCLC	CN	
				wAMD, Diabetic retinopathy	CN	
B	HLX07	Injection	EGFR	CRC, HNC	TW	
					US	
					CN	
B	Erbitux biosimilar (HLX05)	Injection	EGFR	mCRC	CN	
				Head & Neck cancer	CN	
B	HLX06	Injection	VEGFR2	Solid tumor	CN	
					TW	
					US	
B	HLX10	Injection	PD-1	Solid tumor	CN	
					TW	
					US	
B	HLX20	Injection	PD-L1	Solid tumor	CN	
B	Perjeta biosimilar (HLX011)	Injection	HER2	BC	CN	
B	HLX08	Injection	PDGFRα, humanized	Solid tumor	CN	
B	HLX31	Injection	Bispecific (HER2+CD3)	Breast+gastric cancer	TW	
B	HLX42	Injection	ADC	N/A	TW	
B	HLX43	Injection	ADC	N/A	TW	
B	HLX44	Injection	ADC	N/A	TW	

Source: Insight database

Exhibit 189: Pipeline by company - part 3

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress
	Fosun Pharma (2196 HK / 600196.SS)					
	Other					
B	Insulin Lispro	Injection	Ultra-short acting insulin	Diabetes	CN	
B	Insulin Glargine	Injection	Long-acting insulin	Diabetes	CN	
B	Human insulin 30R	Injection	Premixed insulin	Diabetes	CN	from Biocon
B	Human insulin R	Injection	Short-acting insulin	Diabetes	CN	from Biocon
B	Human insulin N	Injection	Intermediate-acting insulin	Diabetes	CN	from Biocon
	Fotagliptin (FCN-005)			Metabolism, Alimentary tract	CN	
	FC-110			Cancer	CN	
	FC-102			Cancer	CN	
	PA-824	Tablet		Anti-infective	CN	
	FN-1501	Injection		Leukemia	US	
					CN	
B	Liraglutide	Injection	GLP-1	Diabetes	CN	
	FCN-437c	Capsule		BC	CN	
	FKC876 (Yescarta)	Injection	CD19	LBCL	CN	
	Wan-gliflozin	Tablet	SGLT-2	Type II Diabetes	CN	from Biocon
	FC-109			Metabolism, Alimentary tract	CN	
	FC-108			Cancer	CN	
	BeiGene (BGNE)					
	Zanubrutinib (BGB-3111)	Capsule	BTK	WM	Exl. CN	Pivotal vs. ibrutinib
				Treatment-naïve CLL	Exl. CN	Pivotal vs. BR
				r/r Mantle cell lymphoma	CN	Pivotal
				r/r CLL/SLL	CN	Pivotal
				WM	CN	Pivotal
				r/r DLBCL	CN	
				B-cell malignancies	Global	Ib
				r/r FL	Exl. CN	Pivotal+G vs. G
				B-cell malignancies	Exl. CN	Ib + G
				Hematological tumors	Exl. CN	Ib + A317
B	Tislelizumab (BGB-A317)	Injection	PD-1	2L NSCLC	Global	Pivotal
				1L Hepatocellular carcinoma	Global	Pivotal
				2L ESCC	Global	Pivotal
				2L+ Hepatocellular carcinoma	Global	
				r/r NK/T-cell lymphomas	Global	
				r/r Hodgkin lymphoma	CN	Pivotal
				2L+ Urothelial carcinoma	CN	Pivotal
				Solid tumors	Global	Ib
				Solid tumors	Exl. CN	Ib + BGB-290
				Hematological tumors	Exl. CN	Ib + BGB-3111
				Solid tumors	Exl. CN	Ia +/- BGB-A333
	Pamiparib (BGB-290)	Capsule	PARP1/PARP2	3L gBRCA+ ovarian cancer	CN	Pivotal
				Solid tumors	Exl. CN	
				Solid tumors	Exl. CN	Ia + TMZ
				Glioblastoma	Exl. CN	Ia + Radiation / TMZ
				Solid tumors	Exl. CN	Ib + BGB-A317
	Lifirafenib (BGB-283)	Capsule	RAF Dimer	B-Raf- or K-RAS/N-RAS-mutated solid tumors	CN	
					Exl. CN	
	BGB-A333	Injection	PD-L1	Solid tumors	Exl. CN	Ia +/- BGB-A317

Source: Insight database

Exhibit 190: Pipeline by company - part 4

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress
	Tonghua Dongbao (600867.SS)					
B	Insulin Glargine	Injection	Long-acting insulin	Diabetes	CN	
B	Insulin Aspart	Injection	Ultra-short acting insulin	Diabetes	CN	
B	Insulin Aspart 50	Injection	Premixed insulin	Diabetes	CN	
B	Insulin Aspart 30	Injection	Premixed insulin	Diabetes	CN	
	Trelagliptin	Tablet	DPP-4	Diabetes	CN	
B	Humira biosimilar	Injection	TNFα	Cancer	CN	
B	Insulin Detemir	Injection	Long-acting insulin	Diabetes	CN	
B	Liraglutide	Injection	GLP-1	Diabetes	CN	
B	Insulin Lispro	Injection	Ultra-short acting insulin	Diabetes	CN	
B	Dulaglutide	Injection	GLP-1	Diabetes	CN	
	Enge-liptin	Tablet	SGLT-2	Diabetes	CN	
	GLP-1 oral drug	Tablet	GLP-1	Diabetes	CN	
	3Sbio (1530.HK)					
	Bydureon dual chamber pen	Injection	GLP-1	Type 2 diabetes	CN	
B	301S (prefilled syringes)			RA	CN	
	KW303			Acne vulgaris	CN	
B	Herceptin biosimilar (302H)	Injection	HER2	Metastatic BC, etc	CN	To refile
B	Rituxan biosimilar (304R)	Injection	CD20	Non-Hodgkin lymphomas	CN	To refile
B	NuPIAO (SSS06)	Injection	2nd-gen rhEPO	Anemia associated with CKD	CN	
B	RD001			Anemia associated with CKD	CN	
B	Erbitux biosimilar (602)	Injection	EGFR	Metastatic CRC	CN	
B	Anit-TNFα mAb (SSS07)	Injection	TNFα	Rheumatoid arthritis	CN	
B	Pegsiticase (SSS11)	Injection	Uric acid	Refractory gout	CN	
	SSS24			CRC	CN	
	AP506			Psoriatic arthritis	CN	
B	TPIAO (Indication extension)	Injection	Megakaryocyte production	Hepatic disease	CN	
				Pediatric ITP	CN	
B	601T			Cancer	CN	
B	Avastin biosimilar (601A)	Injection	VEGF, VEGFR, VEGFA	AMD	CN	
	SSS22	Injection	Topoisomerase Inhibitor	Solid tumors	CN	
B	701			Metastatic BC	CN	
	MN709			Dermatology drug	CN	
B	609A			Cancer	CN	
B	Tanibirumab (SSS23)	Injection	VEGFR2	Cancer	CN	
	SSS20			ITP	CN	
	SSS32			Auto-immune diseases	CN	
	SSS17			Anemia	CN	
	SSS18			Nephrology drug	CN	
	SSS12			Nephrology drug	CN	
	SSS13			Nephrology drug	CN	
	SSS26			Metabolic drug	CN	
B	608			Psoriasis, Rheumatoid arthritis	CN	
	610			Auto-immune diseases	CN	
	ND409			Dermatology drug	CN	
	Huadong (000963.SZ)					
B	Pegfilgrastim	Injection	G-CSF	CIN	CN	
	Mihuatinib	Injection	EGFR, HER2	NSCLC	CN	Ib/IIa
B	Liraglutide	Injection	GLP-1	Type 2 diabetes	CN	
	HD-118	Tablet	DPP-4	Type 2 diabetes	CN	
B	Insulin Detemir	Injection	Long-acting insulin	Diabetes	CN	
B	Insulin Aspart	Injection	Ultra-short acting insulin	Diabetes	CN	
B	Insulin Degludec	Injection	Ultra-long acting insulin	Diabetes	CN	
B	Lucentis biosimilar	Injection	VEGF	wAMD	CN	
	TTP273			Diabetes	CN	

Source: Insight database

Exhibit 191: Pipeline by company - part 5

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress (Preclin / IND / Ph 1 / Ph 2 / Ph 3 / NDA)
	CSPC (1093.HK)					
B	Recombinant exenatide-4	Injection	GLP-1	Diabetes	CN	
	Levamlodipine+Atorvastatin	Tablet	HMG-CoA	Hypertension, hyperlipidemia	CN	
	DBPR108	Capsule	DDP-4	Diabetes	CN	
	Butylphthalide (IE)	Soft capsule	-	Vascular dementia	CN	
				ALS	US	Orphan drug designation
	Pinocembrin	Injection	NF-κB	Acute stroke	CN	
	L-Butylphthalide	Tab. / Inj.	-	Acute stroke	CN	
	Baicalein	Tablet	GABA	Viral influenza	CN	
	SKLB1028	Oral	EGFR, FLT3, Abl	Leukemia	CN	
	Ammoxetine	EC Tablet	SLC6A2	Anti-depressant	CN	
	HA121-28	Tablet	EGFR, VEGR, RET	Esophageal, gastric cancers	CN	
	CSPCHA115	Capsule	-	Allergic rhinitis & asthma	CN	
B	Bispecific antibodies	Injection	HER2, CD3	BC, gastric cancer	CN	
B	M701	Injection	EpCAM, CD3	Cancers	CN	
	Vinorelbine tartrate liposome	Injection	TUBB	Cancers	CN	
	Alprostadil liposome	Injection	PGE2	Chronic arterial stenosis	CN	
	Mitoxantrone liposome	Injection	-	Peripheral T-cell lymphoma	US	Orphan drug designation
	DP303c	NA	HER2	Gastric cancer, GEJ cancer	US	Orphan drug designation
	CT133	Oral	CRTH2	Allergic rhinitis & asthma	CN	
	Luye (2186.HK)					
	Risperidone MS (LY03004)	Injection	5-HT2A, D2	Schizophrenia, bipolar disorder	US	
					CN	
B	Avastin biosimilar (LY01008)	Injection	VEGF	NSCLC (Ph3), CRC (Ph1)	CN	Target FY20
	Vincristine MS (LY01609)	Injection	Tubulin beta chain	Acute lymphoblastic leukemia	CN	
	Rotigotine MS (LY03003)	Injection	ADRA2B, DRD1, DRD2, DRD3, HTR1A	Parkinson's disease	US	
					CN	
	Ansofaxine (LY03005)	ER Tablet	SNDRI	Depression	US	
					CN	
	LY02405			Hypercholesterolemia	US	
	30410			Mild to moderate dementia	EU	
	Goserelin MS (LY01005)	Injection	GnRH	Prostate cancer, BC	US	
					CN	
B	Prolia biosimilar (LY06006)	Injection	RANKL	Osteoporosis	CN	Target '22 NDA
					US	
B	Exenatide MS (LY05006)	Injection	GLP-1	Diabetes	CN	
	Triptorelin MS (LY01007)	Injection	GnRH	Prostate cancer	CN	
	LY01011			Bone metastases	CN	
	Huperzine A MS	Injection	Enzyme acetylcholinesterase	Alzheimer's disease	CN	
	Evogliptin (LY05007)	Tablet	DPP-4	Diabetes	CN	In-licensed from Dong A
	Buprenorphine	Patch	Partial opioid agonist	Severe pain	CN	
	LY01610			CRC, pancreatic cancer	CN	
	LY01013		IDO / TDO	Cancer	CN	
					US	
	Rivastigmine	Patch	-	Mild to moderate dementia	DE	
					CN	
	LY-021701			Severe pain	CN	
	Poziotinib (LY01010)	Tablet	pan-HER	Cancer	CN	In-licensed from Hanmi
	Irinotecan MS	Injection	Topoisomerase Inhibitor	metastatic CRC	CN	
	LY03011			Mild to moderate dementia	CN	
	LY02404			Hypercholesterolemia	CN	
	LY03010			Schizophrenia	US	
					CN	

Source: Insight database

Exhibit 192: Pipeline by company - part 6

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress: Preclin / IND / Ph 1 / Ph 2 / Ph 3 / NDA
	Sino Biopharm (1177.HK)					
				CRC	CN	II+III
				Differentiated thyroid cancer	CN	II+III
				Soft tissue sarcoma	CN	II+III
				Medullary thyroid carcinoma	CN	II+III
				Gastric cancer, AEJ	CN	II+III
				GEP-NETs	CN	
				Renal cell carcinoma	CN	
	Anlotinib (IE)	Capsule	TKI	ESCC	CN	
				Small cell lung cancer	CN	
				Hepatocellular carcinoma	CN	
				Melanoma	CN	
				Carcinomas	CN	
				Sarcomas	US	
				Ovarian/Cervical cancer	US	I+IIa
				Carcinomas	US	I+IIa
	TQ-B3139	Capsule		Cancer	CN	
	TQ-B3234	Capsule	B-Raf	Cancer	CN	
	TQ-B3525	Tablet		Lymphoma, solid tumors	CN	
	TQ-B3233	Capsule	B-Raf	Melanoma	CN	
	TQ-B3101	Capsule		Cancer	CN	
	TQ-B3395	Capsule		Cancer	CN	
	TQ-B3203	Injection		Solid tumors	CN	
B	Coagulation factor VIII	Injection	Factor X activation	Bleeding	CN	
B	TQB2450	Injection	PD-L1	Cancer	CN	
B	Rituxan biosimilar	Injection	CD20	Cancer	CN	
B	Avastin biosimilar	Injection	VEGF	Cancer	CN	
B	Herceptin biosimilar	Injection	HER2	Cancer	CN	
B	Humira biosimilar	Injection	TNF-α	Cancer	CN	
B	Perjeta biosimilar	Injection	HER2	Cancer	CN	
B	Cyramza biosimilar	Injection	VEGFR2	Cancer	CN	
B	Liraglutide	Injection	GLP-1	Diabetes	CN	
B	Peginterferon alfa-2a	Injection	JAK, STAT	Chronic hepatitis C	CN	
	TQA3526	Tablet			CN	
	TQA3474	Injection			CN	
	TQ-A3326	Tablet			CN	
	TQ-F3083	Capsule			CN	
	TQB3455	Tablet			CN	
	TQ05105	Tablet			CN	
	TQB3616	Capsule			CN	
	TQB3456	Tablet			CN	
	TQ05510	Capsule			CN	
	TQ-A3334	Tablet			CN	
	Cabozantinib	Capsule	VEGFR, KDR, c-Met, RET	Cancer	CN	
	Tenofovir alafenemide	Tablet	Reverse transcriptase	HIV, chronic HBV	CN	
	Kanghong (002773.SZ)					
B	Langmu (KH902, IE)	Injection	VEGFR	Diabetic macular edema	CN	
				Branch retinal vein occlusion	CN	
				Central retinal vein occlusion	CN	
				wAMD	US	
B	Oncolytic adenovirus (KH901)	Injection	gm-cs	Cancer	CN	
B	Conbercept (KH903)	Injection	VEGFR	CRC	CN	Ic
B	KH906	Eye drop	VEGF	Angiogenesis	CN	
	KH110			Alzheimer's disease	CN	

Source: Insight database

Exhibit 193: Pipeline by company - part 7

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress (Preclin / IND / Ph 1 / Ph 2 / Ph 3 / NDA)
	Livzon (1513.HK / 000513.SZ)					
B	rhCG	Injection	Hormone treatment	Infertility	CN	Target FY18
B	AT132 mAb	Injection	TNFα	Cancer	CN	Taget FY18
B	Anti-CD20 mAb	Injection	CD20	Cancer	CN	
B	Anti-HER2 mAb	Injection	Her2	Cancer	CN	
B	LZM009	Injection	PD-1	Cancer	US	
					CN	
	Dantrolene	Injection	Ryanodine receptor 1	Chronic spasticity	CN	Orphan drug designation
B	Prolia biosimilar	Injection	RANKL	Osteoporosis	CN	
	Triptorelin MS	Injection	GNRHR	Prostate cancer	CN	
B	Anti IL-6R humanized mAb	Injection	IL-6R	Cancer	CN	
B	Anti OX40 humanized mAb	Injection	OX40	Cancer	CN	
					US	
B	Anti IL-17AF humanized mAb	Injection	IL-17AF	Cancer	CN	
					US	
B	Anti-HER2 ADC	Injection	Her2	Cancer	CN	
	Leuprorelin MS	Injection	GnRH	Prostate cancer	CN	
	Goserelin MS	Injection	LHCGR	Hormone-sensitive cancer	CN	
	Octreotide MS	Injection	Somatostatin receptors	Acromegaly	CN	
	Aripiprazole MS	Injection	5-HT2A	Schizophrenia	CN	
	Betta (300558.SZ)					
	X-396	Capsule	ALK	ALK+ NSCLC, 2nd-line	CN	
					US	vs. Xalkori
	CM082 (X-082)	Tablet	VEGFR, PDGFR	Renal cancer	CN	
				wAMD	US	
B	Avastin biosimilar (MIL60)	Injection	VEGF	NSCLC, 1st-line	CN	
	Icotinib (BPI-2009C, IE)	Cream	EGFR	Psoriasis	CN	
	BPI-15086	Tablet	T790M	NSCLC	CN	
	BPI-9016	Tablet	c-Met	Lung, liver, gastric cancers	CN	Ib
B	BPI-3016	Injection	GLP-1	Diabetes	CN	
	BPI-16350	Capsule	CDK 4/6	BC (HR+/HER2), Rb+ cancers	CN	
	BPI-16000			BC, tumor	CN	
	BPI-17000			Solid tumor	CN	
	BPI-18000			Solid tumor	CN	
	BPI-19000			Solid tumor	CN	
	BPI-20000			Solid tumor	CN	
	BPI-21000			Solid tumor	CN	
	BPI-22000			Solid tumor	CN	
	BPI-23000			Solid tumor	CN	
	BPI-24000			Solid tumor	CN	
	BPI-25000			Solid tumor	CN	
	BPI-28000			Solid tumor	CN	
	BPI-30000			Solid tumor	CN	
	BPI-31000			Solid tumor	CN	
	BPI-32000			Solid tumor	CN	
	BPI-33000			Solid tumor	CN	
	BPI-34000			Solid tumor	CN	
	BPI-35000			Solid tumor	CN	
	BPI-39000			Solid tumor	CN	
	BPI-40000			Solid tumor	CN	
	BPI-41000			Solid tumor	CN	
	MRX-2843			Solid tumor	CN	
	BPI-5014B			Renal failure caused anemia	CN	

Source: Insight database

Exhibit 194: Pipeline by company - part 8

	Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress
	Kelun (002422.SZ)					
B	Erbitux biosimilar (A140)	Injection	EGFR	Metastatic CRC, etc.	CN	
B	Anti-PD-L1 mAb (KL-A167)	Injection	PD-L1	NSCLC	CN	
	Irinotecan liposome (A029)	Injection	Topoisomerase Inhibitor	Metastatic CRC	CN	
B	Cyramza biosimilar (A168)	Injection	VEGFR2	Gastric cancer	CN	
B	Romiplostim (A157)	Injection	c-Mpl	ITP, CIT	CN	
	KL070002	Tablet		Solid tumor	CN	
	KL100137 fat emulsion	Injection	GABA	Anesthetic	CN	
	KL130008	Capsule	JAK	RA	CN	
B	A166 (Antibody Drug Conjugate)	Injection	HER2	BC	CN US	
	Albumin-bound paclitaxel (A026-1)	Injection	Bcl-2	Solid tumer	CN	
	Aripiprazole (A120)	Injection	5HT2A	Schizophrenia	CN	
	KL280006	Injection	KOR	Pain killer	CN	
	Docetaxel nanoparticle	Injection	TUBB1	BC	CN	
	United Lab (3933.HK)					
B	Insulin Aspart	Injection	Ultra-short acting insulin	Diabetes	CN	
B	Insulin Aspart 30	Injection	Premixed insulin	Diabetes	CN	
B	Insulin Detemir	Injection	Long-acting insulin	Diabetes	CN	
	Tenofovir	Tablet	Reverse transcriptase	Hepatitis B	CN	
	Tadalafil	Tablet	PDE5A	Erectile dysfunction	CN	
	Clopidogrel	Tablet	P2RY12	Anti-thrombosis	CN	
B	Liraglutide	Injection	GLP-1	Diabetes	CN	
B	Insulin Degludec	Injection	Ultra-long acting insulin	Diabetes	CN	
B	Insulin Aspart 50	Injection	Long-acting insulin	Diabetes	CN	
	Sitagliptin	Tablet	DPP-4	Diabetes	CN	
	Posaconazole	EC Tablet	CYP51A1	Anti-fungal	CN	
	Shanghai Pharma (2607.HK)					
	Deuteporfin	Injection		Cancers	CN	
	SPH3127	Tablet		Hypertension	CN	
	SPH1188-11	Tablet		NSCLC	CN	
B	Enbrel biosimilar	Injection	TNFα	RA	CN	
	LLDT-8	Tablet	RANKL, RANK, OPG	Rheumatoid Arthritis	CN	
B	Rituxan biosimilar	Injection	CD20	Cancer	CN	
B	Anti-CD30 mAb-MCC-DM1	Injection	CD30	Cancer	CN	
B	Anti-HER2 mAb-MCC-DM1	Injection	HER2	BC	CN	
B	Anti-HER2 mAb	Injection	HER2	BC	CN	
	SPH3348	Tablet		Lung, liver, gastric cancer	CN	
B	Avastin biosimilar	Injection	VEGF	Cancer	CN	
	WXFL50010210	Tablet			CN	
	Huahai (600521.SS)					
	Haloperidone (HHT-101)	Tablet	5-HT1A	Depression	CN	
B	Conbercept (HB002.1M)	Injection	VEGF,VEGFR	wAMD	CN	
B	HB002.1T	Injection		Advanced solid tumor	CN	
B	Humira biosimilar (HOT-3010)	Injection	TNFα	RA, AS	CN	
B	Avastin biosimilar (HOT-1010)	Injection	VEGF	CRC, lung cancer	CN	
	HHT-201			Alzheimer's disease	CN	
	Salubris (002294.SZ)					
	Salutaxel	Injection		Cancers	CN	
	S086	Tablets		Anti-heart failure	CN	
	Hybio (300199.SZ)					
	Bromocriptine	Tablets	DRDs	Diabetes	CN	
	Gloria Pharma (002437.SZ)					
B	GLS-010	Injection	PD-1	Solid tumors	CN	
	Meditinib	Tablet	BCR / ABL	Ph+ MCL	CN	

Source: Insight database

Exhibit 195: Pipeline by company - part 9

Drug candidates	Form	Mechanism of action+Target	Potential indications	Area	R&D Progress (Preclin / IND / Ph 1 / Ph 2 / Ph 3 / NDA)
HEC Pharm (1558.HK)					
B rh-INS	Injection	-	Diabetes	CN	
B rh-INS (pre-mixed 30R)	Injection	-	Diabetes	CN	
B Insulin glargine	Injection	-	Diabetes	CN	
B Insulin aspart (pre-mixed 30)	Injection	-	Diabetes	CN	
Yimitasvir	Capsule	NS5A	HCV	CN	
Furaprevir	Capsule	NS3/4A	HCV	CN	
Morphothiadine (GLS4JHS)	Capsule		HBV	CN	
Ningetinib	Capsule	c-Met	NSCLC, AML, RCC	CN	
Larotinib	Capsule	EGFR, HER2	Esophagus cancer	CN	
Yinlitinib	Capsule	EGFR, HER2	BC	CN	
Clifutinib	Capsule	FLT3	AML	CN	
Rongliflozin	Capsule	SGLT-2	Diabetes	CN	
Yifenidone	Capsule		IPF	CN	
B Insulin aspart	Injection	-	Diabetes	CN	
CT413			Solid tumors	CN	
HEC96719			Diabetes	CN	
CT365			IPF	CN	
HEC84048			HCV	CN	
HEC74647			HCV	CN	
Lee's Pharma (0950.HK)					
ZK001			Cardiovascular	CN	
ZK-012			Cardiovascular	CN	
ZK-016			Cardiovascular	CN	
ZK-014			Ophthalmology	CN	
ZK-011			Oncology	CN	
ZK-010			Oncology	CN	
ZK-013			Cardiovascular	CN	
B ZKAB001	Injection	PD-L1	Oncology	CN	licensed-in from Sorrento
ZK003			Dermatology	CN	
ZK002			Ophthalmology	CN	
ZK004			Ophthalmology	CN	
ZK-015			Dermatology	CN	
ZK-009			Ophthalmology	CN	
Changchun High & New Technology (000661.SZ)					
B Jintuoxi-mab	Injection		Solid tumors	CN	
SL Pharma (002038.SZ)					
B Humira biosimilar	Injection	TNF-α	Cancer	CN	
B Insulin aspart	Injection		Diabetes	CN	

Abbreviations:

ACC: adenoid cystic carcinoma
AEJ: adenocarcinoma of esophagogastric junction
BC: Breast cancer
BCC: base cell cancer
BR: Bendamustine+rituxumab
CIN: chemo-induced neutropenia
CIT: Chemotherapy-induced thrombocytopenia
CNS: Central Nervous System
CRC: colorectal cancer
DLBCL: Diffuse large B-cell lymphoma
ESCC: Esophageal squamous cell carcinoma
FL: follicular lymphoma
GC/GEJ: gastric and gastroesophageal junction cancers
GEP-NETs: gastroenteropancreatic neuroendocrine tumor
IE: indication expansion
ITP: idiopathic thrombocytopenic purpura
m-: metastatic
MM: multiple myeloma
NSCLC: non-small cell lung cancer
RA: rheumatoid arthritis
RCC: renal cell carcinoma
TMZ: Temozolomide
AML: acute myeloid leukemia
CIN: chemo-induced neutropenia
CLL/SLL: Chronic lymphocytic leukemia and small lymphocytic lymphoma
CPRC: castration-resistant prostate cancer
EC: Enteric-coated
ER: Extended release
G: Gazyva (obinutuzumab)
GEP-NETs: Gastroenteropancreatic neuroendocrine tumors
GIST: gastrointestinal stromal tumor
ITP: Idiopathic thrombocytopenic purpura
MS: Microsphere
NPC: nasopharyngeal carcinoma
OR: overseas application
r/r: recurrent/refractory
WM: Waldenström's macroglobulinemia

Source: Insight database

Pipeline by target

Exhibit 196: Pipeline by target - part 1

Candidates	Indication	Company	China Status	Global status
Small molecule - Cancers				
ALK				
M Alecensa (Alectinib)	NSCLC	Roche	NDA filed	Approved in Japan in 2014
M Zykadia (Ceritinib)	NSCLC	Novartis	NDA filed	Approved in the US in 2014
X-396 (Ensartinib)	NSCLC	Betta	Ph3	-
HS-10168	NSCLC	Hansoh	Ph1	-
PLB1003	NSCLC	Pearl Biotech	Ph1	-
ZL-2302	NSCLC	Zai Lab	IND approved	-
M Lorlatinib	NSCLC	Pfizer	IND approved	NDA filed in the US, EU, and Japan
RF-A089	NSCLC	Humanwell	IND filed	-
M TPX-0005 (Ropotrectinib)	NSCLC	TP Therapeutics	IND filed	Ph 1/2 in US FDA
BCL				
M Bosulif (Bosutinib)	CML	Pfizer	Ph3	Approved in the US in 2012
Fuma-tinib	CML	Hansoh	Ph3	-
AT-101	CLL	Ascentage / Ascenta	Ph2	-
APG-1252	SCLC	Ascentage	Ph1	-
HQP1351	CML	Jianshun Bio	Ph1	-
Meidi-tinib	CML	Gloria	Ph1	-
SKLB1028	AML	CSPC	Ph1	-
M Iclusig (Ponatinib)	CML, ALL	Otsuka	IND filed	Approved in the US in 2012
M Supect (Radotinib)	CML	Il-yang / Daewoong	IND filed	Approved in South Korea in 2012
B-raf				
M GSK2118436 (Dabrafenib)	Melanoma	GSK	Ph2	Approved in the US in 2013
BGB-283 (Lifirafenib)	Solid tumors	BeiGene	Ph2	Ph 2 in US
TQ-B3234	Cancer	Sino Biopharma	Ph1	-
TQ-B3233	Melanoma	Sino Biopharma	Ph1	-
BTK				
BGB-3111	MCL, CLL, WM	BeiGene	Pivotal Ph2	Pivotal Ph3: WM, 1L CLL
ICP-022	SLL, MCL	Innocare	Ph1	-
SHR1459	BCL	Hengrui	Ph1	-
CT-1530	B-NHL	Centaurus	Ph1	-
DTRMWXHS-12	BCL	Hisun	Ph1a	-
CDK4/6				
M Ibrance (Palbociclib)	BC	Pfizer	Ph3	Approved US 2015, EU 2016, Japan 2017
M Verzenio (Abemaciclib)	BC	Eli Lilly	Ph3	Approved US 2017, EU and Japan NDA
SHR6390	BC	Hengrui	Ph1b / 2	-
Birociclib	Solid tumors	Sihuan / Xuanzhu	Ph1	-
M Kisqali (Ribociclib)	BC	Novartis	IND approved	Approved in the US and EU in 2017
BPI-16350	BC	Betta	IND filed	-
C-MET				
M INC280 (Capmatinib)	NSCLC	Novartis	Ph2	Ph2 in the US
M Savolitinib	Gastric cancer	HCM / AZ	Ph2	Ph2 in South Korea for GC
Volitinib (HMPL-504)	Sarcomatoid Carcinoma	Chi-Med	Ph2	-
M MSC2156119J (Tepotinib)	NSCLC	Merck	Ph1b / 2	Ph2 in the US
CT053PTSA (Ninggetinib)	NSCLC	HEC Pharma	Ph1b	-
BMS-817378	Gastric cancer	Simcere / BMS	Ph1b	BMS licensed out China rights in 2010
CT053PTSA	Gastric cancer	HEC Pharma	Ph1	-
BPI-9016M	NSCLC	Betta	Ph1	-
Borui-tinib	NSCLC	Pearl Biotech	Ph1	-
AL2846	Solid tumors	Advenchen	Ph1	-
CM118	Solid tumors	Zaixin Pharma	Ph1	-
HS-10241	Solid tumors	Hansoh	Ph1	-
Konnitinib	Solid tumors	Konruns	Ph1	-
Glumetinib	Solid tumors	SIMM	Ph1	-
Boxitinib	Solid tumors	HEC	IND approved	-
M Merestinib	Solid tumors	Eli Lilly	IND approved	Ph2 in the US
SHR-A1403	Solid tumors	Hengrui	IND filed	-

Source: Insight database

Exhibit 197: Pipeline by target - part 2

Candidates	Indication	Company	China Status	Global status
Small molecule - Cancers				
EGFR				
Pyrotinib	BC	Hengrui	NDA filed	Ph1 in the US
Nimotuzumab	Esophageal cancer	BioTech Pharma	Ph3	Pls PC regimen, 1L
M Vandetanib	Medullary thyroid cancer	AstraZeneca	Ph3	Approved in the US in 2011
M Dacomitinib	NSCLC	Pfizer	Ph3	NDA filed in the US
HMPL-813 (Epitinib)	NSCLC	Chi-Med	Ph3	-
QLNC-120	BC	Qilu	Ph2	-
AST2818 (Alflutinib)	NSCLC	Allist	Ph2	-
AZD3759	NSCLC	Alpha Biopharma	Ph1 / 2	-
Simotinib	NSCLC	Simcere	Ph1b	-
Beta-tinib	NSCLC	Jinghua	Ph1	-
Hemay022	BC	Hemay Bio	Ph1	-
Larotinib	Esophageal cancer	HEC Pharma	Ph1	-
Allitinib	BC	Allist	Ph1	-
AC0010 (Avitinib)	DBCLC, MCL, SLL/CLL	ACEA Pharma	Ph1	-
ASK120067	NSCLC	Aosaikang Pharma	Ph1	-
BPI-15086	NSCLC	Betta	Ph1	-
HS-10296	NSCLC	Hansoh	Ph1	-
YZJ-0318	NSCLC	Yangtze River Pharma	Ph1	-
Mihuatinib	NSCLC	Huadong	Ph1	-
SH-1028	NSCLC	Sanhome	Ph1	-
ES-072	NSCLC	Bossan	Ph1	-
D-0316	NSCLC	Yifang	Ph1	-
BPI-7711	NSCLC	Beta pharma	Ph1	-
SKLB1028	AML	CSPC	Ph1	
Varlitinib	Biliary Tract Cancer	ASLAN Pharma	IND approved	Ph3 in the US
M Neratinib	BC	Puma Biotechnolog	IND approved	Approved in the US in 2017
ZL-2303 (Olmutinib)	NSCLC	Zai Lab	IND filed	Approved in South Korea in 2016
GMA204	NSCLC	Gmax Bio	IND filed	-
FGFR				
M Erdafitinib	GC, EC, HCC	JnJ	Ph2	Ph2 in the US
M FGF401	HCC	Novartis	Ph1/2	Ph1/2 in the US
Lucitanib / Delitinib	GC, HCC	SIMM	Ph1	-
FLT3				
M AC220 (Quizartinib)	AML	Daiichi Sankyo	Ph3	Ph3 in the US
M ASP2215 (Gilteritinib)	AML	Astellas	Ph3	NDA in Japan in 2018
SKLB1028	AML	CSPC	Ph1	
M Rydapt (Midostaurin)	AML	Novartis	IND approved	Approved in the US in 2017
HER2				
SHR1258 (Pyrotinib)	Gastric cancer	Hengrui	NDA filed	Ph1 in the US
M Dacomitinib	NSCLC	Pfizer	Ph3	NDA filed in the US
QLNC-120	BC	Qilu	Ph2	-
Hemay022	BC	Hemay Bio	Ph1	-
Larotinib	Esophageal cancer	HEC Pharma	Ph1	-
M Neratinib	BC	Puma Biotechnolog	IND approved	Approved in the US in 2017
Varlitinib	Biliary Tract Cancer	ASLAN Pharma	IND approved	Ph3 in the US
IAP				
APG-1387	CRC	Ascentage	Ph1b	
IDH2				
M Idhifa (Enasidenib)	AML	Celgene	Ph3	Approved in 2017
KIT				
M AB1010 (Masitinib)	CRC	AB Science	Ph3	
mTOR				
M Afinitor (Everolimus)	BC	Novartis	Ph2	Approved in the US and EU, 2012
LXI-15029	BC	Luoxin Pharma	Ph1	-
M Torisel (Temsirolimus)	RCC	Pfizer	IND approved	Approved in the US and EU in 2007
FP-208	Cnacers	Foreland Pharma	IND approved	-
ATG-008	Cnacers	Antengene	IND filed	-

Source: Insight database

Exhibit 198: Pipeline by target - part 3

Candidates	Indication	Company	China Status	Global status
Small molecule - Cancers				
PARP				
M Lynparza (Olaparib)	BC	AstraZeneca	Ph3	Approved in the US in 2018
ZL-2306 (Niraparib)	OC	Zai Lab	Ph3	Approved in the US in 2017
BGB-290 (Pamparib)	BC	Beigene	Ph1	-
IMP4297	BC	Impact Therapeutics	Ph1	-
SC10914	Solid tumors	Qingfeng	Ph1	-
Fluzoparib	GC, BC, OC	Hansoh	Ph1	-
HWH340	Solid tumors	Humanwell	Ph1	-
Simmiparib	Solid tumors	SIMM	IND approved	-
M ABT-888 (Veliparib)	NSCLC, BC, OC	AbbVie	IND approved	Ph3 in the US
Mefuparib	Solid tumors	Cisen	IND approved	-
PI3K				
M Aliqopa (Copanlisib)	NHL	Bayer	Ph3	Approved in the US 2017
M Taselisib	BC	Roche	Ph3	Ph3 in the US
BEBT-908	Lymphoma / Leukemia	Bebetter Med	Ph1	-
HMPL-689	B-cell lymphoma	Chi-Med	Ph1	-
CYH33	GC	SIMM	Ph1	-
M BKM120 (Buparlisib)	BC	Novartis	IND approved	Ph2 in the US
YZJ-0673	Cancers	Yangtze River Pharma	IND filed	-
VEGFR, PDGFR				
HMPL-013 (Fruquintinib)	CRC, GC, NSCLC	HCM / AZ	NDA filed	-
M Ofev (Nintedanib)	NSCLC	Boehringer Ingelheim	Ph3	Approved in 2014
M Vandetanib	Medullary thyroid cancer	AstraZeneca	Ph3	Approved in the US in 2011
M Lenvima (Lenvatinib)	HCC	Eisai	Ph3	Ph3 in the US
M Inlyta (Axitinib)	HCC	Pfizer	Ph3	Ph2 in the US
ZL-2301 (Brivanib)	HCC	Zai Lab	Ph2	Ph3 by BMS in the US
ENMD-2076	BC	CASI Pharma	Ph2	Ph2 in the US
Donafenib	Esophageal cancer	Zelgen	Ph1b	2L+
BMS-817378	Gastric cancer	Simcere / BMS	Ph1b	BMS licensed out China rights in 2010
CT053PTSA	Gastric cancer	HEC Pharma	Ph1	-
CM082	wAMD, GC	Betta	Ph1	Ph2 in the US
Small molecule - Auto-immune diseases				
BTK				
M AC0058TA	RA	ACEA Biosciences	IND approved	Ph1 completed in the US
WXFL10230486	RA	Humanwell	IND approved	-
JAK				
M Olumiant (Baricitinib)	RA	Eli Lilly	Ph3	Approved in the US in 2018
SHR0302	RA	Hengrui	Ph2	-
M ASP015K (Peficitinib)	RA	Astellas	IND approved	Ph3 in the US
DTRMHS-07	RA	Hisun	IND approved	-
M Fedratinib	Myelofibrosis	Celgene / Sanofi	IND approved	Ph3 in the US
KL130008	RA	Kelun	IND filed	-

Source: Insight database

Exhibit 199: Pipeline by target - part 4

Candidates	Indication	Company	China Status	Global status
Small molecule - Others				
DPP-4				
M Teneligliptin	Diabetes	Mitsubishi	Ph3	Approved in Japan in 2012
M Trelagliptin	Diabetes	Varsal Health Care	Ph1	Approved in Japan in 2015
Evogliptin	Diabetes	Luye	Ph1	
Imigliptin	Diabetes	Xuanzhu Pharma	Ph1	
Fotagliptin	Diabetes	Salubris; Fuchuang	Ph1	
Youge-liptin	Diabetes	Easton	Ph1	
Cetagliptin	Diabetes	CGene Tech	Ph1	
Besigliptin	Diabetes	Hansoh	IND approved	
Dutogliptin	Diabetes	Huadong	IND approved	
Anagliptin	Diabetes	Maeda	IND approved	
M Gemigliptin	Diabetes	LG life Science	IND approved	Approved in South Korea in 2012
M Omarigliptin	Diabetes	Merck	IND approved	Approved in Japan in 2015
Augliptin	Diabetes	Changao	IND approved	
GLP-1				
Loxenatide	Diabetes	Hansoh; Hansen	NDA filed	
M Semaglutide	Diabetes	Novo Nordisk	Ph3	Approved in the US 2017
M Dulaglutide	Diabetes	Eli Lilly	Ph3	Approved in the US 2014
Albenatide	Diabetes	Changshan	Ph2	
PEG exenatide	Diabetes	Pegbio	Ph1	
Glutazumab (GLP-1R antibody)	Diabetes	Gmax Bio	IND filed	
Supaglutede	Diabetes	Innogenpharm; Yinnuo	IND filed	
M Soliqua 100/33 (Lixisenatide / Insulin glargine)	Diabetes	Sanofi	IND filed	Approved in the US 2016
SGLT-2				
M Steglatro (Ertugliflozin)	Diabetes	Merck	Ph3	Approved in the US in 2017
Heng-gliflozin	Diabetes	Hengrui	Ph3	
Rong-gliflozin	Diabetes	HEC Pharma	Ph1	
Jia-gliflozin	Diabetes	Xuanzhu	Ph1	
M Synjardy (Empagliflozin / Metformin)	Diabetes	Boehringer Ingelheim	Ph1	Approved in the US in 2015
Tofogliflozin	Diabetes	Huawe	IND approved	
Tai-gliflozin	Diabetes	TIPR	IND approved	
M Ipragliflozin	Diabetes	Astellas	IND approved	Approved in Japan in 2014
M Sotagliflozin	Diabetes	Sanofi	IND filed	Ph3 in the US
Wan-gliflozin	Diabetes	Fosun	IND filed	

Source: Insight database

Exhibit 200: Pipeline by target - part 5

Candidates	Indication	Company	China Status	Global status
Antibody - Cancers				
CD20				
M Gazyva (Obinutuzumab)	FL, DLBCL	Roche	Ph3	Approved US 2016, EU 2017; Japan NDA
M Arzerra (Ofatumumab)	CLL	GSK	IND approved	Approved in the US 2009
TAD011	MCL	TOT Biopharm	IND approved	-
M Zevalin (Ibritumomab tiuxetan)	NHL	Biogen	IND filed	Approved in the US 2002
CD22				
SM03	NHL	Longrui	Ph2	-
M Besponsa (Inotuzumab ozogamicin)	ALL	Pfizer	IND approved	Approved in the US 2017
CD19, CD3				
M Blincyto (Blinatumomab)	ALL	Amgen	Ph3	Approved in EU in 2013
M FKC876 (Yescarta)	LBCL	Fosun-Kite	IND filed	Approved in the US in 2017
CD30				
M Adcetris (Brentuximab vedotin)	HL, sALCL	Seattle Genetics	Ph2	Approved US 2012, EU 2013, Japan 2014
Anti-CD30 mAb-MCC-DM1	Cancers	Shanghai Pharma	IND filed	-
CD38				
M Darzalex (Daratumumab)	ENKTL, nasal type	J&J	Ph2	Ph2 in the US
M Isatuximab	Multiple myeloma	ImmunoGen / Sanofi	IND filed	Ph3 in the US
CD147				
HcHAb18	NSCLC	Pacific Meinuoke	Ph1	-
Metuximab	Solid tumors	Haikang	Ph1	-
EGFR				
M Vectibix (Panitumumab)	CRC	Amgen	Ph3	First approval (US) in '06, US$642bn in '17
SCT200	CRC	Sinocelltech	Ph2	-
QL1203	CRC	Qilu Pharma	Ph1	-
GR1401	Solid tumors	Genrix	Ph1	-
M Portrazza (Necitumumab)	Squamous NSCLC	Eli Lilly	IND approved	Approved in the US in 2015
HER2				
M Perjeta (Pertuzumab)	BC	Roche	NDA filed	Approved in the US in 2012; EU/Japan in 2013
M Kadcyla (T-DM1)	BC	Roche	Ph3	Approved in the US/EU/Japan in 2013
BAT8001	BC	Bio-thera	Ph3	-
RC48-ADC	BC	RemeGen	Ph1b / 2	-
HS627	BC	Hisun	Ph1	-
LZM005	BC	Livzon	Ph1	-
ARX-788 (HER2-AS269)	BC	Zhejiang Medicine	Ph1	Licensed from Ambrx in 2013
TGF-β				
M LY2157299 (Galunisertib)	HCC	Eli Lilly	Ph2	Ph2 in the US
VEGFR, PDGFR				
M Zaltrap (Ziv-aflibercept)	CRC	Sanofi / Bayer	Ph3	First approval (US) in '12, US$1.6bn in '17
M Cyramza (Ramucirumab)	GC, HCC	Eli Lilly	Ph3	First approval (US) in '14, US$758m in '17
KH903	CRC	Kanghong	Ph1	-
Antibody - Auto-immune diseases				
CD20				
M Ocrevus (Ocrelizumab)	Multiple sclerosis	Roche	IND approved	Approved in the US 2017
BAT4306F	RA	Bio-Thera	IND filed	
IL-6				
Gerilimzumab (GB224)	RA	Genor Biopharma	Ph1	
M Sirukumab	RA	Johnson & Johnson	IND approved	Ph3 in the US
M Sarilumab (SAR153191)	RA	Sanofi	IND approved	Approved in the US 2017
RANKL				
M Xgeva / Prolia (Denosumab)	RA	GSK	Ph3	Approved in the US in 2010
TNF-α				
M Cimzia (Certolizumab pegol)	RA	UCB	Ph3	Approved in the US in 2008
Hemay007	RA	Hemay Bio	IND filed	-
VEGFR, PDGFR				
HB002.1M	wAMD	Huahai	Ph1	
TK001	wAMD	T-mab Biopharma	Ph1	
BAT5906	wAMD	Bio-Thera	IND filed	
hPV19	wAMD, DME	Stainwei	IND filed	

Source: Insight database

Glossary

Adenocarcinoma: a type of cancer from glandular cells, or found in tissues that line certain internal organs.

Adjuvant therapy: a therapy applied following the primary therapy to reduce the risk of cancer recurrence.

Advanced cancer: a cancer that has progressed to a late stage and has spread to other places in the body. It is usually difficult to cure.

Adverse event: an unexpected medical problem that is observed in disease treatment and could be caused by the treatment or other factors.

AJCC staging system: a system used to describe cancer status using the TNM method, i.e. T for the size and spread of the tumor; N for spread of the cancer to nearby lymph nodes; M for metastasis.

ALK gene: a gene that makes a protein called anaplastic lymphoma kinase (ALK), which may be involved in cell growth of neuroblastoma, non-small cell lung cancer, and anaplastic large cell lymphoma.

Animal experiments: laboratory experiments using animals to test a drug's efficacy and toxicity before testing the drug in humans.

Allogeneic stem cell transplantation: a surgery that transplants blood-forming stem cells (cells from which all blood cells develop) from a genetically similar, but not identical, donor to a patient for the treatment of lymphoma.

Angiogenesis: the generation of new blood vessels from existing blood vessels.

Angiogenesis inhibitor: a drug that prevents new blood vessels from forming, thus cutting the nutrition supply to tumors. Also called antiangiogenesis agent.

Anemia: a symptom that is caused by a lower-than-normal level of red blood cells.

Acquired resistance: a situation where a therapy becomes no longer effective in preventing disease progression due to gene mutation or virus.

Antibody: a protein that the immune system produces to fight against antigens.

Antigen: a substance that triggers an immune response in the body.

Apoptosis: a process that leads to cell death to get rid of unneeded cells in the body.

Autoimmune disease: autoimmune disorders or immune system disorders, such as rheumatoid arthritis, ankylosing spondylitis and psoriasis, in which the immune system mistakenly attacks the body's own organs/tissues.

B cell: a type of white blood cells that comes from bone marrow and makes antibodies.

Biological therapy: a type of treatment that stimulates or suppresses the immune system to defend against diseases. Biological therapies can be an immunotherapy, a gene therapy, or a targeted therapy.

Biosimilar: a drug that is almost the same as, but not identical to the originator drug that has already been approved, given the complexity of the manufacturing process of biologics.

Blood cancer: or hematologic cancer/hematologic malignancy, that includes three major types: (1) leukemia, caused by a high level of abnormal white blood cells; (2) lymphoma, with abnormal lymphocytes (one type of white blood cells) accumulating in the lymph nodes and impairing the immune system; and (3) meyloma, which prevents the normal production of antibodies.

Blood stem cell: An immature cell in the peripheral blood and the bone marrow that can develop into all types of blood cells, including white blood cells, red blood cells, and platelets.

Blood sugar: refers to the glucose (a type of sugar) found in the blood and serving as the key source of energy for the human body. The medical condition of higher-than-normal blood sugar level called hyperglycemia, and lower-than-normal level called hypoglycemia.

BMI: body mass index, which measures whether a person is at a healthy weight.

Bone marrow: the soft tissue in the center of bones, which produces white blood cells, red blood cells, and platelets.

Breast cancer: cancer that forms in the breast and can occur in both men (relatively rare) and women.

BCS: breast-conserving surgery, which removes the tumor and a small portion of the normal tissue associated with the tumor.

Cancer: a disease indicated by cells dividing without control.

Cardia: the upper part of the stomach that is closest to the esophagus.

Cardiovascular: having to do with the heart and blood vessels.

CD20: a protein that is found on B cells and acts as a type of tumor marker for the diagnosis of cancer.

Cell: the building block of all living organisms and the tissues of the body.

Cell cycle: the process a cell goes through each time it divides into two daughter cells.

Cell cycle inhibitor: a substance that is used to block the cell division cycle and may be valuable in the treatment of cancer.

Cell differentiation: the process during which young and immature cells develop into their mature forms.

Cell motility: the ability of a cell to move.

Cell proliferation: an increase in the number of cells as a result of cell growth and cell division.

Chemotherapy: a treatment that uses chemical drugs to kill cancer cells or stop them from dividing.

Carcinoma: a cancer that begins in the skin or tissues that line or cover internal organs.

Cancer pathway: a group of molecules that work together to control cell functions, such as cell division or cell death, that are critical to cancer.

Carcinogens: chemicals or other substances that can cause cancer.

Cytogenetic testing: tests examining the number and structure of chromosomes.

Clinical Trial: a prospective study designed to understand whether an intervention is effective and safe.

Clinical trial phase: Phase I trials - whether it is the best way to treat and what is the best dose; Phase II trials - whether it is effective; Phase III trials - how does the new treatment and standard treatment; Phase IV trials - whether the new treatment is safe given more patients using experience after a drug is launched into the market.

Clinical staging: a method used to find out the stage of cancer using tests that are done before surgery. These include physical exams, imaging tests, laboratory tests (such as blood tests), and biopsies.

Chronic disease: a disease that lasts for three months or longer and becomes worse over time. It occurs mainly in the elderly and can be controlled but not cured.

Classical Hodgkin lymphoma: the most common type of Hodgkin's lymphoma, which is a cancer of the immune system.

Clinical practice guidelines: guidelines developed to help health care professionals make treatment plans.

Clinician: a health professional who takes care of patients.

CLL/SLL: a type of non-Hodgkin's lymphoma.

Colorectal cancer (CRC): Cancer that develops in the colon and/or the rectum.

Combination therapy: or multimodality therapy and multimodality treatment, a therapy that combines more than one method of treatment.

Complete metastasectomy: a surgery to remove all metastases (tumors formed from cells that have spread from the primary tumor).

Complete remission: a situation where all signs of a cancer disappear in response to treatment.

Compliance: the act of following a medical regimen or schedule correctly and consistently.

Complication: a medical problem that occurs during or after treatment and can be caused by the disease, procedure, or treatment.

Concurrent therapy: a treatment that is given at the same time as another.

Continuous infusion: the administration of a fluid into a blood vessel, usually over a prolonged period of time.

CRO: contract research organization, a company providing services of clinical trials.

CTLA-4: a protein on T cells (a type of immune cell) that participates in the body's immune responses. When CTLA-4 is bound to the B7 protein, T cells will stop killing other cells, so drugs blocking CTLA-4 will increase the ability of T cells to kill cancer cells.

Curative surgery: a surgery to remove all malignant (cancerous) tissue and aim to cure the disease.

Diabetes: A high level of blood sugar because the body does not make enough insulin or use it the way it should.

Diagnosis: the process of identifying a disease, condition, or injury from its signs and symptoms.

Diffuse large B-cell lymphoma: the most common type of B-cell non-Hodgkin lymphoma, with rapidly growing tumors in the lymph nodes, spleen, liver, bone marrow, or other organs.

Distant metastasis: a cancer that spreads from the original location to distant organs or distant lymph nodes.

Dose: the amount of medicine or radiation given at a time.

Drug resistance: a situation where drugs can not take effect to defend against cancer cells, viruses, or bacteria.

Drug tolerance: a condition when the body gets used to a medicine so that original therapy won't take effect and other measures are required.

DNA: deoxyribonucleic acid, which is the genetic material of all cellular organisms.

Early-stage cancer: a cancer that is early in its growth, and may not have spread to other parts of the body.

Efficacy: producing a satisfying effect after taking a medicine.

EGFR inhibitor: a substance that blocks the activity of EGFR (epidermal growth factor receptor) and may keep cancer cells from growing.

Endpoint: an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial.

End-stage cancer: a cancer that highly likely leads to death.

Enzyme: a protein that speeds up chemical reactions in the body.

Epidemiology: the study of the patterns, causes, and control of disease in groups of people.

Estrogen receptor test: a lab test to find out if cancer cells have estrogen receptors (proteins to which estrogen will bind).

Estrogen receptor negative: cancer cells that grow without estrogen, and keep growing when treated with hormones that block estrogen from binding.

Estrogen receptor positive: cancer cells that need estrogen to grow, and may stop growing when treated with substances that block the binding and actions of estrogen.

ErbB1/EGFR/HER1: the protein on the surface of some cells, to which epidermal growth factor binds, causing the cells to divide. Its expression is abnormally high in some cancer cells, and these cells may divide excessively when epidermal growth factors are present.

Esophageal cancer: a cancer that forms in tissues lining the esophagus.

Extensive-stage small cell lung cancer: a cancer that has spread outside of the lung.

FDA: Food and Drug Administration, the agency in the U.S. federal government for drug approval and labeling.

First-line therapy: the first treatment recommended for a disease and regarded as the best treatment (other names include induction therapy, primary therapy, and primary treatment).

Five-year survival rate: the percentage of people who are alive five years after being diagnosed or treated.

Follicular lymphoma: a type of B-cell non-Hodgkin's lymphoma that is indolent (slow-growing).

Follow-up: monitoring a person's health over time after treatment.

Gastrectomy: removal of all or a part of the stomach.

Gastric cancer: a cancer that forms in tissues lining the stomach.

Gastroesophageal junction: the place where the esophagus is connected to the stomach.

Gene: the functional and physical unit of DNA that is passed from parents to offspring.

Gene amplification: an increase in the number of copies of a gene.

Gene deletion: the loss of all or a part of a gene.

Gene expression: a process by which a gene gets turned on in a cell to make RNA and proteins.

Generic: official non-brand names of medicines.

Grading: a system for providing information about the probable growth rate of a tumor and its tendency to spread in support of treatment decisions.

HBV: hepatitis B virus that causes hepatitis (inflammation of the liver).

HCV: hepatitis C virus that causes hepatitis (inflammation of the liver).

HER2 negative: cancer cells that have a low expression of HER2 on their surface (which is involved in cell growth).

HER2 positive: cancer cells that have a excessive expression of HER2 on their surface (which is involved in cell growth).

Hereditary: the passing of genetic information from parents to children through genes.

Histology: The study of tissues and cells under a microscope.

Hodgkin disease: a cancer of the immune system.

Hormonal therapy: a treatment that adds, blocks, or removes hormones.

Hormone receptor: a protein that binds a specific hormone.

Hormone receptor test: a test to measure the amount of hormone receptors in cancer tissue. As hormones can attach to proteins, a high level of hormone receptors may mean that hormones help the cancer grow.

Host cell: a cell that is infected by a virus.

Injection: using a syringe and needle to push fluids or drugs into the body.

Intravenous/IV: into or within a vein.

Indication: a symptom that suggests certain medical treatment is necessary.

Immune system: a complex system in the body that helps fight infections and other diseases.

Immunodeficiency: the decreased ability of the body to fight infections and other diseases.

Immunotherapy: a therapy that stimulates or suppresses the immune system to defend against cancer, infection, and other diseases.

Incidence: the number of new cases diagnosed each year.

Infection: the invasion and growth of germs in the body.

Inoperable: a status that the disease cannot be treated by surgery.

Interferon: a substance that can improve the body's natural response to infections and other diseases.

Interleukin: a substance that regulates immune responses.

Kinase inhibitor: a substance that blocks kinase (involved in controlling cell signaling, metabolism, division, survival, etc.).

KRAS gene: a gene related to the KRAS protein, which helps control cell growth, cell maturation, and cell death. Wild-type KRAS is the natural form, while the mutated (changed) forms may cause cancer cells to grow and spread in the body.

Late-stage cancer: a cancer that is far along in its growth, and has spread to the lymph nodes or other places in the body.

Liver cancer: a cancer that forms in the tissues of the liver.

Locally advanced cancer: a cancer that has spread from where it started to nearby tissue or lymph nodes.

Locally recurrent cancer: a cancer that has recurred at or near the same place as the original tumor.

Lung cancer: a cancer that forms in tissues of the lung.

Lymph node: a small bean-shaped structure in the immune system.

Lymph node dissection: a surgical procedure in which the lymph nodes are removed.

Lymphoma: a cancer that begins in cells of the immune system.

Mechanism of action (MoA): the mechanism why a drug takes effect.

Mutation: a change in the nucleotide base sequence of our DNA

Maintenance therapy: a treatment used to prevent cancer from coming back after the initial therapy.

Medicine: a substance used for prevention, treatment, or relief.

Mortality: the number of deaths in a certain group of people in a certain period of time.

Neo-adjuvant chemotherapy: a chemotherapy that is used to shrink a tumor before surgery or radiation therapy.

NHL: non-Hodgkin's lymphoma.

Non-small cell lung cancer: the most common subtype of lung cancer.

Obesity: an abnormally high, unhealthy amount of body fat.

OS: the length of time from the date of diagnosis or the start of treatment.

OTC: medicines that can be bought without a prescription (doctor's order).

Outcome: a specific result or effect that can be measured.

Out-of-pocket cost: the amount of money a patient pays for medical expenses that is not covered by a health insurance plan.

Outpatient: a patient who visits a health care facility without staying overnight.

Outcome: long-term clinical results such as disease-free survival

Oncogenes: genes that stimulate excessive cell growth and division.

Overexpression: making too many copies of a protein or other substance

Pharmacokinetics: the study of how drugs are absorbed, distributed, metabolized, and eliminated by the body

Palliative therapy: a treatment that is used to relieve symptoms and reduce suffering.

Protein: a molecule made up of amino acids.

Prognosis: the likely outcome or course of a disease

Platelet: a type of blood cell that helps prevent bleeding by causing blood clots.

PARP inhibitor: a substance that blocks an enzyme in cells called PARP which helps repair DNA.

PD-1: a protein on T cells that helps prevent T cells from killing other cells when it is bound to PD-L1.

PFS: progression-free survival, which is the length of time during and after the treatment of a disease and used to determine the efficacy of a treatment.

PI3K: a type of enzyme involved in transmitting signals in cells that may help control cell growth.

Prescription: a doctor's order for taking medicines.

Prevalence: total number of people in a specific group who have (or had) a certain disease.

Progression: a disease that becomes worse or spreads in the body.

Recurrent: a cancer that returns after a period of time.

Radiation therapy: the use of radiation aiming to kill cancer cells and shrink tumors.

RNA: ribonucleic acid, which is made from DNA and used to produce protein

Regimen: a treatment plan that specifies the dosage, the schedule, and the duration.

Relapse: the return of a disease or the signs and symptoms of a disease after a period of improvement.

Resection: a surgery to remove a part or all of an organ.

Response rate: the percentage of patients whose cancer responds to the treatment.

Risk factor: substance or events that increase the chance of developing a disease.

Surveillance: the ongoing collection of information about a disease

Signaling pathway: a process where a group of molecules work together to control one or more cell functions, such as cell division or cell death.

Small cell lung cancer: an aggressive (fast-growing) subtype of lung cancer.

Symptom: a physical or mental problem that reflects the presence of a disease.

Systemic therapy: a treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

T cell: a part of white blood cell in the immune system

TACE: transarterial chemoembolization, which is a procedure to treat liver cancers and the blood supply to a tumor is blocked during TACE.

Targeted therapy: a treatment that uses drugs to identify and attack specific types of cancer cells, making them less harmful to normal cells.

Third-line therapy: a treatment that is given after both first-line therapy and second-line therapy fail.

Tumor: an abnormal mass of tissue resulting from excessive cells by dividing more than they should or prolonging life cycle.

Tyrosine kinase inhibitor: a substance that blocks the action of tyrosine kinases in cell signaling, growth, and division.

Tumor suppressor: a type of gene or the protein that it encodes that helps control cell growth.

VEGFR inhibitor: substance that blocks the activity of VEGF and VEGFR to form blood vessels, including VEGFR tyrosine kinase inhibitor and anti-VEGFR antibody.

White blood cells: cells that help the body fight infection and other diseases.

Prices in this report are as of the May 23, 2018 market close unless indicated otherwise.

Disclosure Appendix

Reg AC

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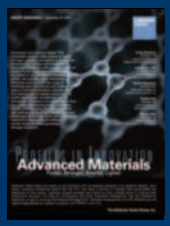

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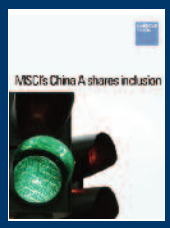

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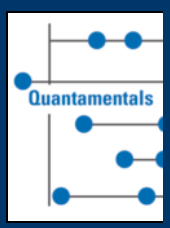

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