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China Cellular Immunotherapy and DC-TC Market Intelligence

Discussion and Due Diligence Document

Meritco Services
June 22, 2016

Over the past two weeks, we have conducted 8 physician and competitor in-depth interviews and 50 hospital cold calls for this study

Physician interview (4)

Hospital	Title	Name
• The 455th Hospital of PLA	Vice Chief	Mr. Chen
• West China Hospital	Vice Chief	Mr. Zhou
• Zhongshan Hospital	Vice Chief	Mr. Huo
• Changhai Hospital	Vice Chief	Mr. Fu

Competitor interview (4)

Company	Title	Name
• Shanghai Hisunbio	Technical Manager	Mr. Fang
• Cellular Biomedicine Group	Technical Manager	Ms. Zhang
• ZMKS Biotechnologies	Lab Supervisor	Mr. Wang
• Shanghai Cell	R&D Director	Mr. Jin

Hospital cold call (50)

Hospital	City
• Fujian Provincial Cancer Hospital	Fuzhou
• Fuzhou General Hospital of Nanjing Military Command	Fuzhou
• Fuda Cancer Hospital	Guangzhou
• The Third Affiliated Hospital, Sun Yat-Sen University	Guangzhou
• Jingzhou Hospital	Jingzhou

Hospital cold call (50)

Hospital	City
• The Second Peoples Hospital of Nantong	Nantong
• Ningbo second Hospital	Ningbo
• The 113th Hospital of PLA	Ningbo
• The 455th Hospital of PLA	Shanghai
• Eastern Hepar and bravery Hospital	Shanghai
• Liaoning Cancer Hospital	Shenyang
• General Hospital of Shenyang Military Command	Shenyang
• Hebei General Hospital	Shijiazhuang
• Tangshan People's Hospital	Tangshan
• Tianjin Medical University Cancer Institute & Hospital	Tianjin
• Tianjin Third Central Hospital	Tianjin
• Wuxi Third People's Hospital	Wuxi
• The Affiliated Hospital of Xuzhou Medical College	Xuzhou
• Jilin Cancer Hospital	Changchun
• The Second Hospital of Jilin University	Changchun
• ……	……

Source: Meritco analysis

Executive summary

Market overview

- **Cellular immunotherapy in China is still at its infancy, and the market size for solid tumor is estimated to be USD ~150 Mn in 2015**
  - The adoption rate of cellular immunotherapy is only 0.3% among patients with solid tumor in China, since only selective patients have received the treatment
  - DC-CIK and CIK, with market shares of 50% and 30% respectively, are the top2 most frequently adopted techniques for lung cancer, stomach cancer, colorectal cancer and liver cancer treatment, while DC-TC is not applied in clinical treatment
- **The operating procedures of DC-TC are standardized, with repeated freeze-thawing being the most frequently adopted method to inactivate tumor cells**
- **National and provincial HFPC play critical roles in supervising the practice of cellular immunotherapy, and setting the pricing and reimbursement standards**
  - 18 provinces have publicized the charging standards for cellular immunotherapy, but hospitals actually charged 20-100% premium
  - 20 provinces have issued reimbursement regulation on cellular immunotherapy, and DC is the second largest technique to be reimbursed

Competitive Landscape Analysis

- **Corporate-hospital joint labs are the major players conducting cellar immunotherapy:** ~90% hospitals were cooperating with corporates to conduct cellar immunotherapy
- The CIK and DC related techniques are used for different solid tumors across institutes, **and lung, liver, colorectal and stomach cancers are the most commonly treated diseases**
- Domestic DC-TC practitioners have been making efforts to **legalize the commercial use of the technique by applying for drug permits**
- Despite prior partnership, **DC-TC has not been the strategic focus of CBMG and Shanghai Cell**
  - CAR-T has been CBMG's strategic focus since 2014, while DC-TC was abandoned after the completion of Phase I study with California Stem Cell
  - Shanghai Cell's DC-CTL is used for clinical application with the record in Shanghai HFPC, while gene-modification techniques have recently become Shanghai Cell's research focus since 2015

Future Trends and Opportunities

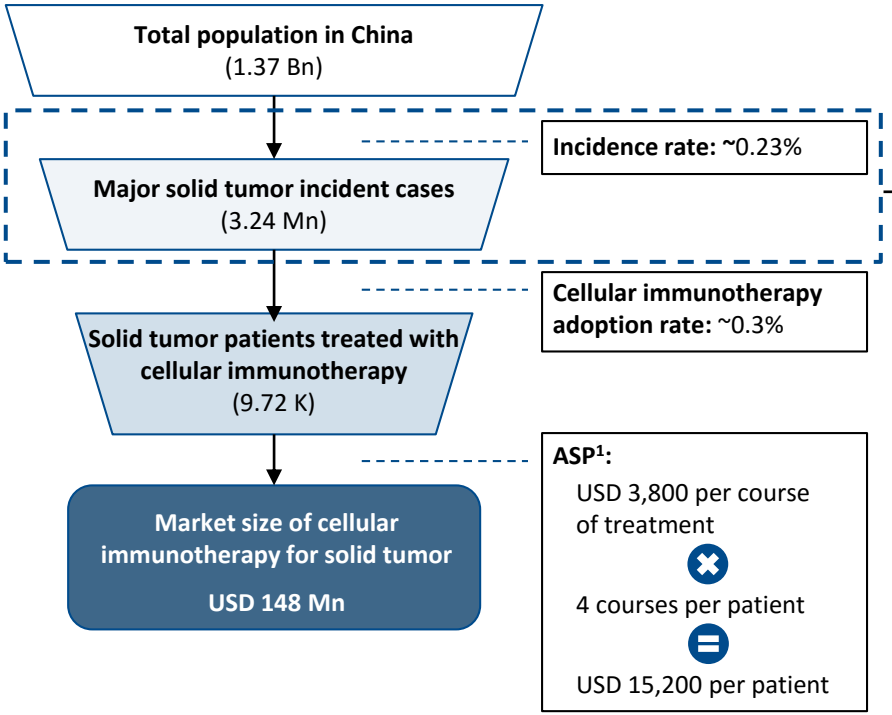
- Currently, cellular immunotherapy is regulated **for not-for-profit use, and most institutes are focusing on CAR-T research to develop its potential application on solid tumors**
- Commercial use may require drug approval by the CFDA in the future, but the door remains open for new therapy entrants
- **Caladrius's DC-TC product may have a successful market entry benefited from educated market, credible clinical data and potential patent advantages**

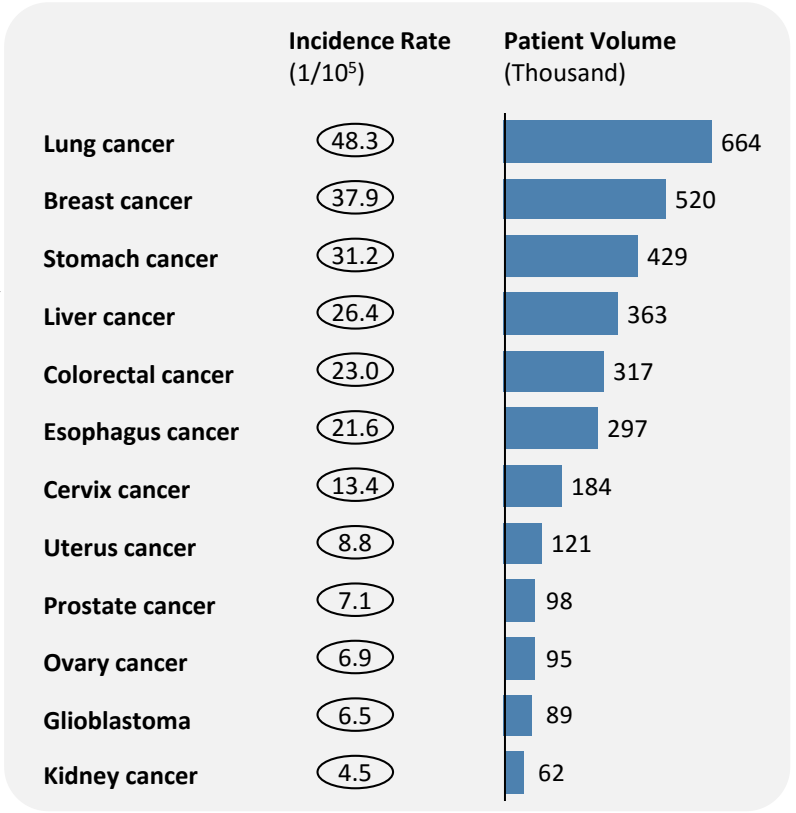
Source: Meritco analysis

I	**Market Overview**
II	Competitive Landscape Analysis
III	Future Trends and Opportunities

The adoption rate of cellular immunotherapy for solid tumor is low in China, and the market size is estimated to be USD ~150 Mn in 2015

Market estimation on cellular immunotherapy for solid tumor in China
2015





1 ASP is projected to rise with new potential western therapies, expecting to command a premium price
Source: National Bureau of Statistics of China; Annual Report on Status of Cancer in China; Meritco analysis

Selective solid tumor patients have received cellular immunotherapies, among which CIK and DC-CIK represent the main stream

Key characteristics of patients receiving cellular immunotherapy

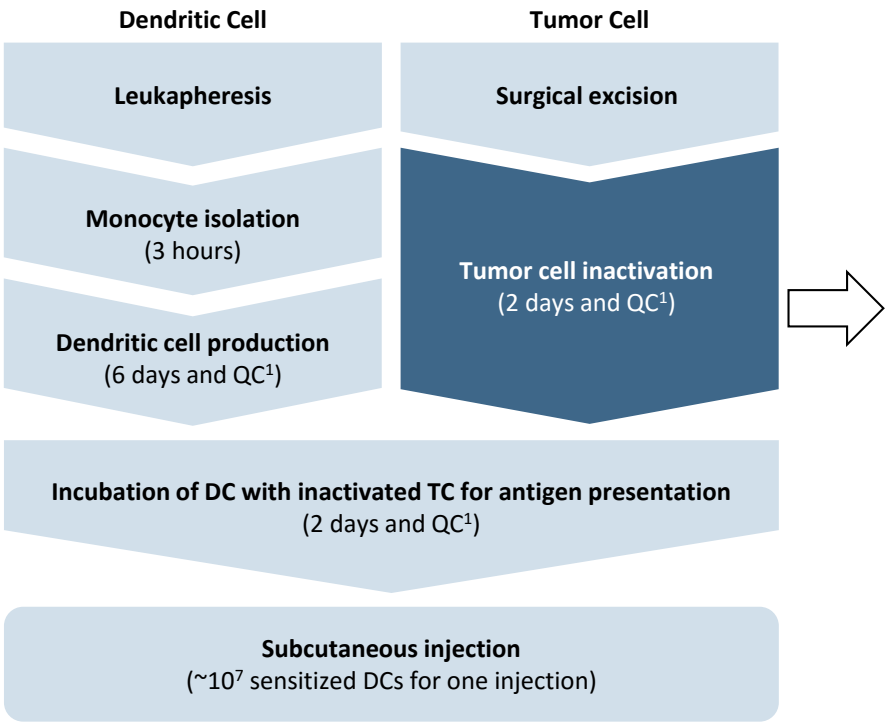
- **Phase IV cancer patients especially those having been failed in other therapies** (operation, chemotherapy, radiotherapy)
- **Patients with normal immunoconpetent**: the success of cellular immunotherapy relies on the function of patients' own immune system
- **Improving affordability**: while cellular immunotherapy may be expensive (> USD 15 K per year) and is not covered by health insurance in some provinces, a small but growing population is emerging at private hospitals that may support out-of-pocket expenditure

	Market share	Target indication	Process
DC (TC sensitized)	~0%	• Colorectal cancer	• DCs collected from patients **are sensitized by tumor cell (cracked by radiation or frozen-thawed)** and then infused into the patients' blood after amplified in vitro
DC (polypeptide sensitized)	2-3%	• Lung cancer, stomach cancer, colorectal cancer, liver cancer	• DCs collected from patients **are sensitized by tumor-specific antigen peptide** and then infused into the patients' blood after amplified in vitro
DC (non-sensitized)	2-3%	• Lung cancer, stomach cancer, colorectal cancer, liver cancer	• DCs collected from patients are cultured and amplified in vitro **without sensitization** and finally infused into the patients' blood
CIK	~30%	• Lung cancer, stomach cancer, colorectal cancer, liver cancer	• The cells (i.e. CIK and CTL) collected from patients are cultured and amplified in vitro and finally infused into the patients' blood
CTL	8-10%	• Lung cancer, stomach cancer, colorectal cancer, liver cancer	
DC-CIK	~50%	• Lung cancer, stomach cancer, colorectal cancer, liver cancer	• DCs and CIKs are separated from patient's blood respectively and then infused into the patients' blood together after **co-cultured** and amplified
DC-CTL	~5%	• Lung cancer, stomach cancer, colorectal cancer, liver cancer	• DCs and CTLs are separated from patient's blood respectively and then infused into the patients' blood together after **co-cultured** and amplified

Source: Cnki database; Meritco analysis

The operating procedures of DC-TC are standardized, with repeated freeze-thawing being the most frequently adopted method to inactivate tumor cells

Current DC-TC operating procedures in China



Three ways of tumor cell inactivation

Effectiveness: Low -> High ◔ ◑ ◕ ●

	Adoption rate	Duration	Effect
Repeated freeze-thawing	~90%	• ~2 days	◑ • Antigens in crushed TCs are incomplete
Irradiation[2]	<10%	• ~15 min	◕ • Irradiation is regulated while keeping more antigens
Ultrasound	1-2%	• ~2 hours	◑ • Antigens in crushed TCs are incomplete

A mismatch exists among radiation operators and qualification holders

- While many hospitals have radiation qualification, they are deficient in operation and quality control of tumor inactivation and cell culture
- Corporates assist hospitals with their quality control capability but the majority of them do not have radiation qualification

1 QC only involves microbiological test, which requires little time

2 Irradiation, while regulated and more expensive, is the standard process used in Caladrius's DC-TC approach, and may provide a better chance of technical success and higher barriers for entry

Source: Expert interviews; Meritco analysis

National and provincial HFPC play critical roles in supervising the practice of cellular immunotherapy, and setting the pricing and reimbursement standards

	Supervision authority	Surveillance mode	Guideline/ regulation
1 Clinical research qualification	• Provincial Health and Family Planning Commission (HFPC) • Hospital Clinical Research Management Committee (CRMC) • Hospital Ethics Committee	• Supervised by the provincial HFPC, the clinical research shall be legit and **free of charge for subjects** • The **CRMC is in charge of clinical trial approval** and implementation control • The Ethics Committee will make sure that the clinical research is carried out within the ethics norms	• *"Notice on the Regulations on Healthcare Institutions Conducting Clinical Research Project"* by national HFPC in 2014
2 Clinical application qualification	• National HFPC	• Cellular immunotherapies were **approved for clinical applications as Type III medical technology** by the national HFPC **before 2015** • The healthcare institutions carrying out cellular immunotherapy shall be on the record of provincial HFPC	• *"Notice on the First Batch of Type III Medical Technologies permitted in Clinical Application"* by national HFPC in 2009
3 Pricing standard	• National Development and Reform Commission (NDRC) • National and provincial HFPC	• Cellular immunotherapy was listed **on the national healthcare service price catalog** by the NDRC and national HFPC **in 2012** • The provincial HFPC will decide the cost per case for cellular immunotherapy	• *"Notice on Standardizing the Healthcare Service Pricing Management"* by NDRC and national HFPC in 2012
4 Reimbursement policy	• Provincial HFPC	• **The provincial HFPC will** decide whether cellular immunotherapy is **entitled for reimbursement or not, and what is the reimbursement portion of the therapy**	• *"Provincial Medical Insurance Price Catalog of Diagnosis and Treatment Service"* by HFPC

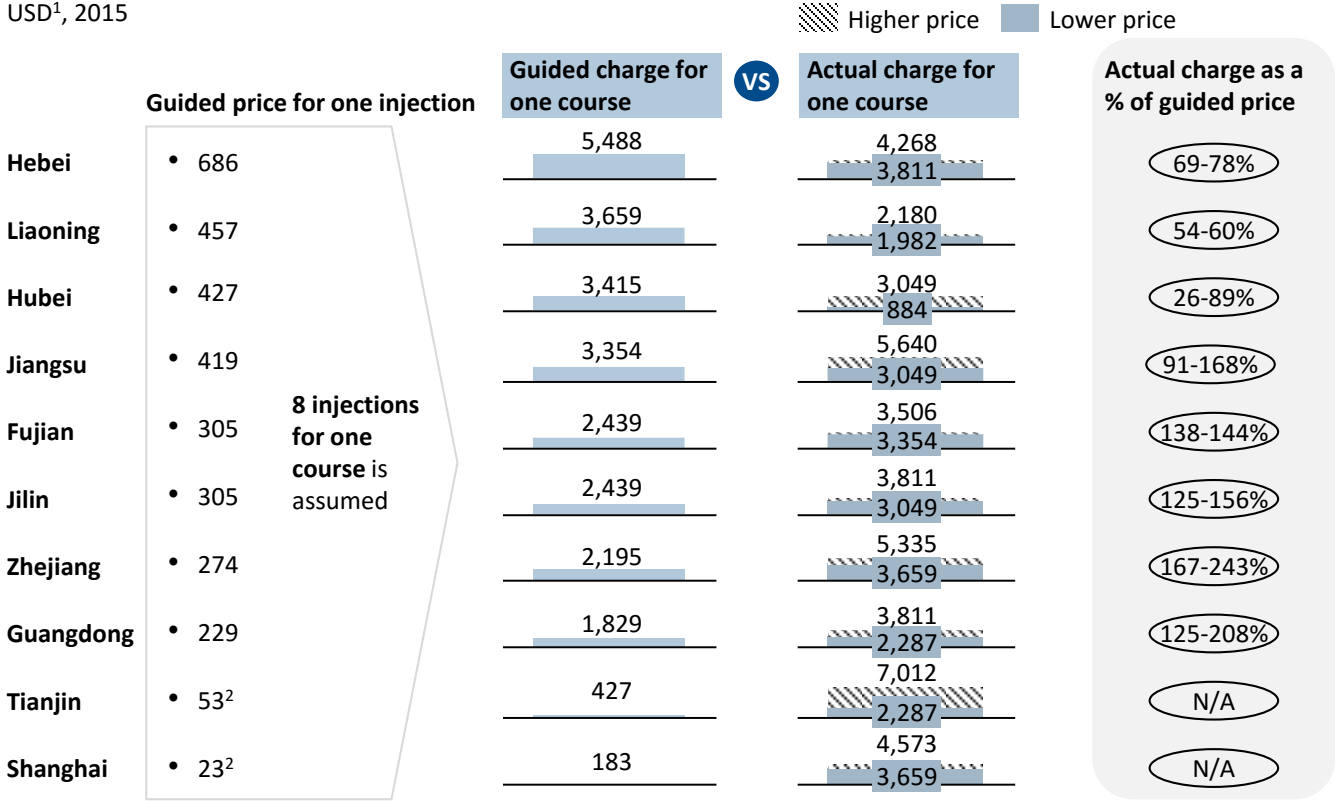
Source: national and provincial Health and Family Planning Commission; National Development and Reform Commission; Meritco analysis

Based on provincial standards, hospitals actually charged 20-100% premium for cellular immunotherapy

Pricing mechanism

- **Provincial HFPCs establish pricing standards and guidelines**
  - Most provincial HFPCs only regulate the price for one injection, while some provincial HFPCs regulate the price for one course of treatment
  - a course of treatment requires 6-12 injections
- **Hospitals set the treatment prices according to therapeutic regimens**
  - Prices usually consist of expenses for cell collection, cell expansion, a few injections and other expenses
  - Hospitals in non-reimbursable provinces are not required to follow the guided prices

Pricing comparison for DC-CIK immunotherapy in 10 major provinces
USD[1], 2015



1 USD to CNY exchange rate = 6.56
2 DC-CIK immunotherapy is not reimbursable in Tianjin or Shanghai
Source: Hospital cold calls; Provincial health and family planning committees; Meritco analysis

Reimbursement policy on cellular immunotherapy varies across provinces, and DC is the second largest technique to be reimbursed, suggesting a market acceptance with a new DC-TC product

Reimbursement mechanism

- Provincial HFPC decides whether cellular immunotherapy is entitled for reimbursement or not
- Provincial HFPC also specifies the therapy's reimbursement details
  - Different techniques are categorized and charged as treatment service
  - HFPC sets the reimbursement ratio
  - Some HFPCs may limit the scope of reimbursement such as the technique categories, indications and disease seriousness

Reimbursement scope and ratio of different provinces

	Approved technology			Refunded ratio		Approved technology			Refunded ratio
	LAK	CIK	DC			LAK	CIK	DC	
Shaanxi		✓		100%	Zhejiang		✓	✓	85%
Qinghai		✓		100%	Inner Mongolia		✓	✓	80-85%
Tianjin	✓			100%	Heilongjiang		✓		80%
Jiangxi		✓	✓	95%	Jiangsu		✓	✓	80%
Jilin		✓	✓	92%	Fujian	✓	✓	✓	80%
Hainan		✓		90%	Hubei	✓	✓	✓	80%
Sichuan		✓		90%	Guangdong		✓		80%
Yunnan	✓	✓	✓	90%	Anhui		✓		80%
Gansu		✓		90%	Guizhou	✓	✓	✓	80%
Hebei		✓	✓	80-90%	Shandong		✓		60%

Requisition

- **Zhejiang** restricts reimbursement to patients with lung cancer, kidney cancer, lymphatic cancer or melanoma who cannot be effectively treated by other therapies
- **Shaanxi** restricts reimbursement to patients with lymphatic and hematopoietic cancer

Source: national and provincial Health and Family Planning Commission; Provincial Human Resources and Social Security Bureau; Meritco analysis