

MARKET ASSESSMENT OF IMMUNOTHERAPY FOR TREATMENT OF NSCLC IN CHINA: PRESENT AND OUTLOOK

Dissertation Submitted to



The IIHMR University, Jaipur

for the partial fulfillment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

by

Urvashi Lakhani

Under the Supervision and Guidance of

Dr. Sudhinder Singh Chowhan

2022

MARKET ASSESSMENT OF IMMUNOTHERAPY FOR TREATMENT OF NSCLC IN CHINA: PRESENT AND OUTLOOK

Dissertation Submitted to



The IIHMR University, Jaipur

for the partial fulfillment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

by

Urvashi Lakhani

Under the Supervision and Guidance of

Dr. Sudhinder Singh Chowhan

2022

DECLARATION BY STUDENT

I hereby declare that this dissertation titled “**Market Assessment of Immunotherapy for treatment of NSCLC in China: Present and Outlook**” is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

(Signature)

Urvashi Lakhani

Date

CERTIFICATE

This is to certify that (Name of Student) in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management)/MBA (Pharmaceutical Management)/MBA (Rural Management) from the IIHMR University, Jaipur has successfully completed her/his internship at (name of the organization) during March 22, 2022 to June 19, 2022.

Place:
Date:

Preceptor/Head of the Organization
Name of the organization

CERTIFICATE

This is to certify that dissertation titled is a record of the research work undertaken by (Name of Student) in partial fulfillment of the requirements for the award of the degree of MBA (Hospital and Health Management)/MBA (Pharmaceutical Management)/MBA (Rural Management) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide
IIHMR University, Jaipur
Date

School Dean
IIHMR University, Jaipur

Table of Contents

List of Figures	vi
List of Tables.....	vii
1. Introduction	1
1.1 Lung cancer classification	1
1.2 Stages of NSCLC and Standard of Care (SOC)	1
1.3 Biomarker testing for NSCLC.....	2
1.4 Treatment for NSCLC	3
2. Research question.....	5
3. Objectives.....	5
4. Literature review	6
5. Methodology	9
5.1 Study area.....	9
5.2 Study design	9
5.3 Study duration	9
5.4 Data collection method.....	9
5.5 Plan of Analysis	9
6. Results	10
6.1 China Demographics	10
6.2 China disease burden.....	10
6.3 Prevalent patients of NSCLC in China.....	11
6.4 Multi-tiered healthcare system of China	13
6.5 Overview of PD-1 and PD-L1	15
6.6 Future Outlook	21
7. Conclusion.....	23
8. References	24

List of Figures

Figure No.	Title	Page No.
1	Global vs. China population	10
2	Global vs. China new cancer cases	11
3	Top 5 cancer types in males	11
4	Top 5 cancer types in females	11
5	NSCLC Patient funnel	12
6	Global PD-1 sales (in \$ Bn) & contribution by Brands	16
7	Trend of NRDL Inclusion: MNSc vs. Domestics	22
8	Average NRDL price cut	22

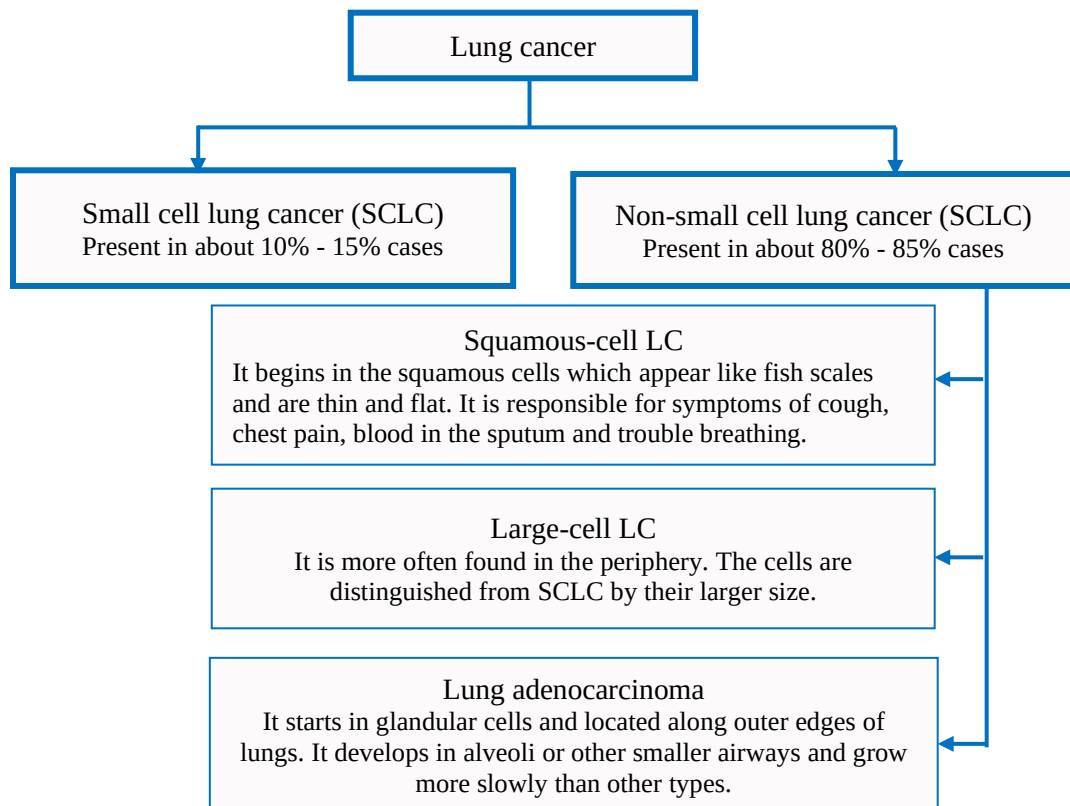
List of Tables

Figure No.	Title	Page No.
1	BHSI schemes	13
2	Keyytruda	17
3	Opdivo	17
4	Tecentriq	18
5	Imfinzi	19
6	Daboshu	19
7	Tuoyi	20
8	Airuika	20
9	Baizean	21

1. Introduction

Globally, lung cancer is the second most common cancer type, accounts for 1 out of 5 malignancies in men and 1 out of 9 in women. Over past few decades, lung cancer incidence has gradually declined in men but has been rising in women (from 7 women out of 100,000 in 1940 to 42 out of 100,000 today). Active and passive Smoking, air pollution, chronic lung disease, radiations, family history are some common risk factors for lung cancer. Sign symptoms are persistent cough, blood in sputum, changes in voice, chest pain, recurrent pneumonia, difficulty swallowing, etc.

1.1 Lung cancer classification



1.2 Stages of NSCLC and Standard of Care (SOC)

The staging classification of NSCLC is based on the size, location and tumor spread. There are five stages from stage 0 to stage IV.

- Stage 0- This is called in situ disease, meaning the tumor is “in place” and has not developed to nearby normal lung tissues or spread out to nearby organs. SOC is Wedge resection segmentectomy or (removal of part of the lobe of the lung)

- Stage I- In this stage tumor has grown but not yet spread to nearby lymph nodes. SOC is radical surgery (lobectomy, sleeve resection, segmentectomy, or wedge resection). Stage I is further divided into 2 sub-stages.
 - Stage IA- Tumor size is less than or equal to 3cm
 - Stage IB- Tumors size is between 3-4cm.
- Stage II-This is further divided into 2 sub-stages, based on spread of tumor to lymph node. SOC is adjuvant cisplatin-based for completely resected NSCLC tumours. Additionally, radiotherapy for patients with N2 lymph nodes.
 - Stage IIA-Tumor size is more than 4 cm but less than or 5 cm and it is not spread to the nearby lymph nodes.
 - Stage IIB- Tumor size is less than 5 cm, and it is spread to the N1 lymph nodes within the lung.
- Stage III- In this stage, cancer has spread to lymph nodes present in the area between the lungs called mediastinum. Further, divided into 3 sub-stages IIIA, IIIB, or IIIC. SOC is 4 cycles of cisplatin-based chemotherapy plus a 3rd generation cytotoxic agent or a cytostatic (anti-EGFR, anti-VEGFR) drug.
- Stage IV- SOC is combination of cisplatin-based chemotherapy and 3rd generation cytotoxic agent or a cytostatic (anti-EGFR, anti-VEGFR) drug.
 - Stage IV 4-In this stage, cancer spreads to entire chest and/or one organ outside chest.
 - Stage IVB has spread outside of the chest to more than 1 place in 1 organ or to more than 1 organ.

1.3 Biomarker testing for NSCLC

Driver mutation and PD-L1 are two types of biomarkers for NSCLC testing. Driver mutations cause normal cells to become cancerous and further support their growth. Driver mutation that are found in NSCLC are: Anaplastic lymphoma kinase (ALK) rearrangement, Epidermal growth factor receptor (EGFR) mutation, BRAF-V600E mutation, Kirsten Rat Sarcoma (KRAS) mutation, Mesenchymal-epithelial transition factor (MET) exon 14 skipping, NTRK (neurotrophic receptor kinase) gene fusion, ROS2 (receptor tyrosine kinase). PD-L1 is the protein found on surface of cells and prevent T-cells from destroying cancer cells. PD-L1 is high if it is found on more than 50% of cells and low if it is found on 1% to 49% of cells.

1.4 Treatment for NSCLC

1.Surgery- Surgery to remove cancer is carried out for initial stages of NSCLC. Types of surgeries are:

- **Lobectomy:** Lobectomy is surgery done to remove entire lobe and it is by far most effective type of surgery.
- **Wedge resection:** Wedge resection is surgery to remove tumour and some nearby health tissues. When slightly large amount of tissue and lymph nodes are taken, it is called segmentectomy.
- **Pneumonectomy:** Pneumonectomy is surgery performed to remove entire lung.
- **Sleeve resection-**Sleeve resection is surgery performed to remove part of bronchus.

2.Radiation therapy- Radiation therapy involve high intensity x-rays or other particles to kill cancer cells or prevent their growth. It can be external or internal. In external-beam radiation therapy, radiations are aimed at cancer from machine outside body, while in internal radiation therapy, radioactive substance is placed close to cancer and delivered via needle, wires, seeds, or catheters.

3.Chemotherapy- Chemotherapy is use of anti-cancer drugs that are either taken through IV or orally. Commonly used drugs are Carboplatin, Cisplatin, Docetaxel, Gemcitabine, Etoposide, Paclitaxel, Pemetrexed among others. Chemotherapy can cause side effects like Hair loss, Mouth sores, Loss of appetite or weight changes, Nausea, and vomiting, Diarrhoea, or constipation.

4.Targeted therapy- Targeted therapy is a treatment targeted to specific genes, proteins, or the tissue that catalyses cancer growth and survival. This type of treatment prevents the growth and spread of cancer cells and limits damage to healthy cells. Targeted therapy for NSCLC includes:

- **EGFR inhibitors-**10% to 15% of all lung cancer are EGFR positive. EGFR are proteins found on the surface of cells. Epidermal growth factor attaches to EGFR and supports cell growth. EGFR inhibitors block epidermal growth factor to attach to cancer cells, thus stops cancer cells from growing and dividing. EGFR inhibitors approved for NSCLC are Afatinib, Dacomitinib, Entrectinib, Erlotinib, Gefitinib, Osimertinib

- Anaplastic lymphoma kinase (ALK) inhibitors- Like EGFR, ALK is also a protein that contributed to cell growth process and ALK inhibitor stops this process. About 4% of NSCLC are ALK positive. ALK inhibitors approved for NSCLC are Alectinib, Brigatinib, Ceritinib, Crizotinib, Lorlatinib
- ROS1 fusion-About 1%-2% of NSCLC have rearrangement in ROS1 gene. This rearrangement causes problem with cell growth and differentiations. Drugs targeting abnormal ROS1 gene are Critotinib, Ceritinib, Loratinib and Enterctinib.
- KRAS G12 mutation-About 20%-25% of NSCLC are having KRAS mutation. Drug approved for KRAS G12 C mutation is Sotorasib.
- NTRK mutation-It is rare (<1%) in lung cancer, cells with this gene mutation can lead to abnormal cell growth. Drugs approved for NTRK mutation are Loratectinib and enrecitinib.
- BRAF V600E mutation- BRAF mutation is found in about 4% of NSCLC cases. Drugs approved for this mutation is Dabrafetinib and Trametinib.
- MET exon 14 Skipping-It is found in about 3% of NSCLC cases. Drugs approved for this mutation are Capmatinib and Tepotinib.
- RET inhibitors- Up to 2% of all NSCLC cases are RET fusion positive. Drugs approved for this fusion are Pralsetinib and Selpercatinib.

5.Immunotherapy- Immunotherapy is use of medicines to boost up immune system to recognize and destroy cancer cells. For patients with NSCLC , immune checkpoint inhibitors (ICI) are used. Two major types of ICIs are:

- PD-1 inhibitors- PD-1 is the protein found on surface of T-cells. T-cells are part of body's immune system. When PD-1 attaches to PD-L1, it prevents T-cells from killing cancer cells. Blocking the binding of PD-1 and PD-L1 allows the T-cells to kill tumor cells. Pembrolizumab and Nivolumab are PD-1 inhibitors, Atezolizumab and durvalumab are PD-L1 inhibitors.
- CTLA-4 inhibitors-CTLA-4 is also a protein on surface of T-cell and have similar function to keep them in check. The drug approved for inhibiting this protein is Ipilimumab.

2. Research question

- What is the current market scenario of PD-1 and PD-L1 inhibitors for treatment of NSCLC in China?
- What would the PD-1 AND PD-L1 inhibitor market look like in coming years?

3. Objectives

- To study population demographics of China and disease burden
- To study multi-tiered healthcare system
- To identify the number of prevalent cases of NSCLC
- To study competitor landscape of Immunotherapy
- To understand outlook of PD-1 and PD-L1 inhibitors therapy

4. Literature review

Author: Markus Gores

Study title and publish date: In the Eye of the Storm: PD-(L)1 Inhibitors Weathering Turbulence Challenges and opportunities as the immune checkpoint inhibitor market matures, May 2022

Source: IQVIA

Insights: According to study conducted by IQVIA, PD-1 and PD-L1 inhibitors is most dynamic market segment and has outperformed the global oncology market with growth rate of CAGR 45% (reaching \$ 36 billion in 2021) over the past 5 years, which is almost three times the growth of overall oncology segment. However, growth for next five year is expected to slow down, estimated to reach % 58 billion by 2025 globally with CAGR of 15%. Taking about different geographies, top 7 developed countries hold share of 79% of global PD-1 AND PD-L1 sales. US holds highest share of 47% in global sales in 2021, EU represent quarter of global market. The sales contribution from China is limited because all MNCs have been excluded from China's NRDL, and domestic offering discounts up to 80% to secure their position in the list.

Author: Jiadi Gan, Wenfeng Fang and Li Zhang

Study title and publish date Therapy of lung cancer in China: introducing the special collection, 2021

Source: <https://journals.sagepub.com/doi/pdf/10.1177/17588359211038199/>

Insights: Lung cancer has the highest incidence and mortality among all cancer types, and is divided into two subtypes, NSCLC and SCLC, account for about 85% and 15% of lung cancer cases in China respectively. Main predictive biomarker for these cancer types is PD-1 and PD-L1 protein expression in tumor cells. As per treatment is concerned, Immune checkpoint inhibitors have become the latest treatment modalities and it is benefitting Chinese population significantly.

Author: Ying Wang

Study title and publish date: China's PD-1 inhibitor market is becoming more competitive, March 2020

Source: https://www.acuitykp.com/blogpdf/?blog_id=9733&download=no

Insights: The article mainly talks about The National Reimbursement Drug List (NRDL) of China. NRDL is set and managed by National Development and Reform Commission (NDRC), Ministry of Human Resources and Social Security (MoHRSS), China Food and Drug Administration (CFDA), and Ministry of Finance. The drugs inclusion in NRDL is done after strict screening and is approved by State medical insurance administration. This allows the brands to have an edge over the competitors thus gaining better market share. However, up to date none of MNCs have been able to secure their position in NRDL, and only one domestic drug Tvyvt(Sintilimab) by Innovent Biologics and Eli Lilly is listed after heavy price cut of 64% from Jan 2020. Despite the heavy price cuts, oncology drugs that are included in NRDL for first time gains revenue sharply and have sales growth of average 20 times vs volume growth of average 47 times.

Author: Shun Lu and Bruce A. Chabner

Study title and publish date: Immuno-Oncology in China, Feb 2019

Source: PubMed(<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6394771/>)

Insights: According to article, about 4 million new cancers cases are diagnosed each year in China, and among them lung cancer has the highest incidence and mortality rate, followed by liver cancer and gastric cancer. Two major types of Immunotherapies that are currently being used include first, Checkpoint inhibitors such as programmed cell death protein 1 (PD-1) and its ligand (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Second is CAR-T cells (Chimeric antigen receptor-T), produced by genetic alteration of human T-cells. Nivolumab (Opdivo) was the first to market PD-1 inhibitor worldwide, subsequently Pembrolizumab (Keytruda), Atezolizumab (Tecentriq), Avelumab (Bavencio) and Durvalumab (Imfinzi) were launched for various cancers. Tisagenlecleucel (Kymriah), and Axicabtagene ciloleucel (Yescarta) are two CAR-T drugs approved for hematologic malignancies. First PD-1 inhibitor to be approved in China was Nivolumab in 2018 for

treating NSCLC in adult patients.

Author: Jin Zhang

Study title and publish date: The PD-1 Race in China Heats Up, 2019

Source: <https://www.pharmexec.com/view/pd-1-race-china-heats>

Insights: The disease spectrum of China is very different from that of the West. Currently, the most prevalent solid tumor types of lung cancer, stomach cancer, liver cancer and esophageal cancer. Due to this, the patient pool for PD-1 AND PD-L1 inhibitors in China is around 2.04 million. This is resulting in companies to focus on development of first line treatment options for these four major indications. On the other hand, domestic Chinese companies like , Hengrui Medicine, Innovent, BeiGene, and Junshi Pharma are applying the approach of targeting the less prevalent indications like melanoma, lymphomas etc due to less competition.

Author: Bicheng Zhang , Yuxiao Song et al.

Study title and publish date: Current status of the clinical use of PD-1/ PD-L1 inhibitors: a questionnaire survey of oncologists in China

Source:

https://www.researchgate.net/publication/338963038_Current_status_of_the_clinical_use_of_PD-1PD-L1_inhibitors_A_questionnaire_survey_of_oncologists_in_China

Insights: According to study conducted by authors, IO therapies for NSCLC have seen the shift from monotherapy to combination therapy, first-line therapy for advanced tumor from second-line therapy and consolidation therapy for locally advanced tumor and neoadjuvant for early0mid stage from salvage therapy. As far the use of PD-1 AND PD-L1 is concerned, they are very popular mong oncologist as about 78% of clinicians used the drugs for indications based on foreign approvals owing to slower approvals in China. One biggest barrier for prescription is poor understanding of mechanism and efficacy of PD-1 AND PD-L1 drugs. Other problems that require attention is the identification of pseudoprogression, hyperprogression and immunity-related adverse effect management.

5. Methodology

5.1 Study area

The study is based on entire China market with the therapy of interest being Immunotherapy for Non-small cell lung cancer.

5.2 Study design

Descriptive and analytical study to evaluate and assess current market of Immunotherapy in China.

5.3 Study duration

The study was carried out for 3 months from 21 March 2022 to 19 June 2022.

5.4 Data collection method

Primary data received from company and secondary search using open sources like PubMed, Globocan, Cancer today, WHO cancer observatory, Sage journals etc.

5.5 Plan of Analysis

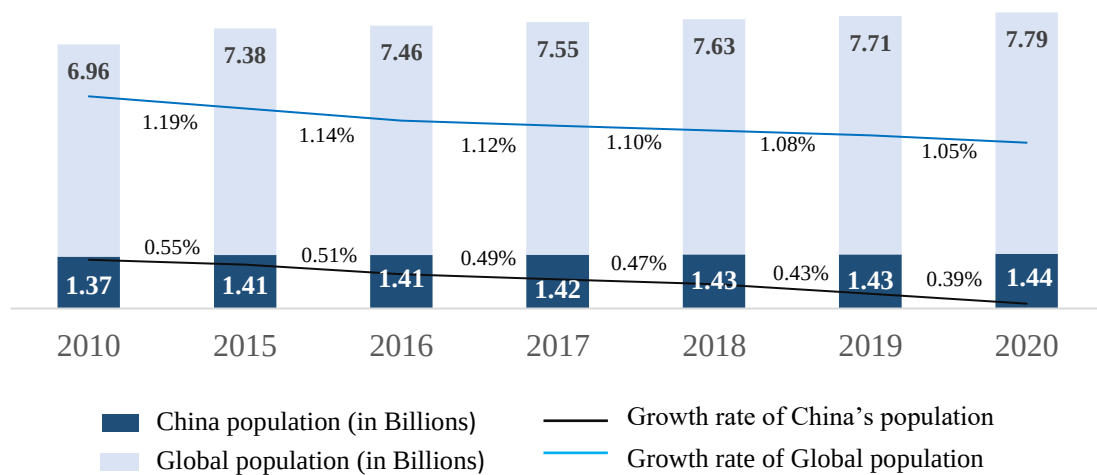
The plan of analysis intends to determine the eligible patient pool by applying all the necessary population filters like disease prevalence rate, diagnosis rate, treatment rate and finally patients on Immunotherapy for NSCLC. Further, the market share of immunotherapy would be calculated after studying the market landscape. The market shares would be then extrapolated to forecast future period of 5 years.

6. Results

6.1 China Demographics

China's total population is 1.44 billion and its 18.47% of global population. Over the past decade, the growth of China's populations had slowed and estimated to degrow after 2030. The female population is 48.71% compared to 51.29% male population. In 2021, approx. 64.7% of the total population in China resides in urban areas.

Figure 1: Global vs. China population



6.2 China disease burden

According to latest Global data of cancer burden, 4.6 million people in China had cancer in 2020, ranking 1st in the world. 3 million people died from cancer which accounts for 30% of world figure. Per capita medical expense stands at USD 936.2/year (RMB6000/year) China Oncology market size stood at US\$ 23.70 billion in 2021, estimated to reach US\$ 35.24 billion by 2027.

China's oncology market alone represents 37% of all lung cancer, 44% of stomach cancer and 52% of liver cancer patients globally.

6.3 Prevalent patients of NSCLC in China

Globally total cancers cases in 2020 were 19,292,789 and lung cancer were estimated at 2,206,771 representing 11.4% of total cases. In comparison, percentage share of lung cancer is 17.9% in China, which is higher than Global. Lung cancer cases in China were estimated to be 815,563 in 2020.

Figure 2: Global vs. China new cancer cases

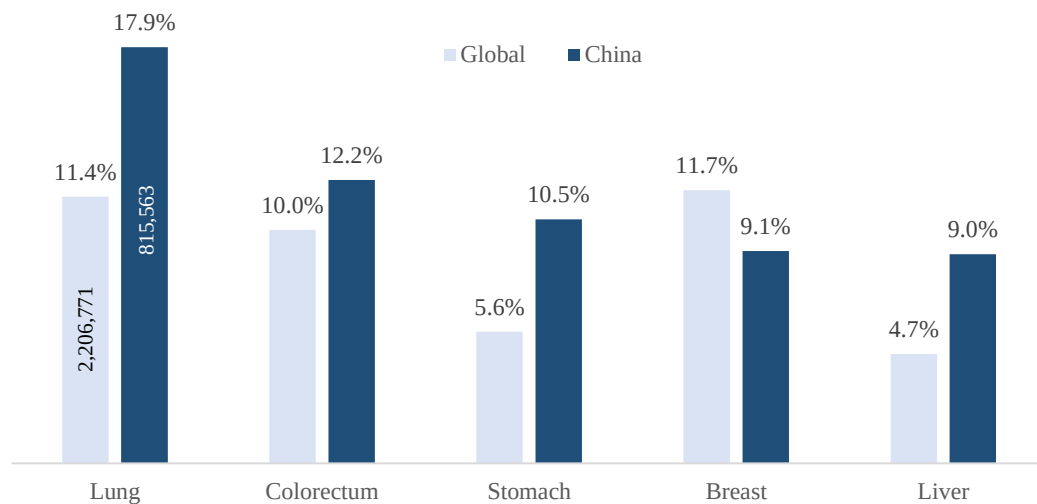


Figure 3: Top 5 cancer types in Males

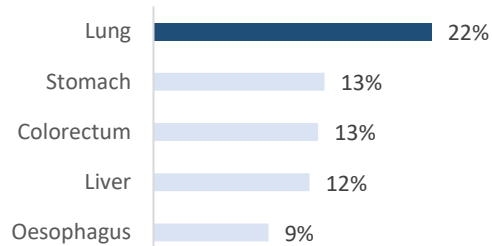
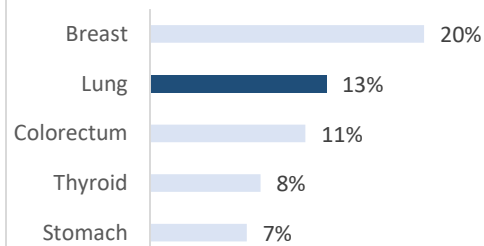


Figure 4: Top 5 cancer types in Females



The bar chart shows top 5 cancer types in males and females. Lung cancer is most prevailing cancer in males, number of cases being 539,181 in 2020. In case of females, it is second highest cancer type and is present in 416,371 females.

To identify NSCLC patient pool epi cuts were applied on total lung cancer cases in China in 2020. Out of total lung cancer cases, 82% cases are of NSCLC. The NSCLC patients that are eligible to take PD-1 and PD-L1 inhibitors are the ones without EGFR/ALK mutations. The average EGFR mutation rate was found to be 45.1%. Further, first-line patient numbers are calculated by applying treatment rate. Patients in following lines of therapy are calculated using progression rate.

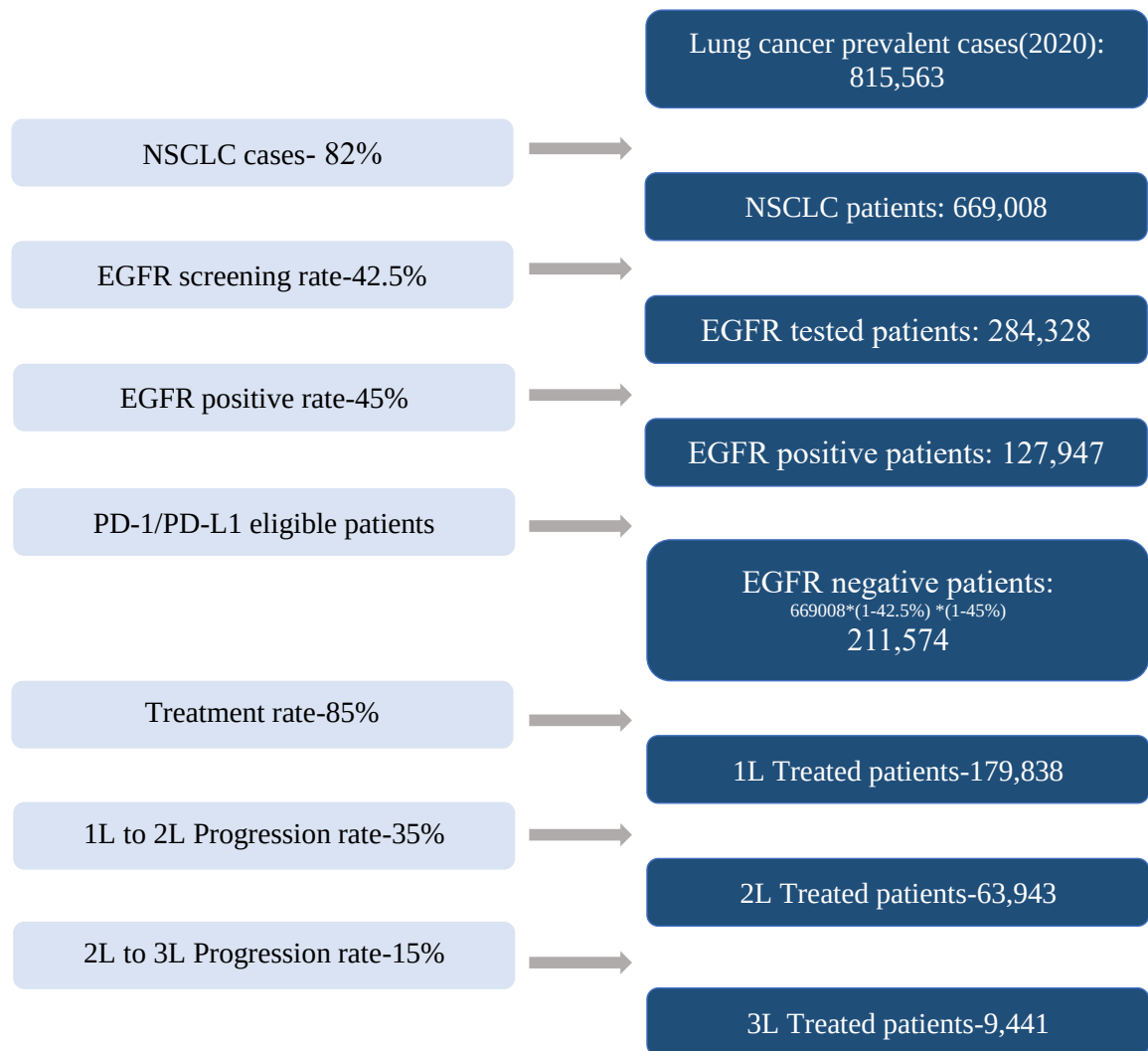


Figure 5: NSCLC Patient funnel

6.4 Multi-tiered healthcare system of China

In China, there is multi-tiered medical insurance system, established to achieve the goal that healthcare is accessible to all, and poor can afford medical costs. The healthcare system includes

- universal health care system (by the national agency): basic medical insurance, urban and rural medical assistance, serious illness aid, and critical illness insurance.
- commercial medical insurance (by commercial insurance organizations),
- medical charity aid (by charity institutions)

6.4.1 Basic medical health insurance (BHSI): Sponsored by central and local government, covering 95% of Chinese population. In the recent updates, Basic Social Health Insurance (BSHI), was divided up into two groups based on employment status and urban/rural resident status as Urban Employee Basic Medical Insurance (UEBMI) for urban and retired employees and Basic medical insurance for urban and rural residents (BMIURR).

Table 1: BHSI schemes

Features	Urban Employee Basic Medical Insurance	Urban Resident Basic Medical Insurance	New Rural Cooperative Medical Scheme
Year established	1998	2007	2003
Target population	Employed urban population	Unemployed urban population	Rural residents
Risk-pooling unit	Municipal level	Municipal level	County level
No of people insured by 2015	288.93 million	376.89 million	670.00 million
Benefit package	75% of OPD and IPD	50% OPD and 55% IPD	50% OPD and 55% IPD
Financing	~8% of salary by employers and ~3% of salary by individual	80% from govt. subsidy and 20% by individual	80% from govt. subsidy and 20% by individual
Annual coverage ceilings	Six times average wage of employee in city	Six times disposable income of local residents	Eight times income of local farmers

6.4.2 Critical illness insurance (CII): CII provides reimbursements to patients with critical illness for out-of-pocket healthcare expenditures the exceeds certain level of BMI reimbursement. It does not required patients to pay additional premium, as it is funded through BHSI surplus. The reimbursement rate of CII is decided by central government, and it should not be less than 50%-60%. The specific financing patterns can be divided into two types.

- Allocation of a certain percentage (~ 5%) of the SRBMI fund to the CII fund. It has been implemented in provinces of Beijing, Fujian, Guangdong, Guizhou, Hubei,
- Using a certain amount (RMB 28 to RMB 80/ person) from the SRBMI.

The National Reimbursement Drug List: NRDL is major mechanism for improving access and reimbursement of hospital purchased drugs. It was established in China 2000 and covers almost 98% of the entire population. The list is regulated and negotiated by National Healthcare Security Administration (NHSA) and drugs listed are reimbursed by public insurance. It was updated thrice before 2017 but is updated yearly post that. It is currently standing at 2,800 inclusions, compared to 2,588 in 2017.

NRDL has two category lists:

- **List A:** Low-priced and Essential drugs that are 100% reimbursed
- **List B:** Higher-priced or innovative that are partially reimbursed (10%-90%) with the aim to increase affordability, access and reduce patient's out of pocket expenses.

To get into NRDL list, products must fulfill standards set based on

- Product clinical efficacy and high unmet need
- Cost effectiveness and budget impact (Favorable pharmacoeconomic profile)
- Physician familiarity and comfort in prescribing the drug
- International reference pricing (IRP)
- Product price in the private market
- Initiate voluntary price cuts

Inclusion in NRDL offers advantages like surge in sales, increased market penetration,

greater transparency helping manufacturers understand drivers for access to list. However, there are drawbacks linked to NRDL inclusion like heavy price cut demanded by government, domestic products are more favored by government etc.

6.4.3 Value Based Procurement: VBP was implemented in 2019 with aim of lowering the prices of generic drugs and to eliminate poor grade generics. It works by group purchasing order (GPO). GPOs are medical institutes that participate in bidding and supply chain management. Bidding process is as follows:

- The purchaser decides on a volume based on historic data
- The volume decided by the purchaser is put forward through an application
- The seller bargains/bids for a final price
- The bidding takes place via a centralized procurement system
- Final price is determined, and the deal moves to a procurement transaction mode.

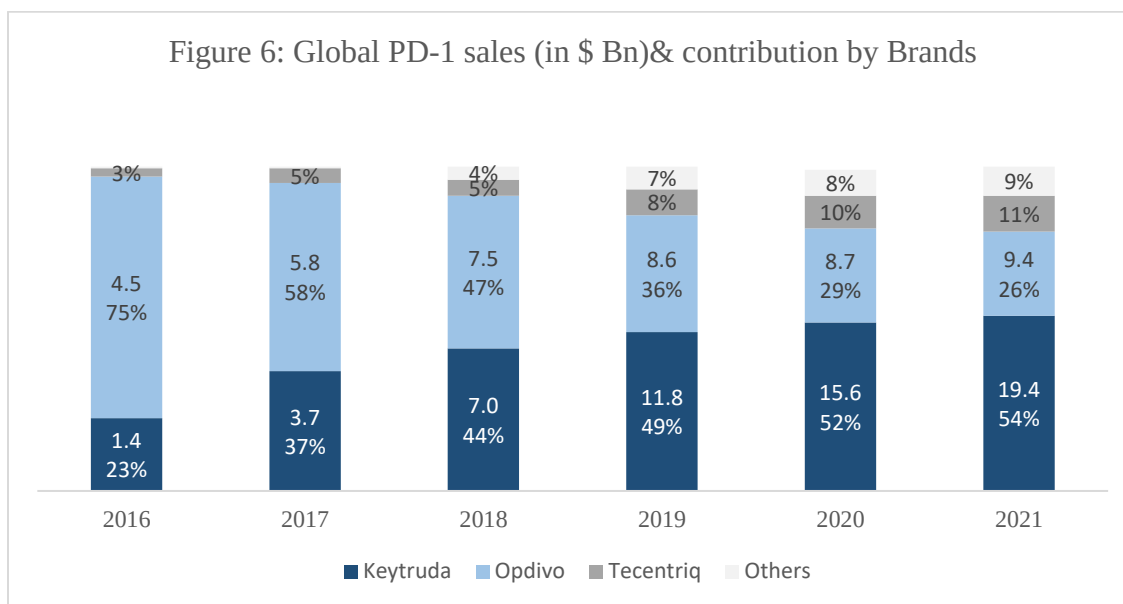
Although VBP inclusion has advantages like rise in sales volume, but it lowers revenue generation by manufacturers, other drawbacks include excessive demand hindering supply chain, creation of monopoly etc.

6.5 Overview of PD-1 and PD-L1

6.5.1 Market overview

The global PD-1 and PD-L1 inhibitors market is set to record market value of US\$ 43.7 Bn in the year 2022 with a CAGR of 10.7% for period of 2022-2030. By indication, NSCLC segment will lead the market and is projected to account for 37.0% of the total market revenue share in 2022. Major brands in global markets are — Keytruda, Opdivo, Tecentriq, Imfinzi, Bavencio, Libtayo, and Jemperli. However, 80% of market is captured by Opdivo and Keytruda together, although Opdivo shares are being squeezed by Keytruda. Apart from these two leading brands, Tecentriq holds sizeable market share of about 11%, whereas all other brands have limited share of 9% combined. This also includes three domestically approved ones in China— Tyvyt, Baizean, Tuoyi.

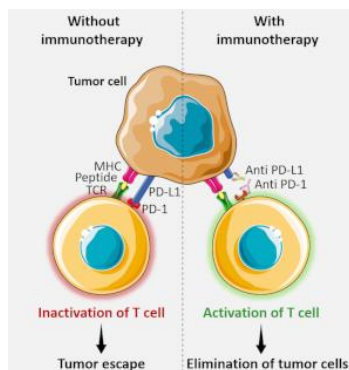
Figure 6: Global PD-1 sales (in \$ Bn)& contribution by Brands



6.5.2 Mechanism of action

One of the important characteristics of immune cells is it's ability to distinguish between healthy cells and tumor cells, and this helps them to selectively attack foreign cells. This characteristic is due to presence of “checkpoint” proteins on the surface of immune cells. The checkpoints act like a switch that turns on/off to generate immune response.

One such protein is Programmed cell death protein 1 or PD-1. It is present on surface of T-cells and keeps it from attacking healthy body cells by attaching to PD-L1. Sometimes, these checkpoints are used by cancer cells to avoid being attacked by immune cells. Binding of PD-L1 to its receptor suppresses T cell mediated tumor killing. Inhibitors of PD-1 and PD-L1 disrupt PD-1 axis thereby reverses T cell suppression and generates antitumor responses for patients with a wide range of cancers.



6.5.3 Competitor Landscape

Keytruda	
Company	Merck
API	Pembrolizumab
China approval date	2018
Loss of exclusivity	2036(US)
Total number of indications approved in China	8 indications among 5 different types of cancers including, 1L NSCLC (monotherapy and combination), 2L advanced Melanoma, 1L Advanced Esophageal, 2L advanced esophageal PD-L1positive
NSCLC targeted indication	1L treatment of patients with non-squamous NSCLC without EGFR or ALK mutations in combination with Eli Lilly's pemetrexed and platinum chemo, 1L treatment of patients with metastatic squamous NSCLC in combination with carboplatin and paclitaxel, Monotherapy for first-line treatment of local advanced or metastatic NSCLC whose tumors express PD-L1 (tumor proportion score [TPS] $\geq 1\%$)
NRDL inclusion	No
SKUs	100 mg/4 mL (25 mg/mL) solution in a single-dose vial

Table 2: Keytruda

Opdivo	
Company	Bristol Mayer Squibb
API	Nivolumab
China approval date	2018
Loss of exclusivity	2027
Total number of indications approved in China	5 indications including 1L advanced Gastric cancer, non-small cell lung cancer, squamous cell carcinoma of the head and neck, 1L Melanoma
NSCLC targeted	Locally advanced or metastatic NSCLC after prior platinum-based

indication	chemotherapy in adult patients without EGFR or ALK genomic tumor aberrations
NRDL inclusion	No
SKUs	40 mg/4 mL, 100 mg/10 mL, 120 mg/12 mL in a single-dose vial solution in a single-dose vial

Table 3: Opdivo

Tecentriq	
Company	Roche
API	Atezolizumab
China approval date	2020
Loss of exclusivity	2028(US)
Total number of indications approved in China	5 including non-squamous non-small cell lung cancer, small cell lung cancer, hepato-cellular carcinoma.
NSCLC targeted indication	Adjuvant treatment following resection and platinum-based chemotherapy in patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on $\geq 1\%$ of tumor cells 1L treatment of adult patients with metastatic NSCLC (PD-L1 stained $\geq 50\%$ of tumor cells [TC $\geq 50\%$] or PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq 10\%$ of the tumor area [IC $\geq 10\%$]), with no EGFR or ALK genomic tumor aberrations IL treatment of adult patients with non-squamous NSLCL in combination with chemotherapy
NRDL inclusion	No
SKUs	840 mg/14 mL (60 mg/mL) and 1,200 mg/20 mL (60 mg/mL) solution in a single-dose vial

Table 4: Tecentriq

Imfinzi	
Company	AstraZeneca
API	Durvalumab
China approval date	2019
Loss of exclusivity	2031(US), 2032 (China)
Total number of indications approved in China	2 including maintenance therapy for advanced stage NSCLC and first-line extensive stage small-cell lung cancer
NSCLC targeted indication	Unresectable stage III NSCLC whose cancer has not progressed after treatment with chemotherapy and radiation (chemoradiation)
NRDL inclusion	No
SKUs	120mg/2.4ml (50mg/ml) and 500mg/100ml (50mg/ml)

Table 5: Imfinzi

Daboshu (Tvyvt)	
Company	Innovent biologics and Eli Lilly
API	Sintilimab
China approval date	2018
Loss of exclusivity	-
Total number of indications approved in China	4 including 1L sq NSCLC, 1L nsq NSCLC, Chronic Hodgkin lymphoma and hepatocellular carcinoma
NSCLC targeted indication	1L nsq NSCLC in combination with pemetrexed and platinum chemotherapy 1L sq NSCLC In combination with gemcitabine and platinum chemotherapy
NRDL inclusion	Yes in 2019
SKUs	100mg(4ml) and 100mg(10ml)

Table 6: Daboshu

Tuoyi	
Company	Junshi Biosciences
API	Toripalimab
China approval date	2018
Loss of exclusivity	
Total number of indications approved in China	4 including Nasopharyngeal carcinoma, melanoma, and urothelial carcinoma
NSCLC targeted indication	-
NRDL inclusion	Yes
SKUs	240mg(6ml) and 80mg(2ml)

Table 7: Tuoyi

AiRuiKa	
Company	Jiangsu Hengrui Medicine
API	Camrelizumab
China approval date	2018
Loss of exclusivity	-
Total number of indications approved in China	8 including chronic Hodgkin lymphoma, 1L sq NSCLC, 1L nsq NSCLC, Hepatocellular carcinoma, Nasopharyngeal carcinoma and esophageal squamous cell carcinoma
NSCLC targeted indication	1L non-squamous NSCLC in combination with chemotherapy, 1L squamous NSCLC in combination with chemotherapy
NRDL inclusion	Yes
SKUs	200mg

Table 8: AiRuika

Baizean	
Company	Beigene Ltd.
API	Tislelizumab
China approval date	2019
Loss of exclusivity	-
Total number of indications approved in China	8 including multiple approvals in NSCLC, chronic Hodgkin lymphoma, Hepatocellular carcinoma, esophageal squamous cell carcinoma
NSCLC targeted indication	1L non-squamous NSCLC in combination with chemotherapy, 1L squamous NSCLC in combination with chemotherapy, 2L/3L locally advanced or metastatic NSCLC
NRDL inclusion	Yes
SKUs	100mg/10ml

Table 9: Baizean

6.6 Future Outlook

Increasing Healthcare spending will contribute to growth of PD-1 and PD-L1 market

The health expenditure in China has raised from 500 billion yuan in 2000 to higher than 6.5 trillion in 2019. The drivers for this growth are increasing living standard and aging population. The share of population being covered by basic health insurance has also grown in last decade. Number of people covered in BHSI surpassed 1 billion in 2017 and as of 2019 more than 96% of population got covered.

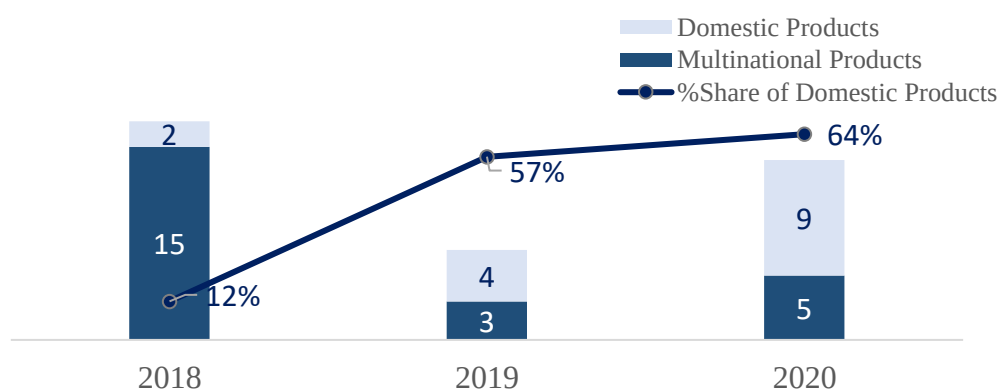
Fragmentation of marketplace: Opportunity for late-comers

The market is getting increasing crowded with brands aiming to get market share. But as brands like Keytruda, Opdivo, Baizean are deeply entrenched, thus will be able to hold dominant position in coming years as well. Late-comers might face fragmentation that will drive them to smaller market segment.

Current regulatory framework to be in favor of domestic firms, Challenge for MNCs

Over the past few years, the ratio of domestic oncology brands getting listed in NRDL is being constantly increasing in comparison with MNCs. Securing position into NRDL list will help brands like Baizean, Daboshu, AiRuiKa and Tuoyi to penetrated deeper into marketplace. However, as none of the MNCs are yet into NRDL, there market share might be taken over by these emerging domestic brands.

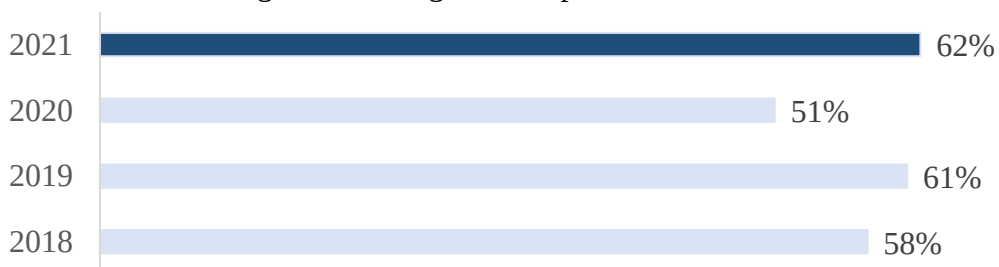
Fig 7: Trend of NRDL Inclusion: MNSc vs. Domestic



Impact of NRDL listing on market shares

For getting included into NRDL list, brands are required to bear heavy price cuts, sometimes as high as 90%, brands like BaiZean, AiRuika and Tuoyi have slashed their prices by almost 80% to win their places. However, 80% discounts is too much for brands like Keytruda and Opdivo as they were already launched with almost half the price as in U.S. This lack of inclusion is likely to affect their market share in future.

Figure 8: Average NRDL price cut



7. Conclusion

Lung cancer has the highest incidence and mortality among all cancer types, and is divided into two subtypes, NSCLC and SCLC, account for about 85% and 15% of lung cancer cases in China respectively. Main predictive biomarker for these cancer types is PD-1 and PD-L1 protein expression in tumor cells. As per treatment is concerned, Immune checkpoint inhibitors have become the latest treatment modalities and it is benefitting Chinese population significantly. The MNC brands that have established strong foot in China market are Keytruda, Opdivo, Tecentriq and Imfinzi. In recent year, a lot of domestic companies like Daboshu, BaiZean, Tuoyi and AiRuika are also entering into PD-1 drug categories. Current regulatory framework of China seems to be in favor of domestic firms as they are being preferred to be included in National drug reimbursements list, while MNCs still struggling for it. The future seems bright for PD-1 inhibitors due to changing population demographics, increasing prevalence of lung cancer and entry of new comers.

8. References

- Gco.iarc.fr. 2022. [online] Available at:
<<https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf>>
- Gco.iarc.fr. 2020. [online] Available at:
<<https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf>>
- GORES, M., 2022. [online] Iqvia.com. Available at: <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia_in-the-eye-of-the-storm_pd-1-inhibitors-weathering-turbulence_05-22-forweb.pdf>
- [https://www.jto.org/article/S1556-0864\(20\)30375-0/fulltext](https://www.jto.org/article/S1556-0864(20)30375-0/fulltext)
- <https://remapconsulting.com/may-nrdl-china/>
- [https://www.jto.org/article/S1556-0864\(20\)30375-0/fulltext](https://www.jto.org/article/S1556-0864(20)30375-0/fulltext)
- <https://www.pharmexec.com/view/china-2021-national-reimbursement-drug-list-outlook>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6465746/>
- <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/types-treatment>
- <https://www.cancer.gov/types/lung/patient/non-small-cell-lung-treatment-pdq>
- <https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/by-stage.html>
- <https://www.nccn.org/patients/guidelines/content/PDF/lung-metastatic-patient.pdf>
- <https://www.cancerresearch.org/en-us/news/2020/pd-1-l1-combination-drug-trial-strategies-increase>
- <https://www1.hkexnews.hk/listedco/listconews/sehk/2020/1210/9543812/sehk20112200230.pdf>
- <https://clarivate.com/blog/mainland-chinas-nrdl-the-expensive-yet-priceless-ticket-to-market-access/>
- <https://www.macrotrends.net/countries/CHN/china/healthcare-spending>
- <https://www.frontiersin.org/articles/10.3389/fimmu.2020.01508/full>
- <https://www.fiercepharma.com/pharma-asia/merck-follows-opdivo-s-suit-prices-keytruda-china-at-half-its-u-s-tag-report>