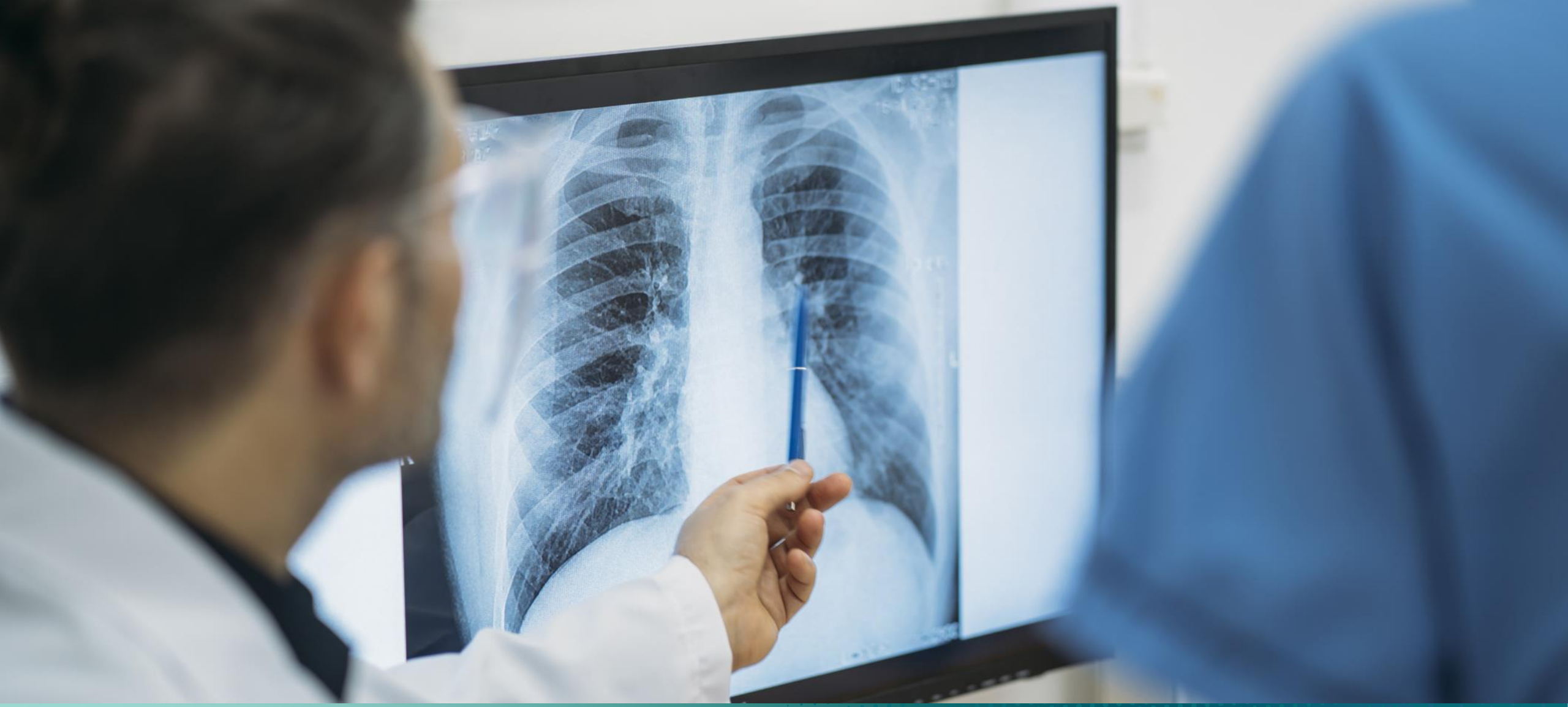

Advancing Lung Cancer Clinical Trials:
Diagnosis, Epidemiology, and Pivotal Endpoints

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Introduction

Lung cancer is a critical health issue worldwide, characterized by uncontrolled cell growth in lung tissues. As one of the most prevalent and deadly cancers, it significantly impacts cancer-related mortality.

Lung cancer continues to be a leading cause of cancer-related deaths globally, with prevalence varying by geography, gender, and socioeconomic status. In the United States, it accounts for about 13% of all new cancer cases but nearly 25% of cancer deaths.

From 2013 to 2023, incidence rates showed a slight decline, mainly due to reduced smoking prevalence . However, this decline is offset by cases linked to environmental exposures and an aging population. The American Cancer Society estimated 228,820 new lung cancer cases in the U.S. in 2023.

Future projections indicate that while smoking-related cases may decrease, the overall incidence may remain steady due to other risk factors such as air pollution and occupational hazards.

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Key Characteristics

Lung cancer is primarily classified into two types: Non-Small Cell Lung Cancer and Small Cell Lung Cancer. These types differ significantly in their prevalence, biological behavior, and treatment approaches.

Non-Small Cell Lung Cancer (NSCLC)

Prevalence: Accounts for approx. 80-85% of all lung cancer cases.

Subtypes:

- **Adenocarcinoma:** The most common subtype, originating in glandular cells.
- **Squamous Cell Carcinoma:** Arises in the flat cells lining the airways.
- **Large Cell Carcinoma:** A less common subtype that can appear in any part of the lung.

Symptoms:

- Persistent cough, chest pain, shortness of breath, unexplained weight loss, coughing up blood.

Risk Factors:

- **Smoking:** The leading cause, significantly increasing the risk.
- **Exposure to Carcinogens:** Radon gas, asbestos, and other harmful substances.
- **Genetic Mutations:** Family history and specific genetic mutations such as EGFR and ALK.

Small Cell Lung Cancer (SCLC)

Prevalence: SCLC accounts for about 15-20% of all lung cancer cases.

Characteristics:

- SCLC is known for its aggressive nature and rapid growth.
- It often spreads (metastasizes) quickly to other parts of the body.

Symptoms:

- Persistent cough, chest pain, shortness of breath, unexplained weight loss, coughing up blood.

Risk Factors:

- **Smoking:** Almost exclusively found in smokers; heavy smoking is the primary risk factor.
- **Exposure to Carcinogens:** Similar to NSCLC, exposure to radon gas and asbestos.
- **Genetic Mutations:** While less commonly associated with specific mutations, genetic predispositions can still play a role.

Market Analysis

Market for Treatment

The lung cancer treatment market is significant and dynamic, driven by advances in targeted therapies and immunotherapies. In 2023, the global market was valued at around $20 billion and is expected to grow due to ongoing research, new therapies, and rising healthcare expenditures. The shift towards personalized medicine, which tailors treatment based on genetic profiles, is a key growth driver.

The table below highlights top-earning drugs in the U.S. market, demonstrating significant clinical benefits and widespread adoption. Market growth is also supported by the increasing use of combination therapies, which enhance therapeutic efficacy and improve patient outcomes.

Drug Name	Company	Revenue (2023)
Keytruda	Merck	$3.2 billion
Opdivo	Bristol-Myers Squibb	$2.7 billion
Tagrisso	AstraZeneca	$1.9 billion
Imfinzi	AstraZeneca	$1.3 billion
Tecentriq	Roche	$1.0 billion

Real-World Data and Analysis

According to a report by Grand View Research, the lung cancer therapeutics market is anticipated to expand significantly due to the high prevalence of the disease, advancements in treatment options, and increased government initiatives to improve healthcare infrastructure and cancer care. The report also highlights the impact of the COVID-19 pandemic, which has accelerated the adoption of telemedicine and digital health solutions in cancer care, further driving market growth.

A market research report by Market Research Future projects similar growth, emphasizing the role of biotechnology in developing novel treatments and the increasing approval of biosimilars, which are expected to provide cost-effective treatment options and enhance market accessibility.

Future Projections for the Lung Cancer Treatment Market

Market Projections

Based on the below drivers, the global lung cancer treatment market, valued at approximately $20 billion in 2023, is projected to grow at a compound annual growth rate (CAGR) of around 13.6% over the next decade. By 2033, the market is expected to reach an estimated value of $55 billion. This growth is underpinned by the increasing adoption of new therapies, expanded indications for existing drugs, and the development of combination therapies that enhance therapeutic efficacy.

Market Growth Drivers

1. Advancements in Targeted Therapies and Immunotherapies

- The introduction of new targeted therapies and immunotherapies has revolutionized lung cancer treatment. These therapies offer more effective and personalized treatment options, leading to better patient outcomes. Examples include drugs like Keytruda (pembrolizumab), Opdivo (nivolumab), and Tagrisso (Osimertinib).

2. Increased Research and Development

- Ongoing research and development efforts are continuously identifying new therapeutic targets and developing novel treatments. This pipeline of innovative therapies is expected to drive market growth. Pharmaceutical companies are investing heavily in R&D to develop next-generation treatments.

3. Growing Prevalence of Lung Cancer

- While smoking-related lung cancer cases may decline, other risk factors such as environmental exposures and an aging population are expected to maintain or even increase the overall incidence of lung cancer. This sustained prevalence will drive the demand for effective treatments.

4. Rising Healthcare Expenditures

- Globally, healthcare expenditures are rising, with a significant portion allocated to cancer treatment. Increased spending on healthcare, especially in emerging economies, is expected to boost the lung cancer treatment market. Countries such as China and India are experiencing significant growth in healthcare spending, driven by economic growth and increased government investment in healthcare infrastructure. This rise in expenditure is facilitating better access to advanced diagnostic and treatment options for lung cancer. Additionally, increased awareness and early detection efforts in these regions are contributing to a growing demand for lung cancer therapies.

5. Personalized Medicine

- The shift towards personalized medicine, where treatments are tailored based on individual genetic profiles, is a key growth driver. Personalized therapies improve treatment efficacy and reduce adverse effects, making them highly desirable in the market.

Diagnostic Criteria According to ICD-11

ICD-11 Code for Lung Cancer: 2C25

The diagnostic criteria for lung cancer according to ICD-11 focus on clinical presentation, imaging findings, and histopathological confirmation. Key diagnostic steps include:

Clinical Evaluation:

- **Symptoms:** Common symptoms include persistent cough, coughing up blood, chest pain, shortness of breath, hoarseness, unexplained weight loss, and fatigue.
- **History:** Detailed patient history, including smoking history, occupational exposures, family history of cancer, and other risk factors.

Imaging Studies:

- **Chest X-ray:** Often the first imaging test performed when lung cancer is suspected.
- **CT Scan:** Provides detailed images of the lungs and helps identify the size, shape, and location of lung tumors.
- **PET Scan:** Used to detect spread of cancer to other body parts.
- **MRI:** Used for detailed images, especially of the brain or spine if metastasis is suspected.

Pathological Confirmation:

- **Biopsy:** Obtaining a tissue sample for microscopic examination is crucial for definitive diagnosis.
  - Bronchoscopy: A flexible tube is passed down the throat to collect tissue samples from the lungs.
  - Needle Biopsy: A needle is inserted through the chest wall to collect tissue from the lung tumor.
  - Surgical Biopsy: More invasive and may be performed if other methods are inconclusive.
- **Cytology:** Examination of sputum or pleural fluid for cancer cells.

Laboratory Tests:

- **Blood Tests:** While not specific for lung cancer, blood tests can provide information about the overall health and help assess organ function.
- **Molecular Testing:** Identifying specific genetic mutations or markers that can influence treatment decisions.

Staging:

- Determining the extent of the disease spread is crucial for treatment planning. Staging involves assessing the size of the tumor, lymph node involvement, and metastasis (TNM system).

Epidemiology

1. Age

- The risk of developing lung cancer increases significantly with age. According to the American Cancer Society, the average age at diagnosis is about 70 years. Approximately two-thirds of people diagnosed with lung cancer are 65 or older. The incidence rates rise sharply after the age of 50 and peak in individuals aged 70-79.

2. Racial and Ethnic Disparities

- Racial and ethnic disparities in lung cancer incidence and outcomes are well-documented. In the US, African American men have the highest incidence and mortality rates for lung cancer compared to other racial groups. This is attributed to a combination of factors, including differences in smoking patterns, socioeconomic status, access to healthcare, and genetic susceptibility.

3. Geographic Variations

- In the US, states in the Southeast and Midwest regions have higher lung cancer rates, which correlate with higher smoking rates and lower implementation of tobacco control measures.
- Globally, lung cancer rates are highest in countries with high smoking prevalence and industrial pollution, such as China and Russia. Countries with robust public health initiatives and smoking cessation programs, such as Australia and Sweden, show declining trends in lung cancer incidence.
- Urban areas often report higher lung cancer rates due to greater exposure to air pollution and industrial emissions.

4. Genetic Predisposition

- While smoking remains the primary risk factor, genetic factors can influence an individual's susceptibility to the carcinogenic effects of tobacco smoke and other environmental exposures. Specific genetic mutations, such as those in the EGFR, ALK, and KRAS genes, are associated with increased risk and can drive the development of lung cancer, particularly non-small cell lung cancer (NSCLC).
- Family history is also a significant risk factor. Individuals with a first-degree relative (parent, sibling, or child) who has had lung cancer have a higher risk of developing the disease themselves.

5. Environmental and Occupational Exposures

- Beyond smoking, several environmental and occupational exposures significantly increase lung cancer risk. Radon gas, a naturally occurring radioactive gas found in soil and rock, is the second leading cause of lung cancer in the United States, especially among non-smokers. Long-term exposure to high radon levels in homes and buildings can lead to lung cancer.
- Asbestos exposure, common in industries such as construction, shipbuilding, and manufacturing, is a well-established risk factor for lung cancer and mesothelioma. Workers exposed to asbestos fibers have a significantly higher risk, especially if they are also smokers.

6. Socioeconomic Status

- Lower SES is associated with higher smoking rates, limited access to healthcare, and delayed diagnosis and treatment.

Pivotal Endpoints in Lung Cancer Clinical Trials

Clinical trials for lung cancer rely on specific endpoints to assess the efficacy and safety of new treatments. These endpoints provide measurable outcomes that help determine whether a treatment can improve patient health and prolong survival.

1. Overall Survival (OS):

Overall Survival is the time from randomization or treatment initiation to the time of death from any cause.

Challenges: Long follow-up periods, confounding factors, and crossover effects.

2. Progression-Free Survival:

PFS is the length of time during and after the treatment that a patient lives with the disease but it does not worsen.

Challenges: Measurement consistency, pseudo-progression, and subjectivity.

3. Objective Response Rate:

ORR is the proportion of patients whose tumor size is reduced by a predefined amount for a minimum period.

Challenges: Short-term endpoint, assessment variability, and lack of standardization.

4. Disease Control Rate (DCR):

The sum of complete responses, partial responses, and stable disease observed in patients during a trial.

Challenge: Duration of control, and composite endpoint that includes different levels of response.

5. Quality of Life (QoL):

QoL endpoints assess the impact of the disease and its treatment on patients' overall well-being, including physical, emotional, and social aspects.

Challenge: Subjectivity, instrument selection, and response bias.

6. Time to Progression (TTP):

Time from randomization or treatment initiation to the time of disease progression, excluding death from causes other than cancer progression.

Challenge: Differentiating progression/ survival, and assessment variability.

Addressing Challenges in Determining Endpoints in Lung Cancer Clinical Trials

1. Endpoint: Overall Survival (OS)

- Stratified analysis based on key patient characteristics can help mitigate the effects of population heterogeneity.
- Designing trials with protocols that account for potential crossover treatments can provide clearer insights.
- Utilizing adaptive trial designs and interim analyses can shorten the time required to reach conclusive results.

2. Endpoint: Progression-Free Survival (PFS)

- Implementing standardized imaging protocols and employing centralized review by blinded radiologists can enhance measurement consistency and reduce subjectivity.
- Improve accuracy of assessments by incorporating biomarkers that differentiate true progression from pseudo-progression.
- Training investigators on radiologic assessment criteria and establishing clear guidelines for progression assessment can minimize variability.

3. Endpoint: Objective Response Rate (ORR)

- Adopting harmonized criteria for response assessment can enhance consistency and comparability across studies.
- Using ORR in conjunction with other endpoints like PFS and OS can provide a more comprehensive evaluation.
- Ensuring regular and consistent monitoring can improve the accuracy and reliability of ORR data.

4. Endpoint: Disease Control Rate (DCR)

- Providing detailed reporting of the duration of each component of DCR can enhance the interpretability.
- Ensuring consistency in the definition and measurement of stable disease across studies can improve comparability and reliability of DCR data.

5. Endpoint: Quality of Life (QoL)

- Utilizing validated and disease-specific PRO instruments can improve the accuracy and relevance of QoL assessments.
- Frequent QoL assessments can capture changes over time and provide a more dynamic understanding of impact.
- Providing training and support for patients to accurately complete PRO instruments can reduce response bias and improve data quality.

6. Time to Progression (TTP)

- Employing standardized imaging protocols, such as the RECIST guidelines, can help reduce variability in TTP measurements by ensuring consistent and uniform assessment criteria.
- Utilizing a blinded independent review committee to assess radiologic images can enhance objectivity and reduce bias in progression assessment.
- Extending follow-up periods beyond the initial progression can capture long-term progression data.

Five Most Commonly Prescribed FDA-Approved Treatments for Lung Cancer

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Pembrolizumab (Keytruda)	2014	Merck	PD-1 inhibitor	**Immune checkpoint inhibition**: Pembrolizumab binds to the PD-1 receptor on T cells, blocking its interaction with PD-L1 and PD-L2, thereby reactivating T cells to attack cancer cells.
Osimertinib (Tagrisso)	2015	AstraZeneca	EGFR inhibitor	**Targets EGFR mutations**: Osimertinib is a third-generation tyrosine kinase inhibitor that selectively targets both EGFR sensitizing and EGFR T790M resistance mutations.
Nivolumab (Opdivo)	2014	Bristol-Myers Squibb	PD-1 inhibitor	**Immune checkpoint inhibition**: Nivolumab blocks the PD-1 receptor, preventing its interaction with PD-L1 and PD-L2. This enhances the immune response against cancer cells.
Atezolizumab (Tecentriq)	2016	Genentech (Roche)	PD-L1 inhibitor	**Immune checkpoint inhibition**: Atezolizumab targets PD-L1, blocking its interaction with PD-1 and B7.1 receptors on T cells, thereby boosting the immune response against tumor cells.
Durvalumab (Imfinzi)	2017	AstraZeneca	PD-L1 inhibitor	**Immune checkpoint inhibition**: Durvalumab binds to PD-L1, blocking its interaction with PD-1 and CD80, which enhances T-cell activation and anti-tumor response. It is particularly effective as a consolidation therapy in patients with unresectable stage III NSCLC following chemoradiation.

Approved Product Analysis: Pembrolizumab

14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic nonsquamous NSCLC with pemetrexed and platinum chemotherapy-(NCT02578680)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Metastatic NSCLC (KEYNOTE-189 Study)	Overall Survival (OS)	BICR, RECIST v1.1	Not Reached (NR) (KEYTRUDA) vs Not Reached (NR) (Placebo)	KEYTRUDA: N=410, Placebo: N=206	HR: 0.49 (95% CI: 0.38, 0.64), p<0.00001
Metastatic NSCLC (KEYNOTE-189 Study)	Progression-Free Survival (PFS)	BICR, RECIST v1.1	8.8 months (KEYTRUDA) vs 4.9 months (Placebo)	KEYTRUDA: N=410, Placebo: N=206	HR: 0.52 (95% CI: 0.43, 0.64), p<0.00001

Secondary Endpoints:

- Objective Response Rate (ORR): ORR: 48% (95% CI: 43, 53) vs 19% (95% CI: 14, 25), p<0.00001
- Duration of Response (DoR): DoR: 11.2 months (95% CI: 1.1+, 18.0+) vs 7.8 months (95% CI: 2.1+, 16.4+)

First-line treatment of metastatic squamous NSCLC with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy (NCT02775435)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Metastatic NSCLC (KEYNOTE-407 Study)	Overall Survival (OS)	BICR, RECIST v1.1	15.9 months (KEYTRUDA) vs 11.3 months (Placebo)	KEYTRUDA: N=278, Placebo: N=281	HR: 0.64 (95% CI: 0.49, 0.85), p=0.0017
Metastatic NSCLC (KEYNOTE-407 Study)	Progression-Free Survival (PFS)	BICR, RECIST v1.1	6.4 months (KEYTRUDA) vs 4.8 months (Placebo)	KEYTRUDA: N=278, Placebo: N=281	HR: 0.56 (95% CI: 0.45, 0.70), p<0.0001
Metastatic NSCLC (KEYNOTE-407 Study)	Objective Response Rate (ORR)	ORR %, Complete response, Partial response	Not Specified	KEYTRUDA: N=101, Placebo: N=103	ORR: 58% (95% CI: 48, 68) vs 35% (95% CI: 26, 45), Difference: 23.6% (95% CI: 9.9, 36.4), p=0.0008

Secondary Endpoint:

- Duration of Response (DoR): DoR: 7.2 months (95% CI: 2.4, 12.4+) vs 4.9 months (95% CI: 2.0, 12.4+)

Approved Product Analysis: Pembrolizumab (cont.)

First-line treatment of metastatic NSCLC as a single agent (NCT02220894)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Metastatic NSCLC (KEYNOTE-042, TPS ≥21%)	Overall Survival (OS)	BICR, RECIST v1.1	16.7 months (KEYTRUDA) vs 12.1 months (Chemotherapy)	KEYTRUDA: N=637, Chemotherapy: N=637	HR: 0.81 (95% CI: 0.71, 0.93), p=0.0036
Metastatic NSCLC (KEYNOTE-042, TPS ≥50%)	Overall Survival (OS)	BICR, RECIST v1.1	20.0 months (KEYTRUDA) vs 12.2 months (Chemotherapy)	KEYTRUDA: N=299, Chemotherapy: N=300	HR: 0.69 (95% CI: 0.56, 0.85), p<0.0001

Secondary Endpoints:

- Progression-Free Survival (PFS):
  - TPS ≥21%: 5.4 months (KEYTRUDA) vs 5.5 months (Chemotherapy), HR: 1.07 (95% CI: 0.94, 1.21), NS
  - TPS ≥50%: 7.1 months (KEYTRUDA) vs 6.4 months (Chemotherapy), HR: 0.81 (95% CI: 0.67, 0.99), NS
- Objective Response Rate (ORR):
  - TPS ≥21%: ORR: 27% (95% CI: 24, 31) vs 27% (95% CI: 23, 30), Complete response: 0.5% vs 0.3%, Partial response: 27% vs 26%
  - TPS ≥50%: ORR: 39% (95% CI: 33.9, 45.3) vs 32% (95% CI: 26.8, 37.6), Complete response: 0.7% vs 0.3%, Partial response: 39% vs 32%
- Duration of Response (DoR):
  - TPS ≥21%: ≥12 months: 47% vs 16%, ≥18 months: 25% vs 6%
  - TPS ≥50%: ≥12 months: 43% vs 19%, ≥18 months: 25% vs 17%

Approved Product Analysis: Pembrolizumab (cont.)

KEYNOTE-024 (NCT02142738)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Previously untreated patients with metastatic NSCLC, TPS ≥50%	Progression-Free Survival (PFS)	BICR, RECIST v1.1	10.3 months (KEYTRUDA) vs 6.0 months (Chemotherapy)	KEYTRUDA: N=154, Chemotherapy: N=151	HR: 0.50 (95% CI: 0.37, 0.68), p<0.001
Previously untreated patients with metastatic NSCLC, TPS ≥50%	Progression-Free Survival (PFS)	BICR, RECIST v1.1	10.3 months (KEYTRUDA) vs 6.0 months (Chemotherapy)	KEYTRUDA: N=154, Chemotherapy: N=151	HR: 0.50 (95% CI: 0.37, 0.68), p<0.001

Secondary Endpoints:

- Overall Survival (OS): 30.0 months (KEYTRUDA) vs 14.2 months (Chemotherapy), HR: 0.60 (95% CI: 0.41, 0.89), p=0.005
- Objective Response Rate (ORR): ORR: 45% (95% CI: 37, 53) vs 28% (95% CI: 21, 36), p=0.001
- Duration of Response (DoR): NR (KEYTRUDA) vs 6.3 months (Chemotherapy), NR (95% CI: 1.9+, 14.5+) vs 6.3 months (95% CI: 2.1+, 12.6+)

Approved Product Analysis: Pembrolizumab (cont.)

Previously treated NSCLC (NCT01905657)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Metastatic NSCLC, TPS ≥50%	OS (Overall Survival)	BICR, RECIST v1.1	14.9 months (KEYTRUDA 2 mg/kg) vs 17.3 months (KEYTRUDA 10 mg/kg) vs 8.2 months (Docetaxel)	KEYTRUDA 2 mg/kg: N=139, KEYTRUDA 10 mg/kg: N=151, Docetaxel: N=152	HR: 0.54 (95% CI: 0.38, 0.77) for 2 mg/kg vs Docetaxel, p<0.001; HR: 0.50 (95% CI: 0.40, 0.78) for 10 mg/kg vs Docetaxel, p<0.001
Metastatic NSCLC, TPS ≥50%	PFS (Progression-Free Survival)	BICR, RECIST v1.1	5.2 months (KEYTRUDA 2 mg/kg) vs 5.2 months (KEYTRUDA 10 mg/kg) vs 4.1 months (Docetaxel)	KEYTRUDA 2 mg/kg: N=139, KEYTRUDA 10 mg/kg: N=151, Docetaxel: N=152	HR: 0.58 (95% CI: 0.43, 0.77) for 2 mg/kg vs Docetaxel, p<0.001; HR: 0.59 (95% CI: 0.45, 0.78) for 10 mg/kg vs Docetaxel, p<0.001
Metastatic NSCLC, TPS ≥1%	OS (Overall Survival)	BICR, RECIST v1.1	10.4 months (KEYTRUDA 2 mg/kg) vs 12.7 months (KEYTRUDA 10 mg/kg) vs 8.5 months (Docetaxel)	KEYTRUDA 2 mg/kg: N=344, KEYTRUDA 10 mg/kg: N=346, Docetaxel: N=343	HR: 0.71 (95% CI: 0.58, 0.88) for 2 mg/kg vs Docetaxel, p<0.001; HR: 0.61 (95% CI: 0.49, 0.75) for 10 mg/kg vs Docetaxel, p<0.001
Metastatic NSCLC, TPS ≥1%	PFS (Progression-Free Survival)	BICR, RECIST v1.1	3.9 months (KEYTRUDA 2 mg/kg) vs 4.0 months (KEYTRUDA 10 mg/kg) vs 4.0 months (Docetaxel)	KEYTRUDA 2 mg/kg: N=344, KEYTRUDA 10 mg/kg: N=346, Docetaxel: N=343	HR: 0.88 (95% CI: 0.73, 1.04) for 2 mg/kg vs Docetaxel, p=0.068; HR: 0.79 (95% CI: 0.66, 0.94) for 10 mg/kg vs Docetaxel, p=0.005

Secondary Endpoints:

- TPS ≥50%:
  - Objective Response Rate (ORR): ORR: 30% (95% CI: 23, 39) for 2 mg/kg vs 29% (95% CI: 22, 37) for 10 mg/kg vs 8% (95% CI: 4, 13) for Docetaxel, p<0.001 for both.
  - Duration of Response (DoR): NR (KEYTRUDA 2 mg/kg) vs NR (KEYTRUDA 10 mg/kg) vs 8.1 months (Docetaxel), NR (95% CI: 0.7+, 16.8+) for 2 mg/kg, NR (95% CI: 2.1+, 17.8+) for 10 mg/kg, 8.1 months (95% CI: 2.1+, 8.8+) for Docetaxel.
- TPS ≥1%:
  - Objective Response Rate (ORR): ORR: 18% (95% CI: 14, 23) for 2 mg/kg vs 19% (95% CI: 15, 23) for 10 mg/kg vs 9% (95% CI: 7, 13) for Docetaxel, p<0.001 for both.
  - Duration of Response (DoR): NR (KEYTRUDA 2 mg/kg) vs NR (KEYTRUDA 10 mg/kg) vs 6.2 months (Docetaxel), NR (95% CI: 0.7+, 20.1+) for 2 mg/kg, NR (95% CI: 2.1+, 17.8+) for 10 mg/kg, 6.2 months (95% CI: 1.4+, 8.8+) for Docetaxel.

Approved Product Analysis: Pembrolizumab (cont.)

Small Cell Lung Cancer (NCT02054806) & (NCT02628067)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Small Cell Lung Cancer (SCLC)	Objective Response Rate (ORR)	BICR, RECIST v1.1	Not Specified	KEYTRUDA: N=83	ORR: 19% (95% CI: 11, 29) with 2% complete response and 17% partial response
Small Cell Lung Cancer (SCLC)	Duration of Response (DoR)	Median in months (range)	Not Specified	KEYTRUDA: N=16	Range: 4.1 to 35.8+ months; ≥6 months: 94%, ≥12 months: 63%, ≥18 months: 56%

Approved Product Analysis: Osimertinib

14.1 Adjuvant Treatment of Early-Stage EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) [NCT02511106]

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Stage II-IIIA NSCLC	DFS (Disease-Free Survival)	Reduction in the risk of disease recurrence or death determined by investigator assessment, cobas® EGFR Mutation Test	Median DFS: Not Reached (NR) for TAGRISSO vs 19.6 months for Placebo	TAGRISSO: N=233, Placebo: N=237	HR: 0.17 (95% CI: 0.12, 0.23), p<0.0001
Stage IB-IIIA NSCLC	DFS (Disease-Free Survival)	Reduction in the risk of disease recurrence or death determined by investigator assessment, cobas® EGFR Mutation Test	Median DFS: Not Reached (NR) for TAGRISSO vs 27.5 months for Placebo	TAGRISSO: N=339, Placebo: N=343	HR: 0.20 (95% CI: 0.15, 0.27), p<0.0001

Secondary Endpoints:

- Overall Survival (OS):
  - Stage II-IIIA NSCLC: HR: 0.49 (95% CI: 0.33, 0.73), p=0.0004
  - Stage IB-IIIA NSCLC: HR: 0.49 (95% CI: 0.34, 0.70), p<0.0001

Approved Product Analysis: Osimertinib (cont.)

14.2 Previously Untreated EGFR Mutation-Positive Metastatic NSCL FLAURA – TAGRISSO Monotherapy [NCT02296125])

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Metastatic NSCLC	PFS (Progression-Free Survival)	Assessment by investigator, cobas® EGFR Mutation Test	Median PFS: 18.9 months (TAGRISSO) vs 10.2 months (EGFR TKI)	TAGRISSO: N=279, EGFR TKI: N=277	HR: 0.46 (95% CI: 0.37, 0.57), p<0.0001

Secondary Endpoints:

- OS (Overall Survival):
  - Median OS: 38.6 months (TAGRISSO) vs 31.8 months (EGFR TKI)
  - HR: 0.80 (95% CI: 0.64, 1.00), p=0.0462
- ORR (Objective Response Rate):
  - ORR: 77% (95% CI: 71, 82) for TAGRISSO vs 69% (95% CI: 63, 74) for EGFR TKI, p=0.0462
- DoR (Duration of Response):
  - Median DoR: 17.6 months (TAGRISSO) vs 9.6 months (EGFR TKI)
  - TAGRISSO: 17.6 months (95% CI: 13.8, 22.0)
  - EGFR TKI: 9.6 months (95% CI: 8.3, 11.1)

Approved Product Analysis: Osimertinib (cont.)

CNS ORR and DoR by BICR in Patients with Measurable CNS Lesions at Baseline in FLAURA

- Of 556 patients, 200 patients (36%) had baseline brain scans reviewed by BICR; this included 106 patients in the TAGRISSO arm and 94 patients in the investigator choice of EGFR TKI arm.
- Of these 200 patients, 41 had measurable CNS lesions per RECIST v1.1. Results of pre-specified exploratory analyses of CNS ORR and duration of response (DoR) by BICR in the subset of patients with measurable CNS lesions at baseline are summarized.

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with Measurable CNS Lesions at Baseline	CNS ORR (Objective Response Rate)	BICR, RECIST v1.1	Exploratory analyses	TAGRISSO: N=22, EGFR TKI: N=19	CNS ORR: 77% (95% CI: 55, 92) for TAGRISSO vs 63% (95% CI: 38, 84) for EGFR TKI, Complete response: 18% for TAGRISSO vs 0% for EGFR TKI
Patients with Measurable CNS Lesions at Baseline	CNS DoR (Duration of Response)	BICR, RECIST v1.1	Exploratory analyses	TAGRISSO: N=17, EGFR TKI: N=12	Response Duration ≥6 months: 88% for TAGRISSO vs 50% for EGFR TKI, Response Duration ≥12 months: 47% for TAGRISSO vs 33% for EGFR TKI

Approved Product Analysis: Osimertinib (cont.)

14.3 Previously Untreated EGFR Mutation-Positive Locally Advanced or Metastatic NSCLC FLAURA2 – TAGRISSO in Combination with Pemetrexed and Platinum-based Chemotherapy [NCT04035486])

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive NSCLC	PFS (Progression-Free Survival)	BICR, RECIST v1.1 according to Investigator Assessment, cobas® EGFR Mutation Test	Median in months, Hazard ratio	TAGRISSO with pemetrexed and platinum-based chemotherapy: N=279, TAGRISSO: N=278	25.5 months (TAGRISSO with pemetrexed and platinum-based chemotherapy) vs 16.7 months (TAGRISSO); HR: 0.62 (95% CI: 0.49, 0.79), p<0.0001

Secondary Endpoints:

- OS (Overall Survival): Median OS not reached; data not specified for analysis in this study.
- ORR (Objective Response Rate): 77% (95% CI: 71, 82) for TAGRISSO with pemetrexed and platinum-based chemotherapy vs 69% (95% CI: 63, 74) for TAGRISSO.
- DoR (Duration of Response): 24.9 months (95% CI: 22.1, NE) for TAGRISSO with pemetrexed and platinum-based chemotherapy vs 17.9 months (95% CI: 15.2, 20.9) for TAGRISSO.

CNS Efficacy by BICR in Patients with CNS Metastases on a Baseline Brain Scan in FLAURA2

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive NSCLC and CNS Measurable Lesions	CNS ORR (Objective Response Rate)	BICR, RECIST v1.1	Exploratory Analysis	TAGRISSO with pemetrexed and platinum-based chemotherapy: N=40, TAGRISSO: N=38	ORR: 80% (95% CI: 64, 91) for TAGRISSO with pemetrexed and platinum-based chemotherapy vs 76% (95% CI: 60, 89) for TAGRISSO
Patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive NSCLC and CNS Measurable Lesions	CNS DoR (Duration of Response)	BICR, RECIST v1.1	Exploratory Analysis	TAGRISSO with pemetrexed and platinum-based chemotherapy: N=32, TAGRISSO: N=29	≥6 months: 75% vs 50%, ≥12 months: 65% vs 34%

Approved Product Analysis: Osimertinib (cont.)

14.4 Previously Treated EGFR T790M Mutation-Positive Metastatic NSCLC

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with metastatic EGFR T790M mutation-positive NSCLC	PFS (Progression-Free Survival)	BICR, RECIST v1.1 as determined by Investigator Assessment	Median in months	TAGRISSO: N=279, Chemotherapy: N=140	10.1 months (TAGRISSO) vs 4.4 months (Chemotherapy), HR: 0.30 (95% CI: 0.23, 0.41), p<0.001

Secondary Endpoints:

- OS (Overall Survival): Median in months, 26.8 months (TAGRISSO) vs 22.5 months (Chemotherapy), HR: 0.87 (95% CI: 0.67, 1.12), p=0.277
- ORR (Objective Response Rate): 65% (95% CI: 59, 70) for TAGRISSO vs 29% (95% CI: 21, 37) for Chemotherapy, p<0.001
- DoR (Duration of Response): Median in months, 11.0 months (95% CI: 8.6, 12.6) for TAGRISSO vs 4.2 months (95% CI: 3.0, 5.9) for Chemotherapy

Approved Product Analysis: Nivolumab

14.3 Metastatic Non-Small Cell Lung Cancer (NCT01642004)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with metastatic squamous NSCLC	OS (Overall Survival)	Stratified log-rank test, stratified proportional hazards model, Cochran-Mantel-Haenszel test	Median in months	OPDIVO: N=135, Docetaxel: N=137	9.2 months (OPDIVO) vs 6.0 months (Docetaxel), HR: 0.59 (95% CI: 0.44, 0.79), p=0.0002

Secondary Endpoints:

- PFS (Progression-Free Survival): Median in months, 3.5 months (OPDIVO) vs 2.8 months (Docetaxel), HR: 0.62 (95% CI: 0.47, 0.81), p=0.0004
- ORR (Objective Response Rate): 20% (95% CI: 14, 28) for OPDIVO vs 9% (95% CI: 5, 15) for Docetaxel, p=0.0083
- DoR (Duration of Response): Not reached (OPDIVO) vs 8.4 months (Docetaxel)

Second-line Treatment of Metastatic Non-Squamous NSCLC (NCT01673867)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with metastatic non-squamous NSCLC	OS (Overall Survival)	Stratified log-rank test, stratified proportional hazards model, Cochran-Mantel-Haenszel test	Median in months	OPDIVO: N=292, Docetaxel: N=290	12.2 months (OPDIVO) vs 9.4 months (Docetaxel), HR: 0.73 (95% CI: 0.60, 0.89), p=0.0015

Secondary Endpoints:

- PFS (Progression-Free Survival): Median in months, 2.3 months (OPDIVO) vs 4.2 months (Docetaxel), HR: 0.92 (95% CI: 0.77, 1.11), p=0.39
- ORR (Objective Response Rate): 19% (95% CI: 15, 24) for OPDIVO vs 12% (95% CI: 9, 17) for Docetaxel, p=0.02
- DoR (Duration of Response): 17 months (OPDIVO) vs 6 months (Docetaxel)

Approved Product Analysis: Nivolumab (cont.)

14.4 Small Cell Lung Cancer (NCT01928394)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
ORR (Objective Response Rate)	RECIST v1.1, BICR	Final analysis	Patients with metastatic SCLC post-platinum-based chemotherapy	N=109	12% (95% CI: 6.5, 19.5) with 0.9% complete response and 11% partial response
DoR (Duration of Response)	Median in months (range), % with duration ≥6 months, % with duration ≥12 months, % with duration ≥18 months	Final analysis	Patients with metastatic SCLC post-platinum-based chemotherapy	N=13	Range: 3.0 to 42.1+ months; ≥6 months: 77%, ≥12 months: 62%, ≥18 months: 39%

Approved Product Analysis: Atezolizumab

14.2 Non-Small Cell Lung Cancer (NCT02486718)
Adjuvant Treatment of Stage II-IIIA NSCLC with PD-L1 Expression ≥ 1%

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with Stage II-IIIA NSCLC with PD-L1 expression ≥1% per the Union for International Cancer Control/American Joint Committee on Cancer staging system, 7th edition	Disease-Free Survival (DFS)	VENTANA PD-L1 (SP263) assay	Interim Analysis: Not Reached (NR) for TECENTRIQ vs 35.3 months for Best Supportive Care (BSC)	TECENTRIQ: N=248, BSC: N=228	HR: 0.66 (95% CI: 0.50, 0.88), p=0.004

- Secondary endpoints included Overall Survival (OS), which will be assessed in the final analysis.

Metastatic Chemotherapy-Naïve NSCLC with High PD-L1 Expression (NCT02409342)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with NSCLC with High PD-L1 Expression (TC ≥50% or IC ≥10%)	Overall Survival (OS)	VENTANA PD-L1 (SP263) assay, ECOG	Interim Analysis: 20.2 months (TECENTRIQ) vs 13.1 months (Platinum-Based Chemotherapy)	TECENTRIQ: N=107, Platinum-Based Chemotherapy: N=98	HR: 0.59 (95% CI: 0.40, 0.89), p=0.0106

Secondary Endpoints Included:
- Progression-Free Survival (PFS): Investigator-assessed, HR: 0.63 (95% CI: 0.45, 0.88), Median PFS of 8.1 months (95% CI: 6.8, 11.0) in the TECENTRIQ arm vs. 5 months (95% CI: 4.2, 5.7) in the platinum-based chemotherapy arm.
- Objective Response Rate (ORR): Investigator-assessed confirmed ORR of 38% (95% CI: 29%, 48%) in the TECENTRIQ arm vs. 29% (95% CI: 20%, 39%) in the platinum-based chemotherapy arm.

Approved Product Analysis: Atezolizumab (cont.)

Metastatic Chemotherapy-Naive Non-Squamous NSCLC (NCT02366143)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with NSCLC (Arm B: TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin vs Arm C: Bevacizumab, Paclitaxel, and Carboplatin)	Overall Survival (OS)	VENTANA PD-L1 (SP263) assay, ECOG	Interim Analysis: 19.2 months (TECENTRIQ) vs 14.7 months (Bevacizumab, Paclitaxel, and Carboplatin)	Arm B: N=359, Arm C: N=337	HR: 0.78 (95% CI: 0.64, 0.96), p=0.0164
Patients with NSCLC (Arm A: TECENTRIQ with Paclitaxel and Carboplatin vs Arm C: Bevacizumab, Paclitaxel, and Carboplatin)	Overall Survival (OS)	VENTANA PD-L1 (SP263) assay, ECOG	Interim Analysis: 19.4 months (TECENTRIQ) vs 14.7 months (Bevacizumab, Paclitaxel, and Carboplatin)	Arm A: N=349, Arm C: N=337	HR: 0.84 (95% CI: 0.72, 1.08), p=0.2045

Secondary Endpoints:

- Objective Response Rate (ORR):
  - Arm B: 55% (95% CI: 49, 60) for TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin vs 42% (95% CI: 37, 48) for Bevacizumab, Paclitaxel, and Carboplatin, $p<0.0001$
  - Arm A: 43% (95% CI: 38, 48) for TECENTRIQ with Paclitaxel and Carboplatin vs 42% (95% CI: 37, 48) for Bevacizumab, Paclitaxel, and Carboplatin, p=0.66
- Duration of Response (DoR):
  - Arm B: 10.8 months (95% CI: 8.4, 13.9) for TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin vs 6.2 months (95% CI: 5.6, 7.6) for Bevacizumab, Paclitaxel, and Carboplatin
  - Arm A: 9.5 months (95% CI: 7.0, 13.0) for TECENTRIQ with Paclitaxel and Carboplatin vs 6.2 months (95% CI: 5.6, 7.6) for Bevacizumab, Paclitaxel, and Carboplatin

Approved Product Analysis: Atezolizumab (cont.)

IMpower130 (NCT02367781)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with Stage IV non-squamous NSCLC	Overall Survival (OS)	VENTANA PD-L1 (SP263) assay	18.6 months (TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin) vs 13.9 months (Paclitaxel Protein-Bound and Carboplatin)	TECENTRIQ: N=453, Control: N=228	HR: 0.80 (95% CI: 0.64, 0.99), p=0.0384
Patients with NSCLC	Progression-Free Survival (PFS)	RECIST v1.1	7.2 months (TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin) vs 6.5 months (Paclitaxel Protein-Bound and Carboplatin)	TECENTRIQ: N=453, Control: N=228	HR: 0.75 (95% CI: 0.63, 0.91), p=0.0024

Secondary Endpoints:

- Overall Response Rate (ORR):
  - TECENTRIQ: 46% (95% CI: 41, 50) for TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin vs 32% (95% CI: 26, 39) for Paclitaxel Protein-Bound and Carboplatin
- Duration of Response (DoR):
  - TECENTRIQ: 10.8 months (95% CI: 9.0, 14.4) for TECENTRIQ with Paclitaxel Protein-Bound and Carboplatin vs 7.8 months (95% CI: 6.8, 10.9) for Paclitaxel Protein-Bound and Carboplatin

Approved Product Analysis: Atezolizumab (cont.)

Previously Treated Metastatic NSCLC (OAK; NCT02008227)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
First 850 patients with NSCLC	Overall Survival (OS)	VENTANA PD-L1 (SP263) assay, ECOG	13.8 months (TECENTRIQ) vs 9.6 months (Docetaxel)	TECENTRIQ: N=425, Docetaxel: N=425	HR: 0.74 (95% CI: 0.63, 0.87), p=0.0004

Secondary Endpoints:

- Overall Survival (OS) in All 1225 patients: TECENTRIQ: 13.3 months vs Docetaxel: 9.8 months; HR: 0.79 (95% CI: 0.69, 0.91), p=0.00135
- Progression-Free Survival (PFS): TECENTRIQ: 2.8 months vs Docetaxel: 4.0 months; HR: 0.95 (95% CI: 0.82, 1.10)
- Overall Response Rate (ORR): TECENTRIQ: 14% (95% CI: 11, 17) vs Docetaxel: 13% (95% CI: 10, 17)
- Duration of Response (DoR): TECENTRIQ: 16.3 months (95% CI: 10.0, NE) vs Docetaxel: 6.2 months (95% CI: 4.9, 7.6)

14.3 Small Cell Lung Cancer (NCT02763579)

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with ES-SCLC	Overall Survival (OS)	VENTANA PD-L1 (SP263) assay, ECOG	12.3 months (TECENTRIQ with Carboplatin and Etoposide) vs 10.3 months (Placebo with Carboplatin and Etoposide)	TECENTRIQ: N=201, Placebo: N=202	HR: 0.70 (95% CI: 0.54, 0.91), p=0.0069

Secondary Endpoints:

- Progression-Free Survival (PFS):
  - 5.2 months (TECENTRIQ with Carboplatin and Etoposide) vs 4.3 months (Placebo with Carboplatin and Etoposide); HR: 0.77 (95% CI: 0.62, 0.96), p=0.0170
- Objective Response Rate (ORR):
  - ORR: 60% (95% CI: 53, 67) for TECENTRIQ with Carboplatin and Etoposide vs 64% (95% CI: 57, 71) for Placebo with Carboplatin and Etoposide
- Duration of Response (DoR):
  - 4.2 months (95% CI: 4.1, 4.5) for TECENTRIQ with Carboplatin and Etoposide vs 3.9 months (95% CI: 3.1, 4.2) for Placebo with Carboplatin and Etoposide

Approved Product Analysis: Durvalumab

14.1 Non-Small Cell Lung Cancer (NSCLC)- NCT02125461

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with unresectable Stage III NSCLC (PACIFIC Study)	Overall Survival (OS)	(RECIST v1.1, BICR)	NR (IMFINZI) vs 28.7 months (Placebo)	IMFINZI: N=476, Placebo: N=237	HR: 0.68 (95% CI: 0.53, 0.87), p=0.0025
Patients with unresectable Stage III NSCLC (PACIFIC Study)	Progression-Free Survival (PFS)	(RECIST v1.1, BICR)	16.8 months (IMFINZI) vs 5.6 months (Placebo)	IMFINZI: N=476, Placebo: N=237	HR: 0.52 (95% CI: 0.42, 0.65), p<0.0001

Key Points:

- PACIFIC Study (Unresectable Stage III NSCLC):
  - Secondary Endpoints:
    - Objective Response Rate (ORR) (RECIST v1.1, BICR)
    - Duration of Response (DoR) (RECIST v1.1, BICR)

14.1 Non-Small Cell Lung Cancer (NSCLC)- NCT02125461

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Previously untreated ES-SCLC (CASPIAN Study)	Overall Survival (OS)	RECIST v1.1	13.0 months (IMFINZI with Etoposide and Carboplatin/Cisplatin) vs 10.3 months (Etoposide and Carboplatin/Cisplatin)	IMFINZI: N=268, Placebo: N=269	HR: 0.73 (95% CI: 0.59, 0.91), p=0.0047

Key Points:

- CASPIAN Study (Previously Untreated ES-SCLC):
  - Secondary Endpoints:
    - Progression-Free Survival (PFS) (RECIST v1.1, Investigator Assessed)
    - Objective Response Rate (ORR) (RECIST v1.1, Investigator Assessed)

Summary of Failed Drug Candidates for Lung Cancer Over the Last 10 Years

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure
Rociletinib	NCT02147990	• Severe side effects, particularly hyperglycemia • Discontinued development of CO-1686 for NSCLC
Tivantinib	NCT01244191	• Lack of efficacy • Failed to show significant improvement in overall survival or progression-free survival in patients with NSCLC
Necitumumab	NCT00982111	• Trial completed, but did not achieve efficacy endpoints • Increased mortality due to thromboembolic events
Ipilimumab	NCT01471197	• Trial failed to meet primary endpoint of PFS • Termination of drug development for NSCLC
Dacomitinib	NCT01000025	• Trial did not achieve endpoint • Did not improve overall survival compared to placebo

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Common Failure Points in Lung Cancer Clinical Trials

1. Heterogeneity in Tumor Genetics:

Lung cancer exhibits significant genetic variability, leading to inconsistent responses to targeted therapies. The presence of multiple mutations within the same tumor can affect treatment efficacy.

2. Rapid Disease Progression in SCLC:

Small Cell Lung Cancer (SCLC) progresses quickly, often resulting in insufficient time to evaluate the efficacy of new treatments. This rapid progression can lead to early trial termination and inconclusive results.

3. Tumor Microenvironment Influence:

The lung tumor microenvironment, including hypoxia and immune suppression, can limit the effectiveness of therapies, especially immunotherapies. This environment can protect cancer cells from the immune system and reduce drug efficacy.

4. High Rate of Resistance Development:

Lung cancer, particularly NSCLC, often develops resistance to targeted therapies, such as EGFR inhibitors. This acquired resistance limits the long-term effectiveness of treatments.

5. Limited Biomarker Availability:

Many potential biomarkers for lung cancer are still under investigation, and their clinical utility is not fully validated, limiting patient stratification. This can hinder the selection of the most appropriate therapies for individual patients.

6. Metastatic Disease Complexity:

Lung cancer frequently metastasizes to the brain, bones, and other organs, complicating treatment and trial outcomes. These metastases can be difficult to treat and monitor.

7. Immunotherapy Non-Responders:

A significant proportion of lung cancer patients do not respond to immunotherapies like PD-1/PD-L1 inhibitors. This lack of response limits the overall effectiveness of these treatments.

8. Recruitment Challenges:

Lung cancer trials often face difficulties in recruiting a sufficient number of patients, especially for specific subtypes or biomarker-driven studies. This can delay trials and impact their outcomes.

Safety Concerns

Lung cancer treatments have evolved significantly, integrating a range of modalities aimed at improving patient outcomes. However, these treatments come with substantial safety concerns due to the potent nature of the therapies required to combat this aggressive disease. Here, we explore the safety concerns associated with lung cancer treatments and provide an overview of the standard of care options available.

Key Safety Concerns

1. Chemotherapy:

Chemotherapy remains a cornerstone of lung cancer treatment, especially for SCLC and advanced NSCLC. Common chemotherapy agents include cisplatin, carboplatin, paclitaxel, and docetaxel. Despite their effectiveness, these drugs are associated with significant toxicity:

- **Myelosuppression:** Chemotherapy often leads to decreased production of blood cells, causing anemia, leukopenia, and thrombocytopenia, increasing risk of infections, bleeding, fatigue.
- **Nephrotoxicity:** Drugs like cisplatin can cause kidney damage, necessitating regular monitoring of renal function and hydration strategies to mitigate this risk.
- **Ototoxicity:** Cisplatin is also known for causing hearing loss.
- **Peripheral Neuropathy:** Paclitaxel and docetaxel can cause numbness, tingling, and pain in the hands and feet.

2. Targeted Therapies:

Targeted therapies, such as tyrosine kinase inhibitors (TKIs), have revolutionized lung cancer treatment by specifically targeting genetic mutations like EGFR, ALK, and ROS1. These are less toxic than traditional chemotherapy but come with their own safety concerns:

- **Diarrhea and Rash:** Common side effects of EGFR inhibitors, which can impact quality of life and require supportive care.
- **Hepatotoxicity:** Elevated liver enzymes are a frequent issue, necessitating regular liver function tests.
- **Interstitial Lung Disease (ILD):** Although rare, ILD is a serious side effect that can be life-threatening.

3. Immunotherapies:

Immunotherapies have opened new avenues for treating lung cancer by harnessing the body's immune system. However, immune-related adverse events (irAEs) pose significant safety concerns:

- **Pneumonitis:** Inflammation of the lung tissue, which can be severe.
- **Colitis:** Inflammation of the colon, leading to severe diarrhea.
- **Hepatitis:** Immune-mediated liver inflammation, requiring regular monitoring and potential treatment adjustments.
- **Endocrinopathies:** Disorders of the endocrine glands, such as thyroid dysfunction and adrenal insufficiency, requiring lifelong hormone replacement therapy in some cases.

Standard of Care Treatment Options

1. **Surgery:**
   - Surgery is the primary treatment for early-stage NSCLC and involves the removal of the tumor and surrounding lung tissue. Surgical options include lobectomy (removal of a lobe), pneumonectomy (removal of an entire lung), and segmentectomy or wedge resection (removal of part of a lobe).

2. **Radiation Therapy:**
   - Radiation therapy uses high-energy rays to kill cancer cells and is often used in combination with surgery or chemotherapy, or as a palliative treatment to relieve symptoms in advanced stages.

3. **Chemotherapy:**
   - Chemotherapy remains a mainstay for treating both SCLC and advanced NSCLC. It is often used in combination with other treatments to enhance efficacy. Despite its effectiveness, the side effects necessitate careful monitoring and supportive care to manage symptoms and maintain patient quality of life.

4. **Targeted Therapy:**
   - Targeted therapy is used for NSCLC patients with specific genetic mutations. These therapies have revolutionized treatment by offering more precise and less toxic options compared to traditional chemotherapy. Regular monitoring for side effects, such as liver function tests and managing dermatological issues, is essential.

5. **Immunotherapy:**
   - Immunotherapy has become a critical component of the treatment landscape for advanced NSCLC. These drugs have shown significant survival benefits in patients with high PD-L1 expression. Managing irAEs requires a multidisciplinary approach, including early recognition, prompt treatment with corticosteroids, and sometimes additional immunosuppressive therapies.

6. **Combination Therapies:**
   - Combining different treatment modalities, such as chemotherapy with immunotherapy or targeted therapy with radiation, has shown improved outcomes in various clinical trials. The approach aims to maximize the therapeutic benefits while minimizing the risks associated with each treatment.

7. **Palliative Care:**
   - Palliative care is an integral part of lung cancer treatment, especially in advanced stages. It focuses on relieving symptoms, improving quality of life, and providing support to patients and their families. Palliative treatments can include pain management, management of respiratory symptoms, nutritional support, and psychological counseling.

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Strategies to Improve Clinical Trial Protocols for FDA Approval

1. Incorporate Comprehensive Biomarker Testing:

Implement extensive biomarker testing to identify and stratify patients based on genetic profiles. Using advanced genomic profiling tools can help select patients more likely to benefit from specific therapies.

2. Adaptive Trial Designs:

Utilize adaptive trial designs that allow for modifications based on interim results. This approach can accelerate the drug development process, reduce costs, and address emerging safety and efficacy data promptly.

3. Real-World Evidence Integration:

Incorporate real-world evidence (RWE) to complement clinical trial data. RWE can provide insights into how treatments perform outside the controlled settings of clinical trials, offering a more comprehensive view of their effectiveness and safety.

4. Enhanced Patient Recruitment and Retention:

Employ strategies to improve patient recruitment and retention. Leveraging technology to facilitate remote monitoring and telehealth consultations can also enhance participation .

5. Robust Adverse Event Monitoring:

Implement comprehensive adverse event monitoring and management protocols. Early detection and proactive management of side effects can prevent high dropout rates and ensure patient safety.

6. Use of Surrogate Endpoints:

Incorporate surrogate endpoints, such as PFS and ORR, which can provide early indications of treatment efficacy. These endpoints can accelerate the approval process while longer-term data are being collected.

7. Patient-Centric Trial Design:

Design trials that prioritize patient experience, including minimizing the burden of participation and addressing quality of life. Flexible scheduling, reduced travel requirements, and support services can enhance patient satisfaction and compliance.

8. Regulatory Collaboration and Early Engagement:

Engage with regulatory agencies early and frequently during trial design and implementation. Regular consultations with the FDA can help align protocols with regulatory expectations and address potential issues proactively.

Notable Key Opinion Leaders in Lung Cancer Research

Name	Specialty	Designation	Location	Brief Bio
Dr. Benjamin J Solomon (MBBS, FRACP, PhD)	Medical Oncology	Medical Oncologist, Peter MacCallum Cancer Centre	Victoria, Australia	Dr. Benjamin J. Solomon is a renowned Medical Oncologist at the Peter MacCallum Cancer Centre in Melbourne, Australia. He is a Group Leader of the Molecular Therapeutics and Biomarkers Laboratory in the Research Division. His career includes a postdoctoral fellowship at the University of Colorado, where he investigated novel predictive markers for therapy with EGFR inhibitors. Since returning to Peter MacCallum Cancer Centre in 2006, he has been a pivotal figure in lung cancer research, involved in practice-changing clinical trials with novel inhibitors of ALK, ROS1, NTRK, BRAF, cMET, RET, and KRAS. He is a founding board member of the Thoracic Oncology Group of Australasia and is a Board Member of the Cancer Council of Victoria.
Prof. Nick Pavlakis (BSc, MBBS, MMed (Clinical Epidemiology), PhD, FRACP)	Medical Oncology; Oncology	Associate Professor, University of Sydney	NSW, Australia	Professor Nick Pavlakis is a leading medical oncologist with extensive experience in thoracic and gastrointestinal cancers. He serves as a Professor of Medicine at the Northern Clinical School, University of Sydney, and as a Senior Staff Specialist in the Department of Medical Oncology at Royal North Shore Hospital. Dr. Pavlakis has dedicated over two decades to cancer research and treatment, with a particular focus on lung cancer, mesothelioma, and neuroendocrine tumors (NETs). In 2020, Nick led the team that received the International Centre of Excellence Award from the European Neuroendocrine Tumour Society for the NETs service, based at Royal North Shore Hospital and GenesisCare.
Prof. Michael J Boyer (MBBS, PhD, FRACP)	Oncology; Medical Oncology; Biology	Clinical Professor, University of Sydney	NSW, Australia	Professor Michael J. Boyer serves as a Clinical Professor within the Central Clinical School at the University of Sydney and as the Chief Clinical Officer at Chris O'Brien Lifehouse, a comprehensive cancer center in Sydney. In 2021,The International Association for the Study of Lung Cancer (IASLC) named Michael Boyer the recipient of the Adi F. Gazdar IASLC Merit Award. Dr. Boyer continues to be actively involved in research, focusing on the testing of new anticancer drugs for the treatment of lung cancer. In recognition of his contributions, Dr. Boyer was made a Member of the Order of Australia (AM) in 2010.
Prof. Rina Hui (MBBS, PhD, FRACP)	Medical Oncology	Clinical Professor, University of Sydney	NSW, Australia	Professor Rina Hui is a distinguished Clinical Professor at the University of Sydney and a Senior Medical Oncologist at the Crown Princess Mary Cancer Centre, Westmead Hospital. Dr. Hui has held several notable positions, including Co-Chair of the Oncology Block at the University of Sydney and Head of Clinical Trials at the Westmead Breast Cancer Institute. Her contributions to the field are recognized through her involvement in significant committees, including the Immuno-Oncology Program Committee for the World Conference on Lung Cancer and the European Society for Medical Oncology (ESMO) scientific committee.
Dr. Paul L Mitchell (MBBS, FRACP)	Medical Oncology	Associate Professor, University of Melbourne	Victoria, Australia	Dr. Paul L. Mitchell is a Clinical Associate Professor at the University of Melbourne and a prominent figure in the field of medical oncology. Dr. Mitchell was President of the Australasian Lung Cancer Trials Group (ALTG) 2012–16 and has been involved in clinical and laboratory research for over 20 years, more recently focused on lung cancer. He guided the recent establishment and is Chairman, of the Thoracic Alliance for Cancer Trials (TACT) which brings together national and transnational lung cancer trials groups. In addition to his academic and research roles, Dr. Mitchell is also a practicing oncologist at the Peter MacCallum Cancer Centre, where he works closely with patients to provide cutting-edge care.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com