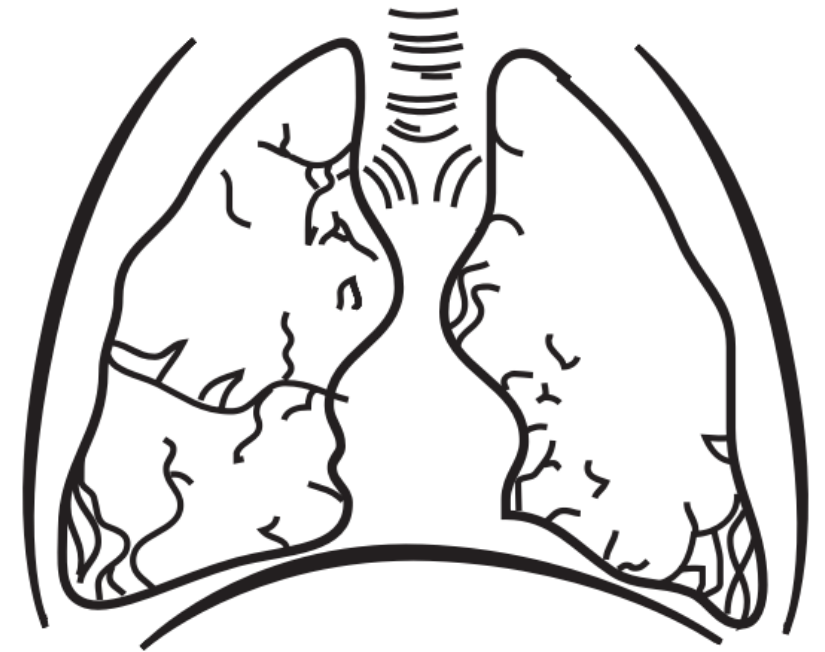


# **IDENTIFYING SUCCESS FACTORS FOR BIOMARKER-BASED DRUGS IN NSCLC (NON- SMALL CELL LUNG CANCER)**

Submitted by: Paras Soni (0258)

Submitted to: IIHMR University, Jaipur



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# Research Question and Objective

## Research Question

This study will focus on the following:

1. What are novel biomarker-based drugs have been approved in NSCLC in the last 3 years?
2. What are top selling biomarker-based drugs in 2021 and key clinical development strategy adopted by these drugs?
3. How critical is choice of diagnostic platforms for biomarker-based drugs and how do top manufacturers think about this in real world practice and in clinical trials?

## Objectives

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

# Introduction

1

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.

2

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.

3

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.

4

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 is used for detection of gene alterations but to limited geography.

5

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.

# Methodology

## 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

## Data Source

- ❑ Understanding key data sources that may be leveraged to capture the right NSCLC drug specific data
- ❑ 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])
- ❑ Understand key information about the products with the help of manufacturer websites.
- ❑ Understand what different treatment guidelines are. (e.g., NCCN, ESMO, ASCO etc)
- ❑ Research articles
- ❑ Companies' annual reports

## Data Analysis

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

# LITERATURE REVIEW



# Importance of biomarker testing in NSCLC

- 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:
  - Biomarkers give details about a person's NSCLC.
  - Biomarkers have transformed lung cancer treatment, allowing for improved precision medicine for your lung cancer.
  - To evaluate your biomarker status, comprehensive biomarker testing involves an advanced sort of diagnostic test that analyzes a small amount of tumor tissue.
  - Knowing your biomarker status could help you get access to medicines that are very successful for your type of NSCLC.
  - 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.
  - 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.

# Different platform used for biomarker testing within NSCLC

Most common techniques that are used for detecting alteration in genes in NSCLC patients are given below:

## Liquid or tissue biopsy

- Liquid or tissue biopsy are the test which are done by taking blood or tissue from the body and see if there are any DNA fragments in the sample of blood and tissue 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 then the cancer can be detected at the early stage and also helps to plan treatment.

## Immunohistochemistry

- 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.

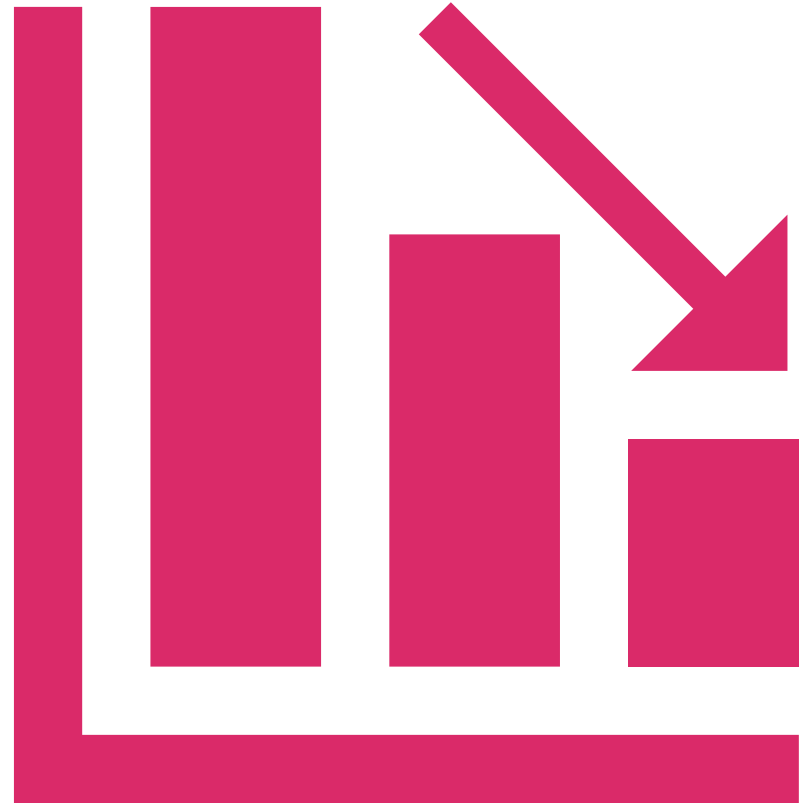
## Polymerase Chain Reaction

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

## Next Generation Sequencing

- 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.

# Results



# 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                                                                                       |

# Biomarker-based drugs approved in NSCLC in the year 2020



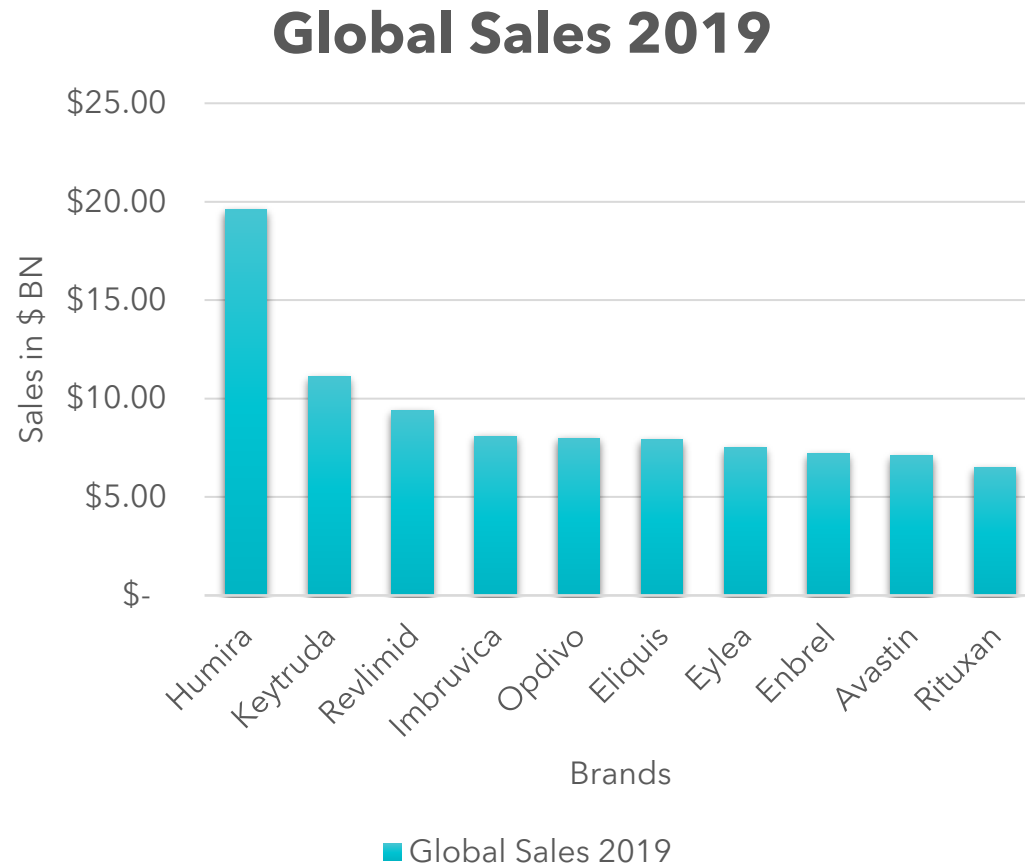
| Brand Name | API/Drug substance | Approved for                                                                                                                                                                                                   |
|------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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                                                                                        |
| Cylramza   | 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                                                                                                                                                            |

# 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 $\geq 1\%$ , 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                                             |

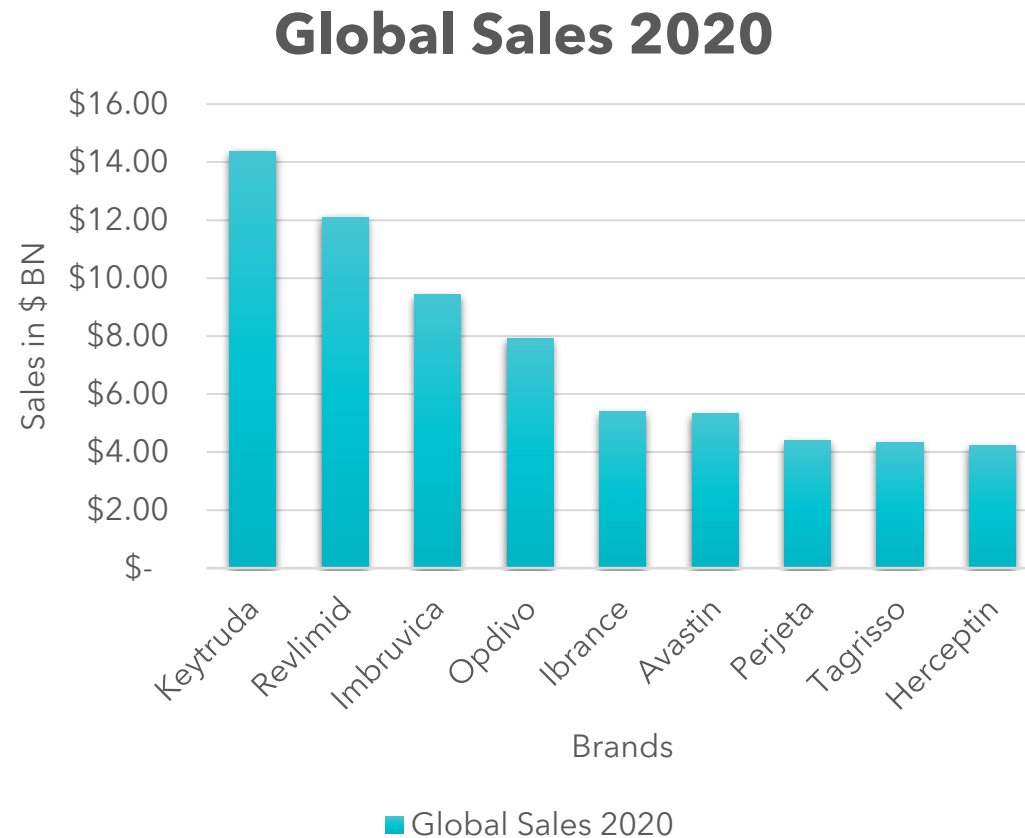
# Overall biomarker drugs sales in the year 2019



- 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.
- Keytruda increased from No. 6 to No. 2 on the best-selling list between 2018 and 2019. Keytruda (pembrolizumab) is the only NSCLC treatment to make the list of top selling biomarker drugs in 2019.

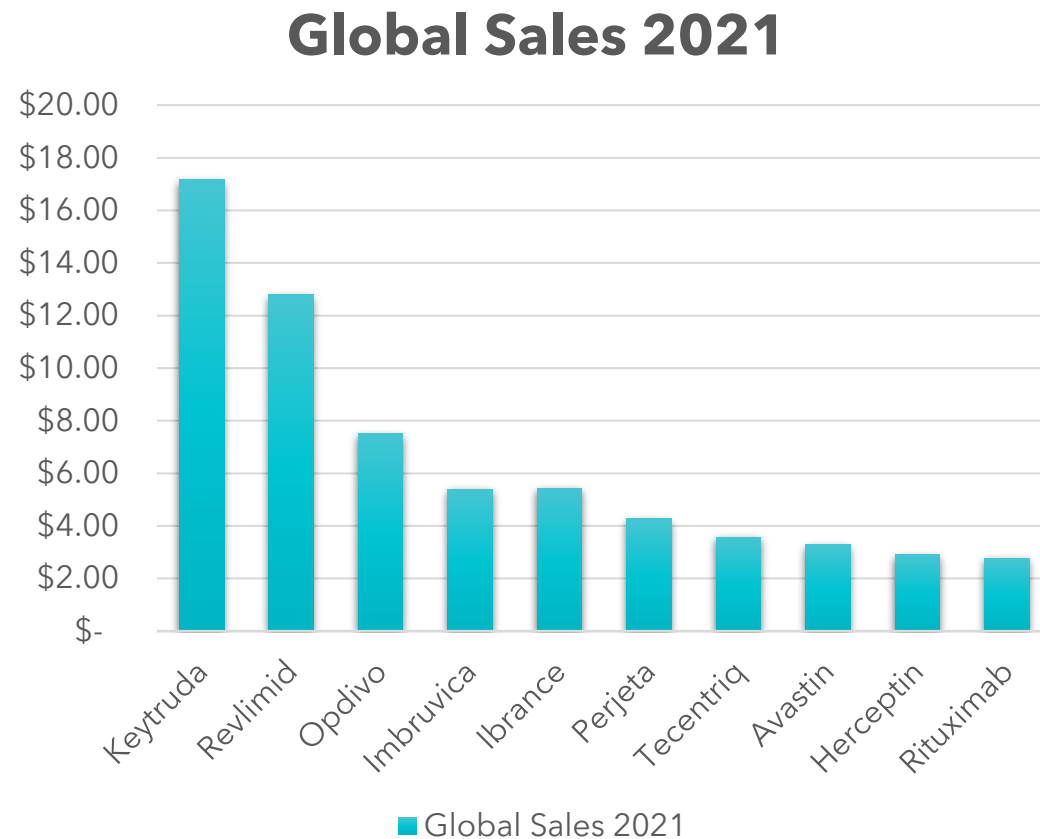
# Overall biomarker drug sales in the year

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 is used in NSCLC, melanoma, HNSCC, CRC, UC, GC, cervical cancer, esophageal cancer, hepatocellular carcinoma, MCC, RCC, TNBC etc., followed by Revlimid (lenalidomide) with sales of 12.11 billion US dollars.

# 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

# Top selling drug in the last three years within NSCLC

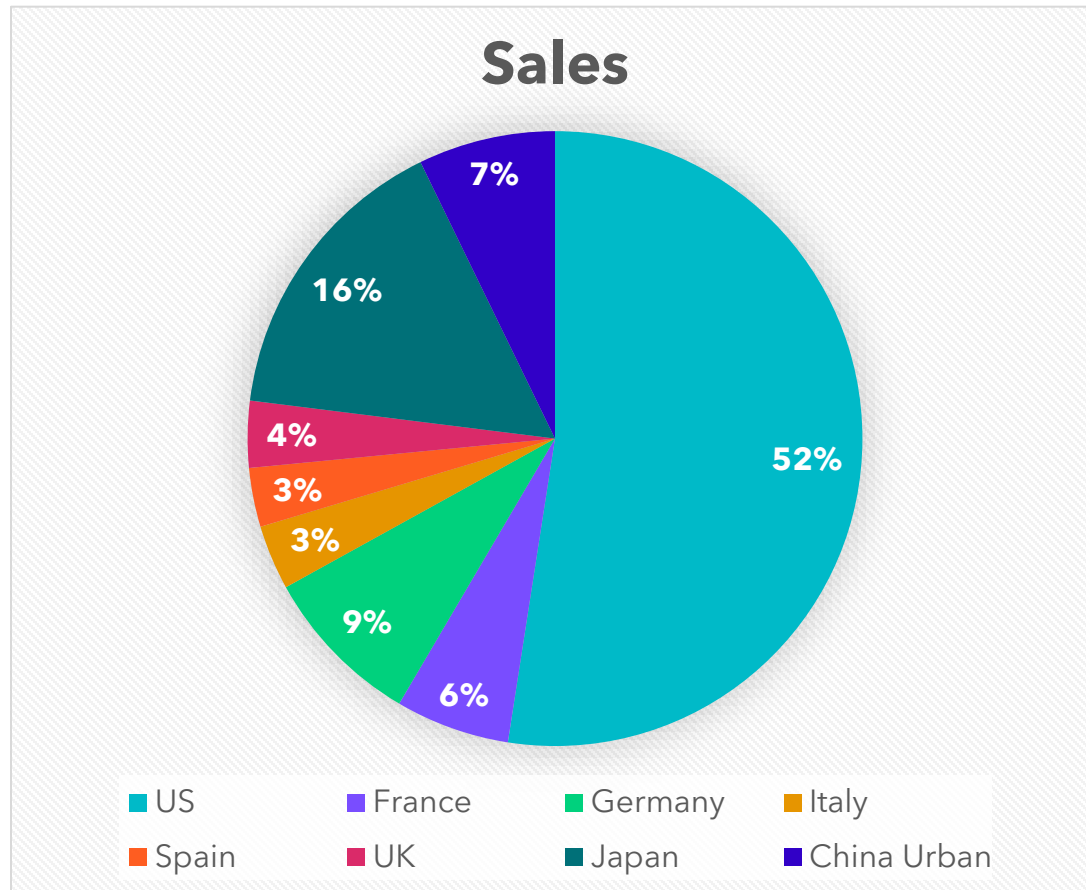


- According to sales data from the last three years, Keytruda (pembrolizumab) is the best-selling drug among the top ten biomarker drugs in NSCLC.
- Keytruda targets PD-1/PD-L1 pathway and in some cancer cells by attaching to the PD-1 receptor. In 2014, Keytruda received its first approval. In 2017, 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.

# Proportion of sales coming from which country within NSCLC

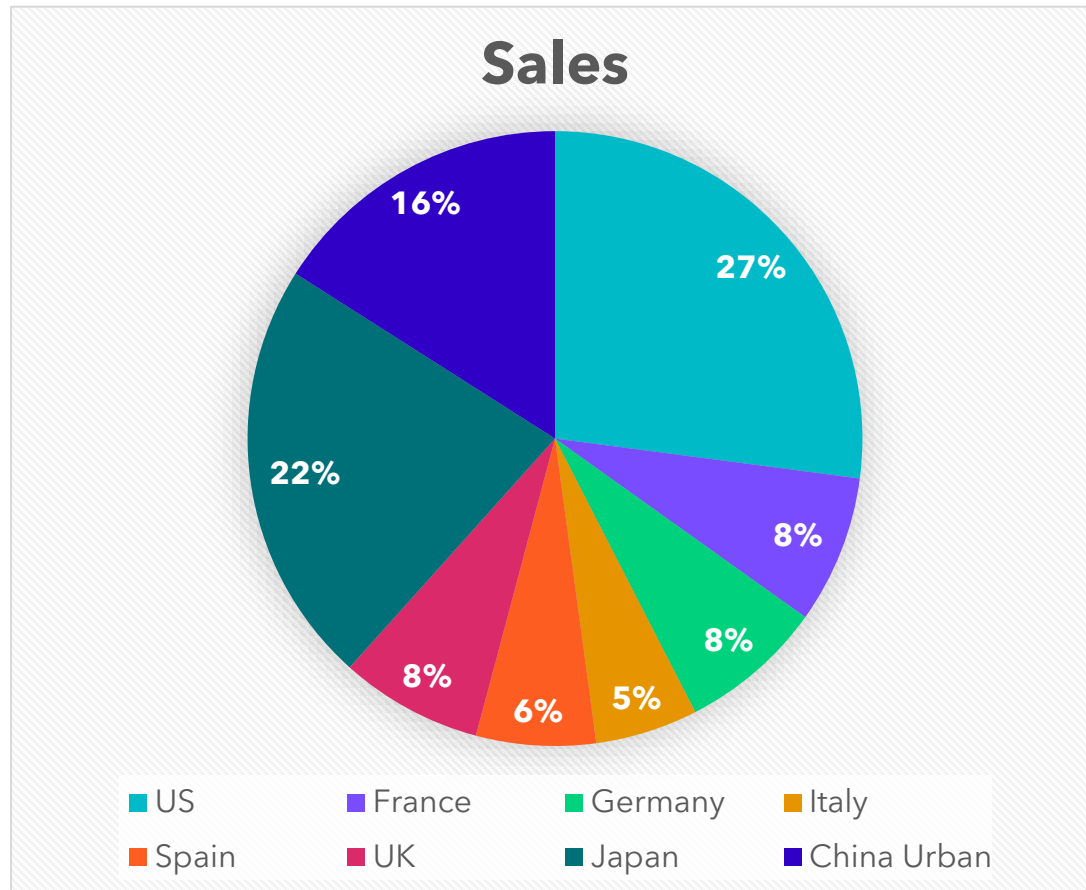


# Sales of biomarker-based drugs by region in the year 2015



- 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.

# Sales of biomarker-based drug by region in the year 2025



- 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.
- 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.

# Clinical trial development strategy for the top selling drug

- 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. These trials represented a mix of locations from US focused to global trials.



# 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. |

# Conclusion

c o n c l u s i o n

# Conti....



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 standard of care soon after its launch. Merck 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.

# Conti....

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:

1

**Clinical development strategy:** This is the most critical strategy to ensure 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

2

**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

3

**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

4

**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



THANK  
YOU!