IDENTIFYING SUCCESS FACTORS FOR BIOMARKER-BASED DRUGS IN NSCLC (NON-SMALL CELL LUNG CANCER)

Dissertation submitted to

IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

In

Pharmaceutical Management

By

Paras Soni (0258)

Under the supervision and guidance of

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2022

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DECLARATION

I hereby declare that this dissertation titled **Identifying Success Factors for Biomarker-Based Drugs in NSCLC (Non-Small Cell Lung Cancer)** is the bonafide record of my original research work. I attest that it has never been used to obtain a degree or diploma from another college or organization. Any information that was obtained from published or unpublished works by other persons has been properly acknowledged in the text.

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CERTIFICATE

This is to certify that dissertation titled **Identifying Success Factors for Biomarker-Based Drugs In NSCLC (Non-Small Cell Lung Cancer)** is a record of the research that **Paras Soni (0258)** performed under my guidance and supervision toward the completion of the prerequisites for the MBA Pharmaceutical Management degree from the IIHMR University, Jaipur. He approached the research study in an honest, rational, and scientific manner.

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ABSTRACT

Cancer is the disease in which aberrant cells in the body start dividing uncontrollably which can attack and kill normal human tissue and have very strong ability to multiply throughout the body and affect other organs also. It is the second largest reason of mortality globally and incident noticed is 236,740 and 130,180 fatalities in the year 2022. Because of advancement in cancer screening, treatment (such as targeted medicines), and preventive or palliative care survival rates for many types of cancer are improving. This is probably due to the continue developments in this area. Biomarker testing Play a vital role as it is required to determine the best treatment for patients diagnosed with NSCLC. Practical guidelines, such as those issued by NCCN, are useful in choosing the best biomarkers and tests to utilize. Biomarker testing looks for changes in DNA such as mutations, additions, deletions, or rearrangements. Other critical signs, such as the levels of proteins or the amount of tumor DNA in the blood. Knowing this information can help you make decisions about your treatment options. In the last few decades there has been numerous developments in this area and one of those promising developments are biomarker-based treatments. Biomarker-based treatments have very promising efficacy and safety because of their targeted nature. One of the key indications where biomarker driver therapies have made significant changes in patients' life in NSCLC (non small cell lung cancer). Within NSCLC 15 drugs have been approved in last three years across the globe. Among all these drugs Keytruda is the one biomarker-based drug which has done exceptionally well with global sales of 11.10 $bn, 14.38 $bn, and 17.18 $bn in the years 2019, 2020, and 2021 respectively.

This research was intended to understand what key activities are that Merck did so that their drug (Keytruda) is very effective and one of them was to have clinical trials in place the right biomarker testing platform, necessary regulatory approval, and overall engagement with different healthcare stakeholders. And considering Keytruda as analog some of the key success factor that are observed is carefully planned clinical trials, adequately planned testing, or diagnosis ecosystem and final very specific engagement plan. These things have helped to define success factors which will be adopted by manufacturers in the future as well.

Keywords: Biomarker-testing, NSCLC, Treatments, Clinical trials strategy, Commercialization Strategy, Biomarker-based treatments

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ABBREVIATION

AUC	Area Under Curve
ALK	Anaplastic Lymphoma Kinase
ASCO	American Society of Clinical Oncology
BRCA	Breast Cancer gene
BRAF	B-Raf and v-Raf murine sarcoma viral oncogene homolog B
CAGR	Compound Annual Growth Rate
DNA	Deoxyribose Nucleic Acid
DTC	Direct to Consumers
EGFR	Epidermal Growth Factor Receptor
ESMO	European Society of Medical Oncology
EU	European Union
FISH	Fluorescence in situ Hybridization
FDA	Food and Drug Administration
IHC	Immunohistochemistry
KRAS	Kirsten rat Sarcoma Viral Oncogene Homolog
KSF	Key Success Factors
MET	Mesenchymal Epithelial Transition Factor Receptor
MM	Major Markets
MOA	Mechanism of Action
NSCLC	Non-Small Cell Lung Cancer
NGS	Next-Generation Sequencing
NTRK1	Neurotrophic Receptor Tyrosine Kinase
NCCN	National Comprehensive Cancer Network
PD-L1	Programmed Death-Ligand 1 Receptor
PCR	Polymerase Chain Reaction
ROS1	Proto Oncogene Receptor Tyrosine Kinase
RET	Rearranged During Transfection
RAS	Rat Sarcoma Virus
SCLC	Small Cell Lung Cancer
SABR	Stereotactic Ablative Body Radiotherapy

SRS	Stereotactic Radiosurgery
TNM	Tumor Node Metastases
VAF	Variant Allele Frequency
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

One of the cancers which have highest incidence and high rate of deaths is lung cancer remains. It is a variegated disorder having numerous subtypes and pathological and clinical importance. Large-cell, adenocarcinoma, squamous-cell carcinoma are frequent subtypes of NSCLC. Furthermore, identification of molecular anomalies in different genes found in lung cancer patients within recent years has supported development of many targeted drugs, opened new horizons and hope. Using prognostic biomarkers to identify tumor types that may respond to targeted drugs has resulted in better lung cancer diagnosis. Several platforms like multiplex genotyping platforms like Next-generation sequencing (NGS), Immunohistochemistry (IHC), polymerase chain reaction (PCR) etc. to detect gene amplifications, oncogene mutations and rearrangement are currently being developed for clinical use. technologies are being used to conduct genome-wide molecular analyses so that we can find molecular abnormalities and find out best treatment and most recently one more genotyping platform has been developed i.e., comprehensive genomic platform (CGP) which s used for detection of gene alterations but to limited geography. Improvement in understanding the molecular aspects in lung cancer has helped to identify multiple biomarkers that are useful in the diseases management. Within NSCLC, Programmed death-ligand 1 receptor (PD-L1), MET, RET proto-oncogene, Epidermal growth factor receptor (EGFR), ALK, KRAS, ROS1, NTRK1 (Neurotrophic receptor tyrosine kinase), etc.

1.1 Overall objectives:

The intent of this research is to understand the following:

- To identify biomarker-based drug approved in the last three years
- To identify top selling biomarker-based drug
- To identify clinical development and commercialization approaches adopted by manufacturer of top selling biomarker-based drug
- To understand importance of biomarker testing
- To understand importance of different platform used in biomarker testing

CHAPTER 2: REVIEW OF LITERATURE

2.1 Cancer

In cancer, cells in the body tend to grow uncontrollably and may affect/spreads to other parts of the body. Human body contains trillion of cells and it can develop almost anywhere in the body. Cell division is the process in which human cells normally multiply and grow to form new cells as per body requirement. Cells die when they get aged or get damaged and replaced by new cells. Due to the breakdown of this normal process, abnormal or damaged cells grow and reproduce when they shouldn't. When these cells join, tumors (tissue lumps) can occur. Tumors are of two types first is malignant (cancerous) and second benign (non-cancerous).

Solid tumors are formed by most of the cancer form, except blood cancers. Cancerous tumors spread to other parts of the body called as metastasis and the cells called metastasized. But benign tumors do not infiltrate or spread to surrounding tissues.

2.1.1 **Normal Cells vs Cancer Cells**

Both normal and cancer cells are differed from each other in many ways:

- Cancer cells develop (uncontrollably growth) when there is absence of signals instructing them to do grow. Only in response to such signals normal cells can form
- Cancer cells disregard signals (of process known as apoptosis) that warn cells to cease dividing or die in the regular course of things
- Cancer cells have tendency metastasized compared to the normal cells as they remain the body as they are. They do not move from one part to other part
- Cancer cells give signals to arteries and veins to metastasized and these blood vessels provide nourishment.
- Cancer cells being remain undetected by person’s own immune system. Anomalous or damaged cells are generally eradicated by person’s own immune system.
- Numerous chromosome alterations (such as duplications and deletions of chromosome segments etc.) developed in the cancer cells compared to normal cells

They often depend on so strongly on atypical activity that they can't live without them. As a result, drugs that target cancer cells' abnormal features have been developed.

2.1.2 **How Does Cancer Develop?**

Cancer is developed due to the mutations in the genes (i.e., deletion, alteration pattern etc.) which control how our cells work, specifically how they divide and develop and theses genetic alterations can occur because of the following factors:

- During cells division errors may occur due to some environmental factors, exposure to some radiation etc.
- When damage is caused to the DNA by some toxic substances in the environment which be chemicals from tobacco some people chew or ultraviolet rays from the sun
- There is risk of having cancer in individual if their parents have so basically they can be inherited from our parents

One of the reasons why older people are more susceptible to acquire cancer because as we glow older our bodies capability to remove abnormal or eradicated cells from the body decreases compared to the younger one whose cells have capacity to remove damaged DNA from the body before they become malignant. Cancer that occurs in different person have different genetic alteration. As the malignancy advances, further changes will occur. Same tumor cells may have different genetic alteration which cause cancer in the body.

2.2 Alteration in the different genes which leads to cancer

The genetic alteration in three different genes in the body which is tumor suppressor, proto-onco, and DNA repair genes cause cancer in body.

2.2.1 Oncogenes

Proto-oncogenes normally promote cell proliferation, and these genes mutates to "bad" gene which remained turn on when it shouldn't be. This leads to uncontrolled cell growth eventually developing cancer. E.g., RAS, HER2 family etc.

Few cancer disorders are caused by the inherited proto-oncogene because of mutation in them mutations by activating the oncogene. This affect in many ways as follows:

- The most common ways through which most oncogenes get activated is due to the chromosomal rearrangements that put genes close to each other, triggering gene activation
- Due to gene multiplication, it can create too much of a specific protein, when a gene has several copies

2.2.2 Tumor suppressor genes

These are normal genes which slow down cell division, fix DNA errors if there are any, or warn cells when to die. Due to the alteration in this gene can lead to uncontrolled growth and cancer formation. Oncogenes are produced when proto-oncogenes are active (turned on), but alteration in these can leads to cancer if inactivated. E.g., BRCA1, BRCA2, and p53 or TP53 etc.

2.2.3 DNA repair gene

Errors in the DNA gene in someone's body go unnoticed if DNA repair gene are faulty and these alterations transform into mutations which may lead to cancer in the future. Mutations that occur in DNA repair genes can be both inherited and acquired. E.g., BRCA1, BRCA2, and p53.

2.3 Various cancer types

More than fifty cancer types are named based on which organ or tissue they develop. For example, if there is a tumor in the lungs, we can call it lung cancer or if the cancer is in the endometrial parts, we can call them endometrial cancer and if there is cancer in the brain it can be pronounce as brain cancer because it begins in the brain. It can also be classified based on in what cells types they have grown such as epithelial or squamous cells. Hence, it can be classified as given below:

2.3.1 Carcinoma

Carcinoma is formed on the epithelial cells, which cover both interior and exterior body surfaces. Several types of carcinomas based on their occurrence on different types of cells are given below:

2.3.1.1 Adenocarcinoma

This cancer develops in epithelial cells that secrete fluids or mucus. For example: glandular tissue.

2.3.1.2 Basal cell carcinoma

This cancer starts in the epidermis (it is a person's outer layer of skin including lower and basal cells)

2.3.1.3 Squamous cell carcinoma

This cancer begins in the epithelial cells just below skin's surface, hence, it may also called a skin cancer, which lines the intestines, stomach, bladder, lungs, and kidneys etc. Sometimes it is also known as epidermoid carcinomas.

2.3.1.4 Transitional cell carcinoma

This cancer progresses in epithelial tissues which may be a urothelium or transitional epithelium and these type of tissues lines several parts of the body like ureters, bladder, some part of the kidneys and few other organs in the body also as many organs made up of epithelial tissue or say multiple layers of epithelial cells which helps them to get smaller and bigger. This type generally occurs in the bladder, ureters, and kidneys as they are lined by epithelial cells and made up of epithelial tissue.

2.3.2 Sarcoma

These are the tumors that progresses into the softer tissues in the body is known as sarcoma, for example, blood vessels, lymph vessels, muscle, fat, etc., The examples of most frequent sarcomas are Kaposi sarcoma, Leiomyosarcoma, dermatofibrosarcoma protuberans etc.

2.3.3 Leukemia

These are the cancers that progresses in the tissues that helps in forming bone marrow's blood. As they are involved in forming cancer in the blood forming tissue so, they didn’t form solid tumors instead of this they lead to the formation of the abnormal white blood cells. This cancer disrupts the body's ability to control bleeding, providing oxygen to its tissues, etc. because of the low number of normal cells in the body because the abnormal white blood cells force out the healthy normal cells. Based on how the disease progresses (it is acute or chronic) and what type of blood cell are involved in the malignancy in which the cancer starts (E.g., lymphoblastic, or myeloid). This cancer grows rapidly in acute types and gradually in chronic variants.

2.3.4 Lymphoma

This cancer develops in T or B cells (lymphocytes) known as Lymphoma. In Lymphoma white blood cells being attacked which fight diseases. In this type of cancer anomalous cells collect in the lymph nodes and arteries and other organs. This cancer is of two types:

2.3.4.1 Hodgkin lymphoma

The aberrant lymphocytes (reed-Sternberg cells) are found in people who suffer from this condition. B cells are most used to create these cells.

2.3.4.2 non-Hodgkin lymphoma

This type of cancer can grow quickly or slowly in the body as this form develop in the T cells and B cells. This form also known as lymphocytic cancer because they start in lymphocytes.

2.3.5 Multiple Myeloma

This cancer starts in plasma cells. They can cause tumors in the bones all over in the body if they pile up in the bone marrow. Multiple Myeloma is also known as Plasma cell myeloma and Kahler disease.

2.3.6 Melanoma

The cancer that starts developed into specialized cells called as melanocytes that produce melanin (It is the pigment that provide skin its color in the body) is called Melanoma. As this cancer develop in the pigmented tissues in the body so, they also have ability to develop in the other pigment tissue in the body.

2.3.7 Brain and Spinal cancer

This cancer develops in the brain or the spinal cord. This cancer has variety of forms and given the name based on what cell type the cancer develops and the location in the CNS. For example, cancer that starts in astrocytes (a star shaped cells in the brain) are called as astrocytic tumor and these cells helps in maintaining healthy nerve cells. Same as all other type of cancer this cancer can also be benign or

2.4 Staging in cancer

There are several other techniques for staging cancer, but the TNM approach is the most prevalent and suitable for most of cancer and their forms. This classification system is maintained by two organization first is American Joint Committee on Cancer and the second is Union for International Cancer Control as a guideline for doctors to stage any cancers which are affected by many common principles as per this staging system.

The stages of cancer can be assessed using the TNM system approach in which cancer is given letter or number to describe different categories as per follows:

- The letter T is denoted as tumor in this staging system and describe the primary tumor
- Followed by letter T, letter N denoted Node it describes cancer spread to nearby lymph node
- And in last the letter M denotes as metastasis which means if cancer spread to other body parts

2.4.1 The primary tumor (T category)

Doctors start by looking at the site where the cancer started means the primary point of the tumor or say primary tumor, to see how much and where it is in the body. Different factors like the location of the tumor, tumor size, or its spread to other body parts. Other neighboring tumors are also checked by doctors.

2.4.1.1 T category is given a number or a letter:

- TX indicates no information of the primary tumor, or it cannot be measured.
- T0 signifies no or absence of primary tumor
- Tis also known as pre-cancer or in situ cancer indicates growth in the layer of cancer cells origination, rather than spreading to deeper layers.

Numbers that are indicated after the word T for example, T1, T2 etc. denotes the size of the tumor and/or the extent of dissemination into surrounding cells. Higher the T number indicates expansion into adjacent tissues.

2.4.2 The lymph nodes (N category)

Cancer often progressed to the lymph nodes which are present near the main tumor, thus these are usually evaluated. Lymph nodes make tiny groupings of immune cells in the shape of a bean. Before spreading to other regions of the body, many kinds of cancer frequently expand to surrounding lymph nodes.

2.4.2.1 The N category can be allocated a number or a letter:

- NX indicates that the information of lymph nodes near primary tumor are not assed hence, cannot be analyzed
- N0 implies that no presence of malignancy in the lymph nodes nearby to the primary tumor

The different number after the letter N is given as N1, N2 etc. to show the location, number, and size of lymph nodes affected. Greater the N number indicates cancer spread to distant lymph nodes.

2.4.3 Metastasis (M category)

To detect cancer spread, doctors may examine different body tissues. The term "metastasis" refers to cancer spreading to sections of the body other than the main tumor.

2.4.3.1 The M category is assigned a number:

- M0 indicates there has been not any evidence of faraway spreading of cancer in the body
- M1 implies metastasis

TNM categories also have subcategories for certain cancer types. After the category, these are identified with lowercase letters. T3a or T3b are examples. There may be fewer category selections for some cancer types than for others. Some malignancies, for example, might not be classified as N3.

2.5 Lung cancer

As discussed earlier the name given to the cancer where it develops. Similarly the cancer that develops in lungs means when the primary tumor develops in the lungs it is called as lung cancer.

2.5.1 Lung cancer types

It is divided into two broad categories, which are treated differently.

2.5.1.1 NSCLC

Most of the incident cases that comes in lung cancer overall is accounts in NSCLC which comprises for around 80% to 85% of total lung cancer incidences. NSCLC can be classified into three basic subtypes based on in which lung cell they have started developing uncontrollably and named as squamous-cell, adeno, and large-cell carcinoma. This carcinomas may have comparable prognoses and therapy.

2.5.1.1.1 Adenocarcinoma

As discussed before cancer that develops in the cells secreting mucous or like material called adenocarcinomas. Usually, this type of cancer most common in smokers and it can also be found in the non-smoker also.

2.5.1.1.2 Squamous-cell carcinoma

These are the flat cells in lung airway lining and if cancer develop in these cells than it is called as squamous cell carcinomas

2.5.1.1.3 Large cell (undifferentiated) carcinoma (LCC)

Cancer that develops in the large cells or in any part/area of the lungs is called large cell carcinoma. This subtype of NSCLC grows and spread quickly because of which make up treatment further complicated. One of the subtypes of LCC known as neuroendocrine carcinoma is the fast-growing malignancy same as small cell lung cancer (SCLC).

2.5.1.1.4 Other subtypes

Other NSCLC subtypes include adenosquamous and sarcomatoid carcinoma.

2.5.1.2 SCLC

It represents 10-15% of total lung cancers. SCLC spreads very quickly and progress faster as compared to NSCLC and nearly 70% of people who have SCLC, the cancer has already metastasized at first diagnosis. The best treatment option is chemotherapy and radiation therapy because SCLC spreads very quickly and once patient is treated with both of these than there is high chance that SCLC will develop again in the body of patients who already got treatment.

2.6 Incidence and Mortality

In 2022, the following are the incidence, mortality:

- Projected new cases are 236,740
- Projected mortality is 130,180

Lung cancer is leading cause of cancer-related death in the United States is because of the because their incident rate is very high. The 5-year survival rate from the year 2011 to 2017 for lung cancer patients was 22%.

2.7 NSCLC

NSCLC occurs in the epithelial cells of the lungs in the body. The most common and frequent subtypes of NSCLC are large cell, adeno, and squamous cell carcinomas. The WHO/IASLC classified NSCLC as:

- Squamous cell carcinoma (SCC) makes up to 25% of NSCLC

- Adenocarcinoma (AC) affects 40 percent of patients in NSCLC
- Lung tumors with large cell carcinoma (LCC) account for 10 percent of all malignancies.

2.8 Molecular Features

Molecularly targeted therapies have emerged in the recent times due to the discovery of various mutations in different genes in the body to help patients with metastatic illness so that they live longer. Specific mutations in genes determining KRAS, PD-L1, EGFR, ROS1, BRAF, ALK, etc. and can now be used to define subsets of adenocarcinoma. The following are genomic abnormalities that can be targeted with licensed medications or for which treatments are being developed:

Table 1: Different biomarkers in NSCLC and their positive genomic alteration

Biomarker name	Genomic alteration
EGFR	EGFR exon 19 deletion or L858R mutation
	EGFR S768I, L861Q, and/or G719X mutations
	EGFR Exon 20 insertion mutation
KRAS	KRAS G12C mutation
ALK	ALK rearrangement
ROS1	ROS1 rearrangement
BRAF	BRAF V600E mutation
NTRK	NTRK 1/2/3 gene fusion
MET	METex 14 skipping mutation
RET	RET rearrangement
PD–L1	PD–L1 ≥50% and negative for actionable molecular biomarkers above
	PD–L1 ≥1%-49% and negative for actionable molecular biomarkers above

	PD–L1 <1% and negative for actionable molecular biomarkers above

Nonsmokers' adenocarcinomas are more likely to have EGFR and ALK mutations, while smokers' and former smokers' adenocarcinomas are more likely to have KRAS and BRAF mutations.

2.9 Importance of biomarkers in NSCLC

2.9.1 Biomarkers

Biomarkers are biological substances detected in the blood or tissue that indicate whether a process in the body is normal or aberrant. Biomarker testing is used to check for biological alterations that could be linked to cancer. Biomarkers allow the cancer treatment unit to acquire as much as evidence possible regarding type of lung cancer in the patient's body because there are many distinct types of cancer, and the specific type differs from person to person.

2.9.2 What are the steps involved in biomarker testing?

Biomarker testing could also know as genetic testing which is performed by taking small piece of tissue (called a biopsy) or collecting a blood sample from a patient's tumor and sending it to a lab for testing that can reveal information about the patient's specific tumor makeup. Biomarker testing results aid in the development and guidance of a patient's specific treatment plan, including determining whether targeted therapy is appropriate. A comprehensive biomarker test varies from a single-gene test in that it looks for a larger number of biomarkers for NSCLC than a single-gene test.

2.9.3 Different biomarker testing

Several biomarker testing's have been identified as below:

2.9.3.1 Cytogenetics

If there is any insertion deletion or defect in the structure of human chromosomes, cytogenetics is performed to detect the abnormality.

2.9.3.2 Fluorescence in situ hybridization

It detects and locates a specific DNA sequence in a chromosome is done by this technique.

2.9.3.3 Immunohistochemistry (IHC)

By using this technique to check antigens in the sample of tissue by using antibodies. The process involves is the antibody which is used in this process is basically linked to an dye which is an fluorescent dye or an enzyme and when these antibody transfer into the sample tissue they bind to specific antigen which deactivated the this enzyme or fluorescent dye and then antigen can easily be seen under the microscope and can assess which type of antigen is this.

2.9.3.4 Liquid Biopsy (also called circulating tumor DNA [ctDNA])

Liquid biopsy is the test which is done by taking blood from the body and see if there are any DNA fragments in the sample of blood or not or if there are any tumor cells in the sample or not which means if the examiner able to detect both of these two than the cancer can be detected at the early stage and also helps to plan treatment. The overall purpose of doing this biopsy test to determine which treatment could be best for patients and to detect if cancer have developed again after the treatment or not.

2.9.3.5 Next-Generation Sequencing (NGS)

In this method of DNA sequencing, it is a tool that can handle many DNA sequences at one time which takes less than any other DNA sequencing technique because in other techniques only one DNA can be sequenced at one time as compared to NGS in which many DNA can be sequenced hence able to show any alteration in many genes at single time. NGS3 stands for massively parallel sequencing.

2.9.3.6 Sanger Sequencing

In this PCR technique is used to detect any defect in the specific region of the genes.

2.9.3.7 Somatic Testing

This kind of testing is done to in the laboratory to study different cells or tissue of the body to check whether is there any kind of alteration or not in the genes, proteins, or in chromosomes that could help physician to indicate the presence any disease or condition, such as cancer.

2.9.3.8 Somatic and Germline Paired Testing

A patient's somatic and germline samples were sequenced simultaneously to inform cancer treatment.

2.9.3.9 Variant Allele Frequency (VAF)

VAF is a surrogate estimate of the proportion of DNA molecules in the original specimen having the variant because NGS offers a near random sample.

2.9.4 Why is biomarker testing so important for NSCLC patients?

Knowing certain biomarkers can assist guide a patient's treatment strategy and provide specific information on how the tumor may respond to a particular treatment. Over half of NSCLC patients tested positive for a recognized biomarker. Biomarker testing is important for several reasons:

I. Biomarkers give details about a person's NSCLC.
II. Biomarkers have transformed lung cancer treatment, allowing for improved precision medicine for your lung cancer.
III. To evaluate your biomarker status, comprehensive biomarker testing involves an advanced sort of diagnostic test that analyzes a small amount of tumor tissue.
IV. Knowing your biomarker status could help you get access to medicines that are very successful for your type of NSCLC.
V. For NSCLC patients with adenocarcinoma, there are 15 FDA-approved biomarker-driven targeted medicines, and numerous additional biomarker-driven therapies are in clinical trials for both NSCLC and SCLC.
VI. One immunotherapy medicine is prescribed depending on the presence of the PD-L1 biomarker. Furthermore, regardless of a patient's PD-L1 status, a variety of immunotherapy medicines can be recommended.
VII. Testing for biomarkers can be used to:
    - Determine the presence of an illness or condition.
    - Inform you of the disease's severity.
    - To know how well your body respond to a disease or condition treatment.

2.10 How are patients identified for biomarker and key treatment guideline used for biomarker-based therapy?

Process through which patients are identify for positive biomarker is:

2.10.1 Biomarker Identification

- The sample from the cancer cell is collected to run biomarker testing if patient and doctor both willing to do it

- Depending upon the type of biopsy whether it is liquid biopsy or solid a sample is collected during the process of surgery (in case of solid tumor) and a blood sample (In case of liquid biopsy) or if is not done then a biopsy of the tumor may require for further testing (In case of solid tumor)
- A liquid biopsy may also require if the doctor not able to get the sample of tumor safely
- After that the sample will send to the high-tech labs where sample will run and after that generate the report showing the table of biomarkers which is involved in causing cancer and there treatment option
- The next step is that after getting results of biomarker testing from the lab the doctor team of the patient discuss the results as well as the course of treatment available to the patient
- There is also requirement of biomarker testing of patient's healthy cells to study them which are them compared to the cancerous cells to know different genetic changes that happen during the course of life

2.10.2 Treatment guidelines used for biomarker-based therapy and testing

There are different treatment guidelines used for biomarker-based therapy:

2.10.2.1 NCCN

These guidelines are the most updated clinical practice guidelines and often comprehensive which is accessible in any field of medicine. These are remarkably the standard for clinical management and strategy in care of cancer patients. These Guidelines are intended to support those involved in the care of cancer patients, which include physicians, pharmacists, nurses, patients, etc. in making decisions with the goal to improve patient health and the outcomes of the treatment or therapies.

2.10.2.2 ASCO

ASCO creates and publishes medical practice guidelines, preliminary clinical opinions (PCOs), and guideline endorsements, which provide evidence-based recommendations that serve as a guide for doctors and explain suitable treatment and care procedures. Specific clinical scenarios (disease-oriented) or the usage of approved medical items, procedures, or tests can also be addressed in the guidelines (modality-oriented). ASCO's clinical practice

guidelines are developed by multidisciplinary teams of professionals, including patient advocates.

2.10.2.3 ESMO

ESMO’s guidelines for NSCLC are based on latest research and analysis. Giving recommendations for advance or metastatic stage of the NSCLC is the main focus of these guidelines which includes an update on immunotherapy's importance and the use of the therapies which are of targeted nature for patients having specific gene alterations in their tumor. Personalized medical advice and novel treatment algorithms are also discussed.

CHAPTER 3: METHODOLOGY

3.1 Data collection

Primarily secondary research used to gather information for respective research objective. Secondary research over clinical trials sites, regulatory sites and academics research publication sites and using sources which are authentic and publicly available is considered

3.2 Data Sources

a) Understanding key data sources that may be leveraged to capture the right NSCLC drug specific data
b) Used that list of identified data sources to collect relevant information about different biomarker-based therapies which include information on clinical trial (e.g., clinicaltrial.gov), regulatory agencies (e.g., US FDA, EMA [Japan])
c) Understand key information about the products with the help of manufacturer websites.
d) Understand what different treatment guidelines are. (e.g., NCCN, ESMO, ASCO etc)
e) Research articles
f) Companies' annual reports

3.3 Data Analysis

Synthesis of information was performed, and analysis is done as a top-down approach:

a) First, we started with the view of opportunity
b) Find which is the top performing biomarker-based drug in the last three years
c) Understand the sales of to the top performing biomarker-based drug in the last three years
d) Find what was the clinical strategy used by top-selling biomarker-based drug in the last three years.
e) Find what was the commercialization strategy adopt by top-selling biomarker-based drug in the last three years at a high level.

f) Finally, to understand Key Success Factors (KSF) which have made the drug blockbuster, and which may be followed by some other manufacturer irrespective of countries

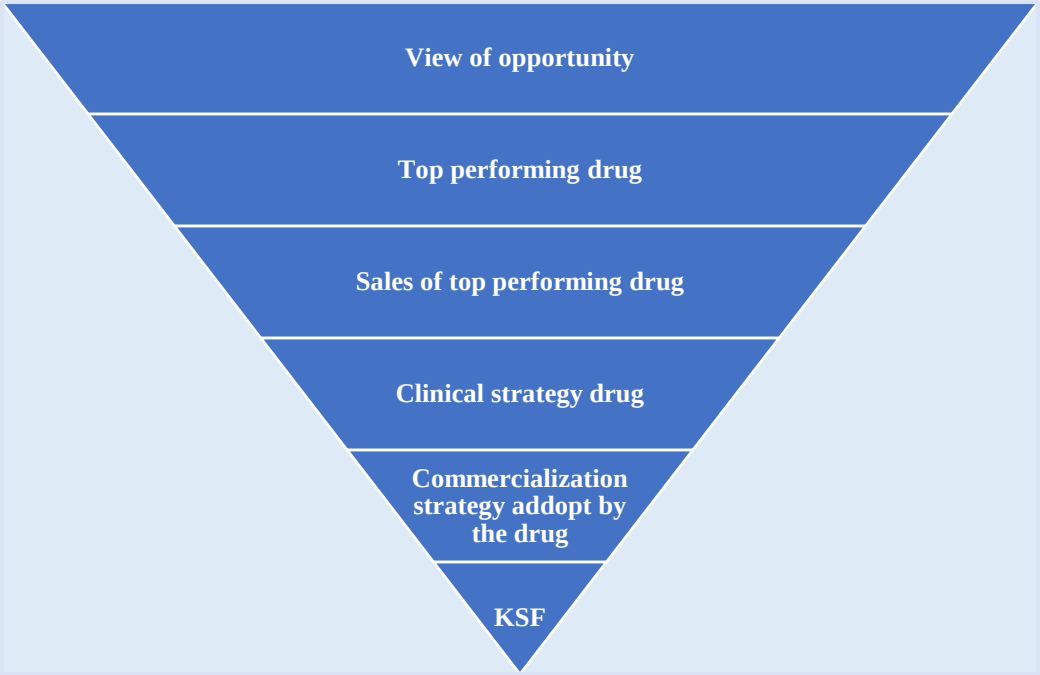

Figure 1: Data analysis (top to bottom) flow chart

CHAPTER 4: RESULTS

4.1 Drug approved for different biomarkers:

Different drugs approved for different biomarkers and their subsequent therapy are given below:

Table 2: Drugs approved for different biomarkers and subsequent therapy

Biomarker name	**Positive Genomic alteration**	**First line therapy**	**Subsequent Therapy**
EGFR	EGFR exon 19 deletion or L858R mutation	Preferred: Osimertinib Other Recommended: Dacomitinib Gefitinib Erlotinib Afatinib Erlotinib + ramucirumab Erlotinib + bevacizumab	**SABR or surgery** **SRS** **Continue Osimertinib**
	EGFR S768I, L861Q, and/or G719X mutations positive	Preferred: Afatinib or Osimertinib Other Recommended: Erlotinib or Gefitinib or Dacomitinib	**Consider definitive local therapy for limited lesion (eg. SABR or surgery)** **SRS** **Osimertinib** **Continue erlotinib (± ramucirumab + bevacizumab) or afatinib or gefitinib or dacomitinib**

	EGFR Exon 20 insertion mutation positive	Systemic therapy Adenocarcinoma Systemic therapy squamous cell carcinoma	**Amivantamab-vmjw or** Mobocertinib Subsequent systemic therapy
KRAS	KRAS G12C mutation positive	Systemic therapy Adenocarcinoma Systemic therapy squamous cell carcinoma	Sotorasib Subsequent systemic therapy
ALK	ALK rearrangement positive	Preferred: Alectinib or Brigatinib or Lorlatinib Other Recommended: Certinib	**Consider definitive local therapy for limited lesion (eg. SABR or surgery)** **Lorlatinib** **Continue Alectinib or brigatinib or certinib or lorlatinib**
ROS1	ROS1 rearrangement positive	Preferred: Entrectinib or Crizotinib or Other Recommended: Ceritinib	**Consider definitive local therapy for limited lesion (eg. SABR or surgery)** **Lorlatinib** **Continue entrectinib or crizotinib or certinib**

BRAF	BRAF V600E mutation positive	Preferred: Dabrafinib + tramtinib Other Recommended: Vemurafenib or Dabrafinib or Systemic therapy Adenicarcinima or squamous cell carcinoma	**Dabrafenib/tranetinib**
NTRK	NTRK 1/2/3 gene fusion positive	Preferred: Larotrectinib or Entrectinib Other Recommended: Systemic therapy Adenicarcinima or squamous cell carcinoma	**Larotrectinib** **Entrectinib**
MET	METex 14 skipping mutation positive	Capmatinib Crizotinib Tepotinib	**Capmatinib** **Crizotinib** **Tepotinib**
RET	RET rearrangement positive	Selpercatinib Pralsetinib Cabozantinib	**Selpercatinib** **Pralsetinib** **Cabozantinib**
PD–L1	PD–L1 ≥50% and negative for actionable molecular biomarkers above	Atezolizumab Cemiplimab-rwlc Pembrolizumab Carboplatin/paclitaxel/bevacizumab/atezolizumab (non-squamous)	
	PD–L1 ≥1%-49% and negative for	Pembrolizumab Carboplatin/paclitaxel/bevacizumab/atezolizumab (non-squamous)	

	actionable molecular biomarkers above		
	PD–L1 <1% and negative for actionable molecular biomarkers above	Systemic therapy Adenicarcinima or squamous cell carcinoma	

4.2 Current treatment practice of biomarker testing in NSCLC

Here are the most popular biomarker testing approaches used in NSCLC to detect the disease and administer the appropriate medication. The following are some common biomarkers tests for detecting distinct biomarkers in NSCLC (according to what tests are now in use for detecting different biomarkers in NSCLC):

Table 3: Current treatment practice for biomarker testing

Biomarker name	Genomic alteration	Tests for detection
EGFR	EGFR exon 19 deletion or L858R mutation	Liquid biopsy, Tissue biopsy, and NGS
	EGFR S768I, L861Q, and/or G719X mutations positive	
	EGFR Exon 20 insertion mutation positive	
KRAS	KRAS G12C mutation positive	NGS and Liquid biopsy

ALK	ALK rearrangement positive	FISH analysis, IHC, NGS, and liquid biopsy
ROS1	ROS1 rearrangement positive	Liquid biopsy, FISH analysis, IHC, NGS
BRAF	BRAF V600E mutation positive	Liquid biopsy, and NGS
NTRK	NTRK 1/2/3 gene fusion positive	Liquid biopsy, NGS
MET	METex 14 skipping mutation positive	Liquid biopsy, NGS, FISH Analysis
RET	RET rearrangement positive	Liquid biopsy, and NGS
PD–L1	PD–L1 ≥50% and negative for actionable molecular biomarkers above	IHC
	PD–L1 ≥1%-49% and negative for actionable molecular biomarkers above	
	PD–L1 <1% and negative for actionable molecular biomarkers above	

4.3 Biomarker based drugs approved with in NSCLC in the last three years

Various biomarker-based drugs approved in the last three years:

4.3.1 Drugs approved in 2019

Table 4: Biomarker-based drugs approved in NSCLC in the year 2019

Brand Name	API/Drug substance	Approved for
Tecentriq	atezolizumab	first-line treatment of metastatic non-squamous NSCLC with no EGFR or ALK genetic tumor abnormalities, use in order with chemotherapy (Abraxane and carboplatin).
Rozlytrek	entrectinib	treatment of NTRK Gene Fusion-Positive Solid Tumors and ROS1-positive NSCLC

4.3.2 Drugs approved in 2020

Table 5: Biomarker-based drugs approved in NSCLC in the year 2020

Brand Name	API/Drug substance	Approved for
Alunbrig	brigatinib	the first line treatment of adult patients with (ALK+) metastatic NSCLC as detected by an FDA-approved biomarker test
Tagrisso	osimertinib	treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC who have progressed on or after EGFR tyrosine kinase inhibitor (TKI's) therapy, as determined by an FDA-approved biomarker test
Tecentriq	atezolizumab	first-line therapy for treatment of metastatic NSCLC with high PD-L1 expression without EGFR or ALK genetic alterations
Cyramza	ramucirumab	first-line therapy in conjunction with erlotinib for metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations
Gavreto	pralsetinib	treatment of RET fusion- positive in NSCLC

Retevmo	selpercatinib	treatment of advanced RET-driven NSCLC
Tabrecta	Capmatinib	treatment of metastatic NSCLC with METex14 mutation

4.3.3 Drugs approved in 2021

Table 6: Biomarker-based drugs approved in NSCLC in the year 2021

Brand Name	**API/Drug substance**	**Approved for**
Tepmetko	tepotinib	treatment of Exon 14 skipping changes in metastatic NSCLC with MET
Lumakras	sotorasib	treatment of KRAS G12C-mutated locally advanced or metastatic NSCLC
Rybrevant	amivantamab-vmjw	treatment of patients with EGFR Exon 20 insertion mutations has NSCLC
Exkivity	mobocertinib	treatment of individuals with EGFR exon 20 insertion mutations who have locally progressed or metastatic NSCLC
Tecentriq	atezolizumab	adjuvant treatment for adults with Stage II-IIIA NSCLC whose tumors express PD-L1≥1%, following surgery and platinum-based chemotherapy
Libtayo	cemiplimab-rwlc	treatment as first line of patients have advanced NSCLC and have high PD-L1 expression in the tumors

4.4 Biomarker drugs sales in the last three years

Overall biomarker drugs sale in the last three years:

4.4.1 Overall biomarker drugs sales in the year 2019

Humira, an immunosuppressive drug developed by AbbVie for psoriasis, arthritis, Crohn's disease, and other conditions, is still the heavyweight champ in the industry. In fact, its $19.6 billion in revenues accounts for 21% of the total sales of the top ten. Humira is also the only drug on this list that hasn't changed from last year, as it maintains its top rank.

Keytruda increased from No. 6 to No. 2 on the best-selling list between 2018 and 2019. From 2018 to 2019, Keytruda has the highest sales rise [among the top 10] with a 54.6 percent increase in global sales." And Keytruda (pembrolizumab) is the only NSCLC treatment to make the list of top selling biomarker drugs in 2019.

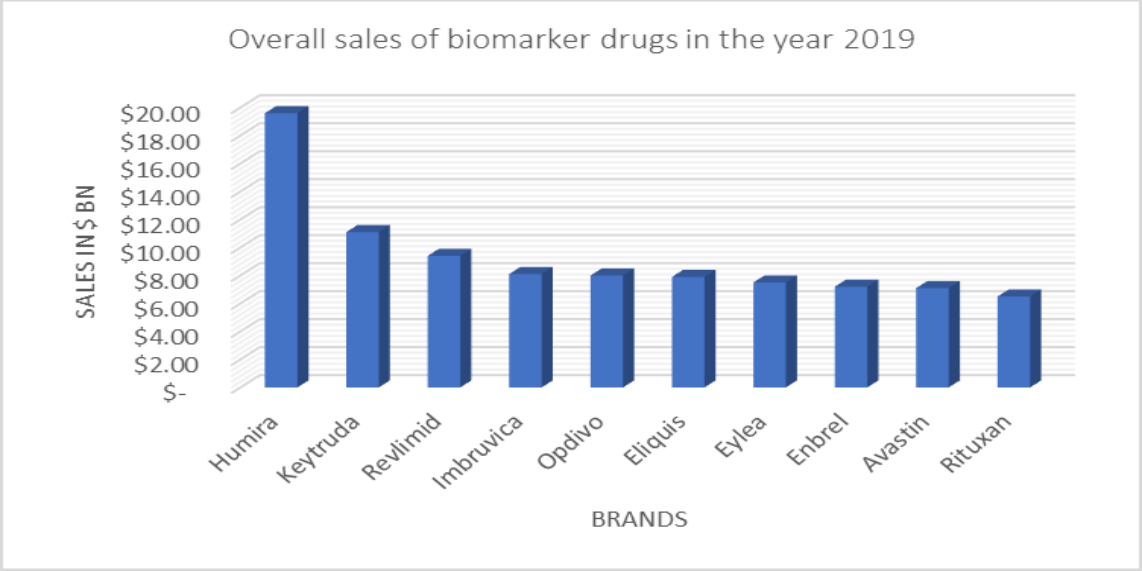

Figure 2: Overall sales of biomarker-based drug in the year 2019

4.4.2 Overall biomarker drugs sales in the year 2020

Merck's Keytruda (pembrolizumab) is the top selling biomarker drug in the year 2020, with global sales of 14.38 billion US dollars. It used in NSCLC, melanoma, HNSCC, CRC, UC, GC, cervical cancer, esophageal cancer, hepatocellular carcinoma, MCC, RCC, TNBC etc,. followed by Revlimid (lenalidomide) had sales of 12.11 billion US dollars.

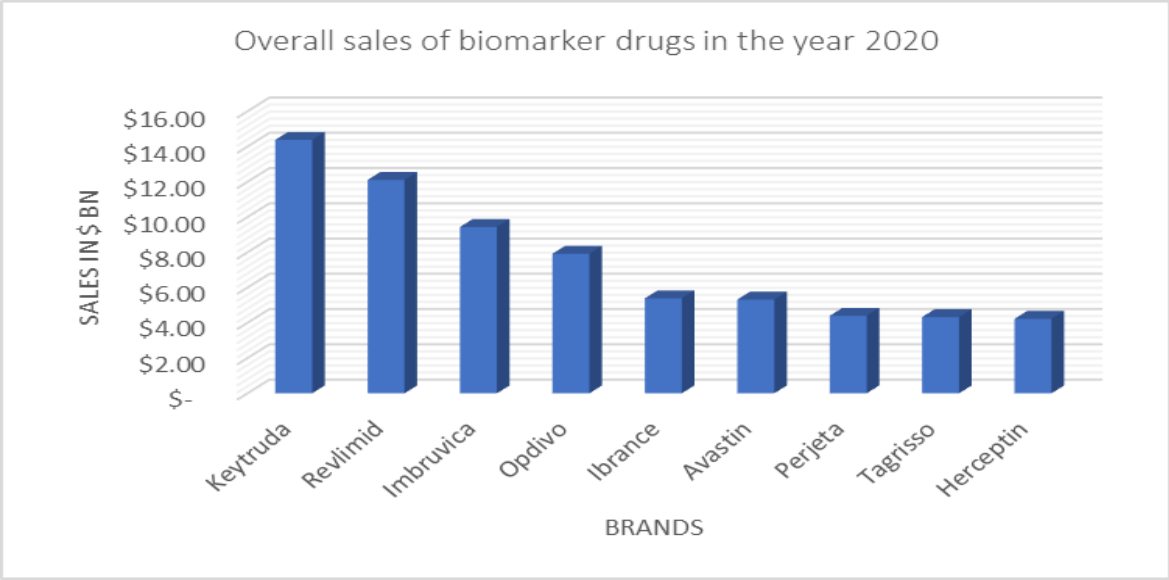

Figure 3 Overall sales of biomarker-based drug in the year 2020

4.4.3 Overall biomarker drugs sales in the year 2021

Merck's Keytruda (pembrolizumab) holds its position as number 1 top selling drug globally with sales of $17.18 billion US dollars followed by **Revlimid** (lenalidomide) at number 2 with sales $12.8 billion US dollars

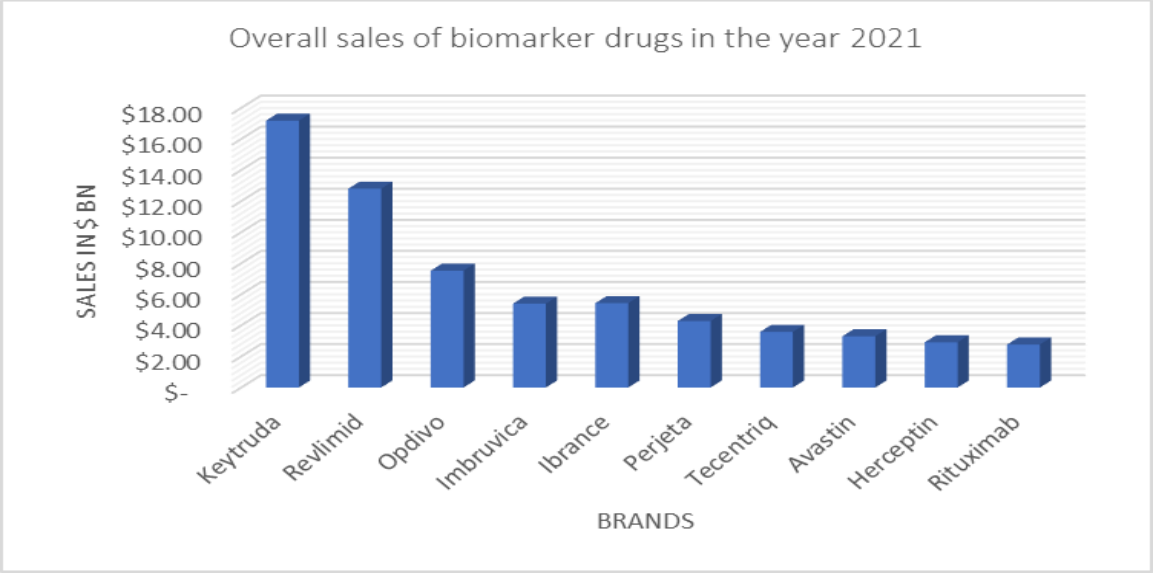

Figure 4: Overall sales of biomarker-based drug in the year 2021

4.5 Top selling drug in the last three years within NSCLC

According to sales data from the last three years, Keytruda (pembrolizumab) is the best-selling drug among the top ten biomarker drugs in NSCLC. It is an immunotherapy for the

treatment of lung cancer, melanoma, Hodgkin lymphoma, stomach cancer, cervical cancer, and many other cancer types. Slow injection into a vein is the way of administered into the body. As this is an IgG4 isotype antibody, allows the immune system to destroy cancer cell and inhibits cancer cells' protective mechanisms.

Keytruda targets PD-1/PD-L1 pathway and in some cancer cells by attaching to the PD-1 receptor. In 2014, Keytruda received its first approval. In 2017, it was approved by the US FDA for unresectable or metastatic solid tumor together with any genetic abnormalities. It is included as the Essential Medicines listed by WHO.

4.6 Proportion of sales coming from which country within NSCLC

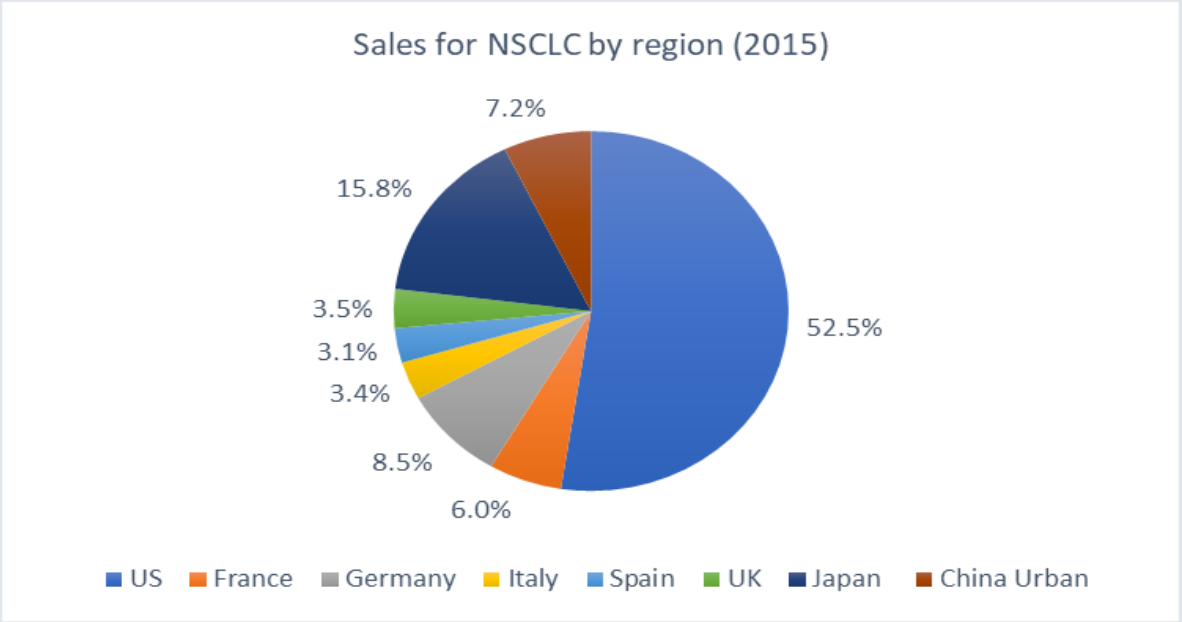

Figure 5: Sales of biomarker-based drugs by region in the year 2015

In 2015, eight major markets contributed $6.21 billion within NSCLC. United States generated around half of these sales which makes 52 % ($3.25 billion), followed by EU5 estimated 25% ($1.53 billion) accounting for the next largest region by sales. Smallest proportions of sales i.e., 16% ($981 million) and 7% ($445 million) is contributed by both Japan and China to the global NSCLC market in 2015.

By 2025, NSCLC forecasted sales are expected to increase by $26.8 billion in 8MM, with a CAGR of 15.7 %. China's NSCLC market will grow the fastest, increased by 16% ($4.3 billion) in the year 2025 at a ~25% CAGR. For US and Japan are sales is expected to fall by 27% and 22%, respectively and EU5 market share will increase from 24% to 34% by 2025.

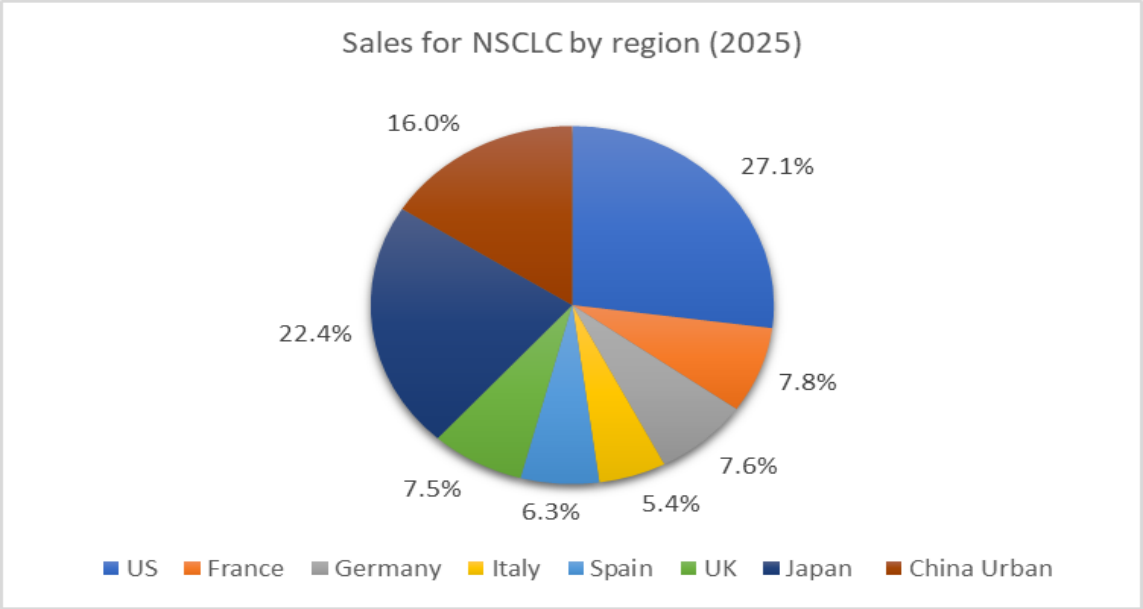

Figure 6: Sales of biomarker-based drug by region in the year 2025

Particularly in the first line setting of the NSCLC treatment process the increasing amalgamation of high-priced immunotherapies is the one major driver. By 2025, 65% of NSCLC sales will be represent by immunotherapies by reaching $17.5 billion in sales. Keytruda, Tecentriq, and Opdivo will have contribute of $13 billion.

4.7 Clinical trial development strategy for the top selling drug

4.7.1 Clinical trial development for Keytruda

Overall Keytruda had more than 4 trials evaluating it in NSCLC before its first launch in US. Of these 4 trials majority were open label and parallel assignment trial designs indicating a focus developed strategy. The trial enrollment for these trials ranges from 11 to 142 indicating a focus on specific patient populations. These trials studied combination with different drugs like chemotherapy, anti-VEGF (vascular endothelial Growth Factor) etc. Theses trails represented a mix of locations from US focused to global trials.

4.8 Activities done by top selling biomarker approved drug at country level

Some of the key activities which are done by Merck for the promotion of Keytruda are given below:

Table 7: Activities done by top selling biomarker approved drug at country level

No.	Key Activities
1	Merck, the maker of Keytruda, has released its first television commercial, which features one woman and her "Tru Story" of the survival of lung cancer with Keytruda. The commercial emphasizes the significance of PD-L1 biomarkers in Keytruda therapy
2	Merck has done advertising in the professional journals and target healthcare professional. In this way Merck pushed its checkpoint inhibitors
3	This time placing a real doctor to work in its Keytruda patient campaign Merck & Co. has changed the game again in oncology ads
4	In 2022 ASCO Annual Meeting, Merck is going to present data of Keytruda from different clinical trials they have conducted and highlight attractive pipeline drugs and in treating earlier stages of certain cancers
5	The first DTC campaign with many indications. Patients' confidence was boosted by the Keytruda Moment campaign, which linked the moment of diagnosis to the possibility of Keytruda being used to treat more than 16 types of advanced malignancies.
6	Merck has released two black-and-white television commercials that discuss "the moment" when people learn they have cancer. Keytruda has been approved to treat 16 forms of advanced cancer and is being tested in hundreds of trials, according to the advertising.
7	KEYTRUDA + chemotherapy has improved patient survival as a first line treatment and this has been proven in the clinical trials and this is the data available publicly at Keytruda website
8	KEYTRUDA used alone help patients live longer compared to chemotherapy, as a first line treatment. This combination has attractive results in clinical trials conducted for it and the data is available publicly at website of Keytruda
9	Clinical trials were run for KEYTRUDA alone after chemotherapy and found in the result that this helped patients live longer compared to chemotherapy and data is available publicly so that patients can know more about there therapy and also can compare it with other therapies as well.

CHAPTER 5: DISCUSSION

5.1 Opportunity

- In cancer NSCLC is the top indication which have incidence of 236,740 adults per year for both SCLC and NSCLC and out of which NSCLC accounts for 82%. It has more incident cases than any other type of cancer and it is a brutal disease.
- Lung cancer 5-yr overall survival rate is 22% and is 18% and 25% for men and women respectively. Likewise, SCLC has 5-yr overall survival rate of 7%.
- 5-yr overall survival rate is 63% for localized NSCLC, 35% for regional NSCLC and 7% for metastatic NSCLC.
- Immunotherapies and some other targeted therapy are allowing people to live longer with metastatic lung cancer.

5.2 Biomarker

- Till now 9 biomarkers have been detected within NSCLC i.e., RET, EGFR, ALK, MET, KRAS, PD-L1 etc. and for which 15 drugs have been approved in the last three years.
- Within NSCLC PD-L1 testing is more critical which is done through IHC. And IHC kits are easily available.
- Tell About Keytruda and its clinical trial before that

5.3 Commercialization

- Merck directly involved the doctors by helding conference with them directly, publish about the Keytruda in the generals etc.
- Patients' awareness campaign, TV advertisement
- Work with pathologist to increase the biomarker testing for PD-L1
- Work with insurance company in the different geographical area so that the drug is available as more as possible to the patients.

CHAPTER 6: CONCLUSION

- Oncology is very actively growing field. It consists of active innovation which leads to more active developments in the therapy areas in last 4 to 5 years. NSCLC is one of the big oncology indication which has a great diseases burden and poor survival outcome. Till recently chemotherapy was the main stay of treatment but in the last 5 years or so this indication has seen lot of biomarker based drug approval which has significantly improve patients life. Of these drugs Keytruda has made a special impact due to its attractive MOA and very promising clinical results. It became a stadard of care soon after its launch. Meck has carefully planned strategy with respect to Keytruda which has now made it a drug of choice not only in NSCLC but in many more indications.
- For Keytruda to succeed it has lots of challenges right from making the physicians aware of the novel MOA to working with pathologist for a successful patient diagnostics. All of this indicate a very critical role of proactive thinking and strategic planning which is very critical for optimal commercialization outputs.
- While there were lot of activities which Merck did to make Keytruda a successful drug but some of the below listed activities can easily be identified as key success factors which the upcoming drugs and manufacturers can consider as part of there product strategy.
    - Clinical development strategy: This is the most critical strategy to insure the product has right set of data for a focused population. For example, Keytruda Initially had open label parallel assignment trial which help Merck to identify the most optimal dosing, combination, and product regimen. Merck played smart with Keytruda with trials focused in US as well as global locations focused
    - Stakeholder Engagement: Even for a good product stakeholder engagement is very critical to drive product awareness and usage. For example, Merck engaged with physician inviting them to key conferences, publishing regular clinical update of Keytruda as well as driving product experience which was helpful when the product launch. Even for patients Merck had various awareness campaigns which further created product buzz and demand

- Product Availability: For drugs approved the manufacturer has to partnered with different agencies and insurance organization to make sure the product is available in hospitals. For example, Merck collaborated with hospitals directors and insurance agencies because of which doctors were able to prescribe Keytruda and patients were able to receive it as insurance paid for all treatment cost
- Stay Focused: Manufactures need to define areas of focused for them so that they are able to develop the right clinical and commercialization strategy to insure a successful launch. Foe example, Merck established the right biomarker diagnosis working with pathologist training them with the technology as well as working with physicians helping them understand which patient is ideal to receive Keytruda so that they have better treatment outcomes and longer overall survival

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