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A Review on Monoclonal Antibodies Used in Lung Cancer

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A B S T R A C T

Treatment for lung cancer, especially non-small cell lung cancer (NSCLC), has been transformed by monoclonal antibodies (mAbs). These treatments reduce tumor growth, boost immune responses, and increase patient survival rates by focusing on particular cancer pathways. T-cells are reenergized to identify and destroy cancer cells by immune checkpoint drugs that target the PD-1/PD-L1 pathway, such as pembrolizumab and nivolumab. These treatments have shown remarkable efficacy in treating metastatic and advanced non-small cell lung cancer. Similar to this, mAbs such as bevacizumab target EGFR signaling and angiogenesis, respectively, providing efficient treatments for particular NSCLC subtypes. The benefits of personalized medicine are highlighted by the clinical breakthroughs made possible by these treatments. Monoclonal antibodies are a viable new therapy option for lung cancer as ongoing research continues to enhance these medicines in conjunction with other therapies.

Keywords: Monoclonal Antibody, Lung Cancer, PD-1 Inhibitor,

Overview

HIV and cardiovascular disease are the two largest causes of death worldwide, with cancer coming in first. Many people receive a cancer diagnosis every year. There are numerous forms of cancer and its subtypes. Numerous factors, including age, gender, location, and local economic conditions, influence the occurrence of this illness. Since tumors can affect an organ's normal function or spread to other parts of the body, it is imperative that aberrant cell growth be treated quickly with medical intervention.

The study of epidemiology

One of the leading causes of cancer-related mortality globally is lung cancer, mainly NSCLC and SCLC. Improvements in molecular biology and therapeutic approaches have increased its efficacy despite late-stage appearances. Among the contributing factors are second hand smoke exposure, smoking, genetic alterations, and environmental factors. (1)

Various Pulmonary Cancer Types

There are two primary types of lung cancer.

1. Non-small cell lung cancer (NSCLC), which comprises a number of subtypes such adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma, accounts for around 85% of all instances of lung cancer. The illness's frequently delayed diagnosis complicates treatment options. Additional subclassification of non-small cell lung cancer (NSCLC) based on specific mutations, such as EGFR mutations or ALK rearrangements, can guide treatment strategies. (2)

2. Rapid growth and early dissemination are characteristics of small cell lung cancer (SCLC), which makes up 10–15% of all cases of lung cancer. It has a strong association with smoking and is typically diagnosed at an advanced stage. There is a significant risk that small-cell lung cancer will recur even if it initially responds to chemotherapy and radiation treatment. (3)

Genetic Mutations in NSCLC The following are the main mutations linked to the onset of non-small cell lung cancer (NSCLC):

• EGFR mutations: NSCLC is often associated with mutations in the epidermal growth factor receptor, and medicines like erlotinib and gefitinib target the most common mutations in adenocarcinomas. (4)

• ALK translocations: ALK inhibitors, such as crizotinib, have been shown to be effective in treating a subset of NSCLC patients who have anaplastic lymphoma kinase (ALK) rearrangements, which are primarily seen in non-smokers. (5)

• KRAS mutations: these are common in non-small cell lung cancer, especially in smokers. Although the most recent trials have explicitly targeted these mutations and produced encouraging outcomes, they confer increased resistance to conventional treatments. (6)

Making a diagnosis

Lung cancer is detected by diagnostic imaging such as chest X-rays and CT scans, which are followed by a biopsy for molecular testing. In order to improve tumor control and patient outcomes, monoclonal antibodies that target immunological checkpoints or cancer-associated antigens are essential in the treatment of lung cancer. (7)

1 Monoclonal Antibodies for lung cancer

Sr.no	Monoclonal Antibody	Type	Mechanism of action
1	**Pembrolizumab (Keytruda)**	PD-1 Inhibitor	Blocks the PD-1 receptor on T-cells, enhancing the immune response against cancer cells.
2	**Nivolumab (Opdivo)**	PD-1 Inhibitor	Blocks PD-1 to reactivate T-cell immune responses to cancer.
3	**Atezolizumab (Tecentriq)**	PD-L1 Inhibitor	Inhibits PD-L1 interaction, boosting immune responses by blocking the immune checkpoint.
4	**Ipilimumab**	Monoclonal antibody (immune checkpoint inhibitor)	Blocks CTLA-4 receptor on T cells, preventing immune suppression and enhancing T-cell activation.
5	**Bevacizumab (Avastin)**	VEGF Inhibitor	Inhibits VEGF (vascular endothelial growth factor), reducing tumor blood supply and limiting tumor growth.
6	**Blinatumomab**	Bispecific T-cell engager (BiTE)	Links CD3-positive T cells to CD19-positive B cells, facilitating targeted T-cell-mediated lysis of B cells.
7	**Cetuximab (Erbitux)**	EGFR Inhibitor	Inhibits EGFR (epidermal growth factor receptor), preventing cancer cell growth and survival.

Talk about

The treatment for lung cancer uses a variety of monoclonal antibodies.

A. ICIs, or immune checkpoint inhibitors

By blocking checkpoint proteins that cancers use to avoid detection, immune checkpoint inhibitors (ICIs), which are cancer immunotherapy medications, improve the immune system's capacity to identify and eliminate tumor cells. This effectively removes the immune response's brakes.

1. Their Mode of Action

Immuno checkpoint inhibitors (ICIs) primarily target two checkpoints:

A) T-cells have a receptor called Programmed Death-1 (PD-1), which inhibits T-cell activation when it attaches to its ligands, PD-L1 or PD-L2. By preventing T-cell function, PD-L1 is expressed by many malignancies to avoid immune surveillance. Immune responses against cancer cells are strengthened when PD-1 is blocked.

B) CD28, which is necessary for T-cell activation, is in competition with cytotoxic T-lymphocyte antigen 4 (CTLA-4). Immuno checkpoint inhibitors can boost anti-tumor immunity and T-cell activation by blocking CTLA-4. (8)

2. Important Inhibitors of Immune Checkpoints

A) Anti-PD-1 Inhibitors: These medications increase T-cell effectiveness against cancer by blocking the PD-1 receptor on T-cells and preventing it from interacting with PD-L1/PD-L2 ligands. Prominent medications include the FDA-approved PD-1 inhibitors pembrolizumab (Keytruda) and nivolumab (Opdivo).

B) Inhibitors that block PD-L1: These substances prevent PD-L1 from interacting with PD-1. Durvalumab (Imfinzi) and atezolizumab (Tecentriq) are two examples.

C) Anti-CTLA-4 Inhibitors: These substances reduce T-cell activation by blocking CTLA-4. The anti-CTLA-4 antibody with the greatest research is ipilimumab (Yervoy). (9)

3. Medical Uses

Melanoma: The treatment strategy for metastatic melanoma has changed with the introduction of ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1). Clinical studies have shown that these medications significantly increase survival rates.

Pembrolizumab and nivolumab are FDA-approved treatments for advanced non-small cell lung cancer (NSCLC), which is not small cell lung cancer. For a certain population, these drugs have produced long-lasting effects.

Other Cancers: Immune checkpoint inhibitors (ICIs) are used to treat bladder cancer, head and neck cancers, and renal cell carcinoma.(10)

4. Negative Impacts

Immune-related adverse events (irAEs) can occur as a result of immune checkpoint inhibitors (ICIs) activating the immune system. From modest side effects like weariness or rash to severe autoimmune diseases like colitis or hepatitis, the negative effects can range widely. Immunosuppressive medicine is often required to address these side effects.(11)

The following medications are among the many that are used as immune checkpoint inhibitors:

1) Pembrolizumab

According to comprehensive data on its mechanism and effectiveness, pembrolizumab is the main immunotherapy for advanced or metastatic non-small cell lung cancer, greatly enhancing overall survival and progression-free survival, especially in patients with high PD-L1 positive tumors.

a) The way that pulmonary cancer works:

A monoclonal antibody called pembrolizumab targets the PD-1 receptor. T-cells include PD-1, which inhibits the immune response when it is triggered by its ligands PD-L1 or PD-L2. PD-L1 is expressed on the surface of many cancer cells, including those found in non-small cell lung cancer (NSCLC). This helps the cancer cells evade immune system identification by deactivating T-cells. Pembrolizumab lessens this immune response suppression by inhibiting the PD-1 receptor, which makes it possible for T-cells to identify and combat cancer cells. (12)

b) Negative Impacts:

Like other immune checkpoint inhibitors, pembrolizumab may have negative immunological consequences. Pneumonitis, a potentially harmful lung inflammation, hepatitis, nephritis, endocrinopathies (such as thyroid dysfunction and adrenalitis), fatigue, persistent coughing and dyspnea, dermatological reactions (such as rashes and itching), and gastrointestinal side effects (such as diarrhea or colitis). Immunosuppressive treatment is frequently necessary to manage severe immune-related side effects.

A humanized monoclonal antibody called pembrolizumab targets PD-1, a crucial component of cancer immunotherapy, particularly for lung cancer. By blocking the PD-1/PD-L1 pathway, it increases immunological response and T-cell activation. With a 26-day half-life and dose-proportional pharmacokinetics, its effectiveness in treating lung cancer has increased survival rates. Its use in tailored cancer treatment will be significantly improved by ongoing clinical trials.

2) Nivolumab

Non-small cell lung cancer (NSCLC) is one of the many cancers that are treated with this monoclonal antibody. Like pembrolizumab, nivolumab is a checkpoint inhibitor that increases the immune system's ability to recognize and destroy cancer cells by blocking the programmed cell death-1 (PD-1) receptor on T-cells. This has been a prominent treatment option for lung cancer, particularly when it is progressed or metastasized.

a) Action Mechanism:

Nivolumab suppresses PD-1, a T-cell receptor that reduces immunological function when activated by its ligands PD-L1 or PD-L2. PD-L1 is expressed on the surface of many tumor cells, including those found in non-small cell lung cancer (NSCLC), which allows them to evade immune monitoring by inhibiting T-cell activation. By blocking the link between PD-1 and PD-L1, nivolumab reverses immune suppression and promotes T-cell activity over time, allowing them to target and destroy cancer cells.

b) NSCLC Indications:

Nivolumab has been approved for a number of uses in non-small cell lung cancer (NSCLC), including:

1. First-line treatment combined with platinum-based chemotherapy for non-squamous non-small cell lung cancer (NSCLC) that has progressed or spread.

2. Second-line treatment for patients who have not responded to prior chemotherapy for advanced or metastatic non-small cell lung cancer (NSCLC), including both squamous and non-squamous forms.

3. Adjuvant treatment for stage 1B to 3A non-small cell lung carcinoma that has been surgically removed after chemotherapy. (13)

c) Adverse Effects:

As an immune checkpoint inhibitor, nivolumab may cause immune-related adverse events (irAEs), which are caused by the immune system attacking healthy organs. Commonly negative outcomes include:

- weariness and weakness,
- cutaneous reactions, including dermatitis, pruritus, and rash.
- endocrine issues, such as adrenalitis and thyroiditis.
- intestinal conditions such hepatic dysfunction (hepatitis), colitis, and diarrhea.
- Serious respiratory issues can arise from pneumonia, an inflammation of the lungs.
- Hepatitis combined with nephritis, or kidney inflammation. effects of the infusion, while rare.

Treatment of these side effects requires close monitoring and timely intervention, and in extreme cases, patients may require immunosuppressive therapies.

Nivolumab has revolutionized the treatment of advanced non-small cell lung cancer (NSCLC) by offering significant survival benefits when used as a first-line or second-line treatment. Its use in conjunction with immune checkpoint inhibitors like ipilimumab and chemotherapy has shown promise, particularly in individuals with a high tumor mutational burden (TMB). Although nivolumab has a generally good safety record when compared to traditional chemotherapy, careful management of immune-related adverse effects is essential to maximizing its therapeutic benefit. (14)

3) Atezolizumab

Non-small cell lung cancer (NSCLC) is treated with this immune checkpoint inhibitor. This monoclonal antibody selectively inhibits programmed death-ligand 1 (PD-L1) from interacting with T-cells' PD-1 receptor. T-cells are better equipped to identify and attack cancer cells thanks to this mechanism, which strengthens the immune response. Since it is approved for both first-line and second-line treatment of non-small cell lung cancer (NSCLC), atezolizumab has emerged as a key element of immunotherapy for this disease.

a) Action Mechanism:

Atezolizumab selectively targets PD-L1, a ligand found on tumor cells and immune cells that infiltrate tumors. PD-L1 normally interacts with T-cells' PD-1 receptor, inhibiting their activity and making it possible for cancers to evade immune identification. By blocking PD-L1, atezolizumab prevents immune suppression and increases T-cells' ability to recognize and destroy cancer cells.

b) NSCLC Indications:

There are several approved uses of atezolizumab in non-small cell lung cancer (NSCLC):

-First-line treatment, independent of PD-L1 status, for metastatic non-squamous non-small cell lung cancer combined with chemotherapy (carboplatin and pemetrexed).

-Second-line treatment for non-small cell lung cancer that has progressed or spread, in patients with PD-L1 expression ≥50% after prior chemotherapy failed.

-Second-line therapy for small-cell lung cancer (SCLC), even though it's a different kind of cancer. (15)

c) Adverse Effects: Atezolizumab frequently causes the following adverse effects, particularly when combined with chemotherapy:

- Weariness
- Coughing
- Shortness of breath, or dyspnea
- Skin symptoms such as pruritus (itching) and rash
- Digestive disorders such as colitis and diarrhea
- Liver enzyme abnormalities and hepatitis
- Endocrine conditions (such as adrenalitis and thyroiditis)

Pneumonia can be quite serious.

Although they are uncommon, infusion-related reactions

Autoimmune illnesses are among the serious immune-related adverse events (irAEs) that may necessitate stopping the medication and receiving corticosteroid treatment.

A crucial treatment for non-small cell lung cancer (NSCLC) is atezolizumab, particularly for patients with increased PD-L1 expression or those who are not responding to traditional chemotherapy. Its effectiveness in first- and second-line treatment is confirmed by studies such as OAK and IMpower110. Atezolizumab is a good choice for advanced or metastatic disease since it improves overall survival and progression-free survival when combined with chemotherapy.

4. Ipilimumab

An immunotherapy drug called ipilimumab is used to treat several types of cancer. Yervoy is the brand name under which it is sold. It belongs to a group of medications called immune checkpoint inhibitors, which are designed to make the body more resistant to malignant cells.

a) Action mechanism:

The monoclonal antibody ipilimumab targets the immunological checkpoint receptor cytotoxic T-lymphocyte-associated protein 4, which is expressed on T cells. CTLA-4 negatively regulates T-cell activation. Ipilimumab inhibits CTLA-4, which promotes T-cell activation and proliferation, hence enhancing the immune response against tumor cells. By doing this, the body is better able to recognize and eradicate cancer cells, which aids in the more efficient treatment of cancers (16)

b) Significance

Ipilimumab can be used to treat the following conditions:

Metastatic or incurable melanoma: either by itself or in combination with nivolumab. Nivolumab is used in combination with renal cell carcinoma (RCC) to treat advanced or metastatic RCC.

Colorectal Cancer: When colorectal cancer has a high metastatic rate or mismatch repair deficit, it is used in combination with nivolumab.

Hepatocellular Carcinoma: For those who have previously been treated with nivolumab and sorafenib. For some advanced or metastatic cases of non-small cell lung cancer (NSCLC), nivolumab is utilized as a first-line treatment.

c) Negative Reaction:

- Experiencing diarrhea
- Rash
- Pruritus, or itching
- feel nauseous.
- Reduced appetite (17)

B. VEGF pathway regulator

The development of new blood vessels for tumor growth and dissemination is made possible via the Vascular Endothelial Growth Factor (VEGF) pathway, which is essential for tumor angiogenesis. Lung, colorectal, and renal cell carcinoma are among the malignancies that have been successfully treated by blocking the VEGF system. The most studied type, VEGF-A, promotes endothelial cell migration, survival, and proliferation via binding to VEGFR-1 and VEGFR-2. Normal vascular development and cancer depend on the VEGF pathway because tumors release VEGF to promote angiogenesis and maintain blood flow. Limiting tumor development and spread can be achieved by blocking vascular formation within tumors through the inhibition of VEGF signaling. (18)

By focusing on and blocking VEGF-A's action, these medications stop it from attaching to its receptors.

1) Bevacizumab

a) Mechanism: VEGF-A is bound by a monoclonal antibody, which prevents it from interacting with VEGFR.

b) Indications: Among the numerous cancers for which it is approved are ovarian, colorectal, renal, and non-small cell lung cancers (NSCLC).

c) Effectiveness: Bevacizumab has been shown to significantly improve overall survival (OS) and progression-free survival (PFS) when used in combination with chemotherapy for a variety of cancer types. (19)

C) Antibodies that are bispecific

The ability of bispecific antibodies (BsAbs) to target multiple antigens at once, increasing the specificity and effectiveness of immunotherapy, is becoming more widely acknowledged in the treatment of lung cancer. Worldwide, lung cancer—in particular, non-small cell lung cancer, or NSCLC—

remains the leading cause of cancer-related death. Both early-stage and late-stage lung cancers can benefit from the use of BsAbs. A thorough examination of the role of bispecific antibodies in the management of lung cancer is provided here. (20)

Above are bispecific antibodies.

1. Blinatumomab

The first approved bispecific antibody for the treatment of cancer, specifically for adult and pediatric relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Additionally, it has a license for B-cell precursor ALL in these populations that has minimum residual disease (MRD).

a) The Action Mechanism

Bispecific T-cell engagers (BiTEs), like blinatumomab, interact with two different targets.

-CD3: A substance found on the surface of T-cells , a subset of white blood cells essential to immunological reactions.

Most B-cells, including those with B-cell precursor acute lymphoblastic leukemia (ALL), include the surface protein CD19.

-Dual Targeting: By binding to CD3 on T-cells and CD19 on B-cells, blinatumomab makes it easier for T-cells to approach cancerous B-cells.

-T-cell Activation: When T-cells are drawn to the tumor location, they get activated and begin attacking the cancerous B-cells, eliminating them.

-Selective and Effective: Blinatumomab's bispecific property makes it easier to destroy cancerous B-cells precisely while causing less damage to healthy cells. (21)

b) Uses Permitted and Indications

Most commonly, blinatumomab is used to treat relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), a kind of leukemia that affects the blood and bone marrow.

It is designed for those whose condition has not improved with traditional treatments such stem cell transplants or chemotherapy, or who have had a relapse after starting treatment.

It is also used for patients with MRD-positive B-ALL, which increases the risk of relapse because it shows that the patient still has leukemia cells in their body after therapy.

For relapsed and refractory acute lymphoblastic leukemia (ALL), blinatumomab significantly increases remission rates, which lowers minimal residual disease (MRD) and lengthens survival.

c) Adverse Reactions

- Syndrome of Cytokine Release (CRS)
- Neurotoxicity
- Infections
- Additional Adverse Reactions. (22)
- EGFR anti-antibodies

Targeted medications known as anti-EGFR (epidermal growth factor receptor) antibodies are mostly used in oncological treatment, especially for non-small cell lung cancer (NSCLC). A protein called EGFR, which is found on the surface of many cancer cells, aids in the development and spread of tumors. EGFR is commonly overexpressed or modified in cancer cells, which leads to unchecked cell division.

1. Erbitux (cetuximab)

The epidermal growth factor receptor (EGFR), a protein that is overexpressed in a number of malignancies, including colorectal cancer (CRC), head and neck cancer, and non-small cell lung cancer (NSCLC), is the specific target of this monoclonal antibody. It works by binding to the EGFR's extracellular domain and preventing its activation, which blocks downstream signaling that promotes angiogenesis, cell survival, and proliferation.

a) Action Mechanism:

On the surface of cancerous cells, cetuximab binds to the extracellular domain of the epidermal growth factor receptor (EGFR). By preventing natural ligands like TGF-α and EGF from attaching to EGFR, this mechanism suppresses the receptor's function. The downstream signaling pathways that promote cell survival and proliferation, like the PI3K/Akt and MAPK pathways, are thereby inhibited. Through antibody-dependent cellular cytotoxicity (ADCC), which activates immune cells like natural killer cells to destroy antibody-coated tumor cells, cetuximab also promotes the recruitment of immune cells to the tumor site, resulting in decreased tumor cell proliferation and possibly inducing apoptosis (programmed cell death). (23)

b) Signs

The FDA has authorized cetuximab for the treatment of:

-Metastatic colorectal cancer (CRC), typically in combination with FOLFIRI or FOLFOX chemotherapy regimens.

HNSCC, or head and neck squamous cell cancer, usually in combination with chemotherapy or radiation treatment.

-NSCLC in patients with tumors exhibiting wild-type EGFR (lacking activating mutations), particularly when chemotherapy is administered.

Tyrosine kinase inhibitors (TKIs), such as erlotinib and gefitinib, are preferred in patients with non-small cell lung cancer (NSCLC) who have EGFR mutations, such as those with changes in the EGFR tyrosine kinase domain. Cetuximab is unsuccessful in these patients.

c) Adverse Reactions

The following are typical and dangerous cetuximab side effects:

Fatigue, gastrointestinal toxicity, electrolyte imbalance, skin reactions, and infusion reactions

d) Efficiency in Lung Cancer Treatment

Patients with non-small cell lung cancer (NSCLC) who have wild-type EGFR—that is, those without activating mutations—are given cetuximab. It is typically used in combination with chemotherapy drugs such as paclitaxel and carboplatin. However, in patients with EGFR mutations, cetuximab's efficacy in non-small cell lung cancer (NSCLC) is lower than that of other cancers like colorectal or head and neck cancer, especially when compared to EGFR tyrosine kinase inhibitors (TKIs).

Although cetuximab is not considered the first-line treatment for EGFR wild-type NSCLC, it has shown modest improvements in overall survival (OS) and progression-free survival (PFS) in clinical trials when used in conjunction with chemotherapy for advanced NSCLC (24)

Conclusion

A possible treatment for lung cancer, especially non-small cell lung cancer (NSCLC), is monoclonal antibodies (mAbs). They increase patients' overall survival, progression-free survival, and quality of life by targeting cancer cells while minimizing damage to healthy tissue. Clinical research is being done on additional monoclonal antibodies that target particular molecular pathways, including EGFR, ALK, ROS1, and tumor-associated antigens. To tailor particular cancer treatments, these targeted medications can be utilized in addition to radiation or chemotherapy. But problems like resistance, negative immunological consequences, and exorbitant expenses still exist. To improve patient selection, deal with resistance, and investigate combination therapy, more research is required. The most cutting-edge treatment for lung cancer is monoclonal antibodies, which give patients with few other options new hope. Their use in lung cancer treatment will be further expanded by upcoming clinical trials and studies on the immune system and tumor microenvironment.

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