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The Potent Anti-Cancer Drug: Pembrolizumab

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ABSTRACT:

Pembrolizumab is a humanized monoclonal antibody that specifically targets programmed cell death protein 1 (PD-1), a receptor located on T cells that helps to dampen immune responses. By blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, pembrolizumab enhances T-cell activation, which in turn boosts the body's ability to fight off tumors.

In clinical trials, anti–PD-1 and anti–PD-L1 antibodies have shown to create lasting responses in about 20% of patients with advanced non–small-cell lung cancer, even when they haven't been specifically selected. One of the ongoing challenges is to develop reliable and validated biomarkers that can pinpoint which patients are more likely to respond positively to these treatments. The PD-1 pathway seems to play a significant role in how some patients with non–small-cell lung cancer evade the immune system, making PD-L1 expression in tumor or inflammatory cells a potential biomarker. However, it's important to note that PD-L1 expression hasn't been officially validated as a biomarker using tumor tissue collected in recent studies.

Important mechanism contributing to the exhausted effector T-cell phenotype. The expression of PD1 on effector T-cells and PDL1 on neoplastic cells enables tumor cells to evade anti-tumor immunity. Blockade of PD1 is an important immunotherapeutic strategy for cancers. Pembrolizumab (Keytruda) is a humanized monoclonal anti-PD1 antibody that has been extensively investigated in numerous malignancies. In melanoma refractory to targeted therapy, pembrolizumab induced overall response rates (ORRs) of 21–34%. It was superior to another immune checkpoint inhibitor ipilimumab (Yervoy) in stage III/IV unresectable melanoma

DISCOVERY & FURTHER HISTORY:

In 2017, the US Food and Drug Administration (FDA) gave the green light to pembrolizumab for use in patients with unresectable or metastatic solid tumors that have specific genetic changes, like mismatch repair deficiency or microsatellite instability. [1]

As of 2019, pembrolizumab is administered through an intravenous infusion to tackle inoperable or metastatic melanoma. It's also used for metastatic non-small cell lung cancer (NSCLC) in specific cases, serves as a first-line treatment for metastatic bladder cancer in patients who can't undergo cisplatin-based chemotherapy and have elevated levels of PD-L1, and acts as a second-line treatment for head and neck squamous cell carcinoma (HNSCC). [2]

Pembrolizumab (brand name *Keytruda*) is a monoclonal antibody used in cancer immunotherapy. It works by targeting the programmed cell death protein 1 (PD-1) pathway, which plays a key role in suppressing the immune response. By inhibiting PD-1, pembrolizumab enhances the body's immune system to recognize and fight cancer cells.

Immune checkpoint inhibitors (ICIs) have truly transformed the landscape of cancer treatment, providing lasting responses for numerous patients battling both solid and blood cancers. However, the steep prices of these drugs, coupled with their rising usage, are placing a significant burden on healthcare budgets around the world, with costs projected to exceed 46 billion USD by 2026. [3]

Merck has just gotten the green light for KEYTRUDA (pembrolizumab) with accelerated approval! This marks a significant milestone as the FDA has officially approved KEYTRUDA, making it the very first anti-PD-1 (programmed death receptor-1) therapy. Plus, it had already earned breakthrough therapy designation from the FDA before this exciting news.

CHEMICAL PROPERTIES

1)**Solubility**- 22.5-27.5 mg/ml (with histidine buffer)

2)**Isoelectric Point**- 6.8-6.9

3)**Molecular Formula**: C6528H10076N1744O2016S44

4)**Molecular Weight**: 149 kDa (kilodaltons).

5)MECHANISM OF ACTION: Pembrolizumab operates by attaching itself to the PD-1 receptor found on T-cells. This action blocks the receptor's interaction with its ligands, PD-L1 and PD-L2. As a result, it stops the immune suppression that cancer cells use to dodge the immune system, enabling the body's defenses to identify and target tumor cells effectively.

PHYSICAL PROPERTIES:

1) **Stability:** Pembrolizumab stays stable when kept at temperatures between 2°C and 8°C (that's 36°F to 46°F), and it's important not to freeze it.

2) **Appearance**: Pembrolizumab usually comes as a clear to pale yellow liquid, packaged in a sterile solution that's ready for intravenous (IV) infusion.

3) **Solubility:** Pembrolizumab dissolves easily in water. It's prepared as a concentrated solution for intravenous use, but typically, it gets diluted before being given to patients.

4) **pH**: The pH level of a pembrolizumab solution usually falls between 5.8 and 6.8, which is slightly on the acidic side. This makes it suitable for intravenous administration.

PHARMACOKINETIC CHARACTERISTICS

ICIs, or immune checkpoint inhibitors, are essentially humanized antibodies, specifically human immunoglobulin G 1 (IgG1) and IgG4. They share similar pharmacokinetic (PK) traits with other therapeutic monoclonal antibodies (mAbs). One of their key benefits is that they have minimal impact on kidney and liver function. These antibodies are known for their low clearance rates, small distribution volumes, and the ability to diffuse outside of blood vessels. They also boast a long half-life and exhibit a consistent timing for both receptor-mediated linear and nonlinear combined clearance.[4]

Pembrolizumab is given through an intravenous (IV) infusion, which means you won't find it in pill form. Its absorption depends on how well it gets into the bloodstream after the infusion. Because it's delivered directly into the veins, the bioavailability is a perfect 100%, meaning that every bit of the drug you receive is available in your systemic circulation.

The main differences between biologics and small molecule drugs lie in their size, structural complexity, and production methods. Small molecule drugs usually have a molecular weight of less than 1 kDa, which means they consist of about 20 to 100 atoms. In contrast, biologics can have molecular weights that range from just a few kDa all the way up to 1000 kDa, like IgM monoclonal antibodies.[5]

The volume of distribution (Vd) for pembrolizumab is quite significant, indicating that it spreads widely throughout the body. This medication attaches to the PD-1 receptor, which is mainly found on T-cells. The binding is very specific, and the drug's effects rely heavily on how it interacts with this receptor. Pembrolizumab also has a long elimination half-life, usually about 26 days, which means it can be administered less frequently typically every three weeks.

MECHANISM OF ACTION OF PEMBROLIZUMAB:

Choosing the right antibody, target antigen, linker, and payload is essential for achieving the best results while keeping unwanted side effects at bay. Each part of an antibody-drug conjugate (ADC) can carry its own risk of toxicity. The type of antibody you select plays a vital role in ADC development because it affects how stable the ADC is in the bloodstream, how specifically it targets the intended antigen, and the likelihood of hypersensitivity reactions.[6]

The PD-1 receptor is a checkpoint protein located on the surface of activated T-cells, B-cells, and natural killer (NK) cells. It plays a vital role in regulating the immune response, helping to prevent autoimmunity and ensuring that the immune system remains tolerant. PD-L1 (Programmed Death-Ligand 1) and PD-L2 are the ligands that interact with PD-1. PD-L1 is found on tumor cells as well as many normal tissues, while PD-L2 is typically present on immune cells. When either PD-L1 or PD-L2 binds to PD-1, it sends a signal that inhibits T-cell activity, allowing tumors to escape detection by the immune system. To protect themselves from immune attacks, tumor cells often increase the expression of PD-L1 on their surface.

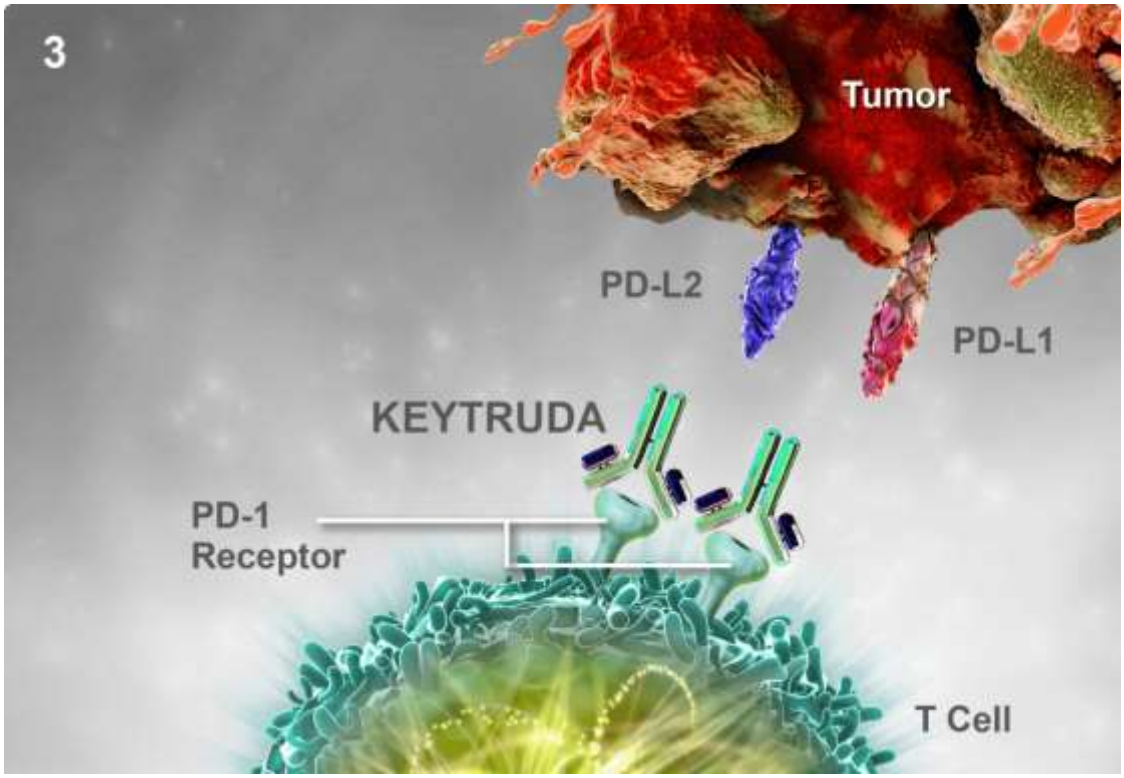

Figure 1 Mechanism of Action of Pembrolizumab[7]

Pembrolizumab binds to the PD-1 receptor on T-cells, preventing its interaction with the PD-L1/PD-L2 ligands on tumor cells and other cells in the tumor microenvironment. This blockade releases the inhibitory effect on T-cells, allowing them to become activated and attack tumor cells. Pembrolizumab enhances the body's immune response, potentially leading to the destruction of cancer cells and long-term anti-tumor immunity.

METHOD OF SYNTHESIS: A total of twenty-five new BBR derivatives, as shown here.

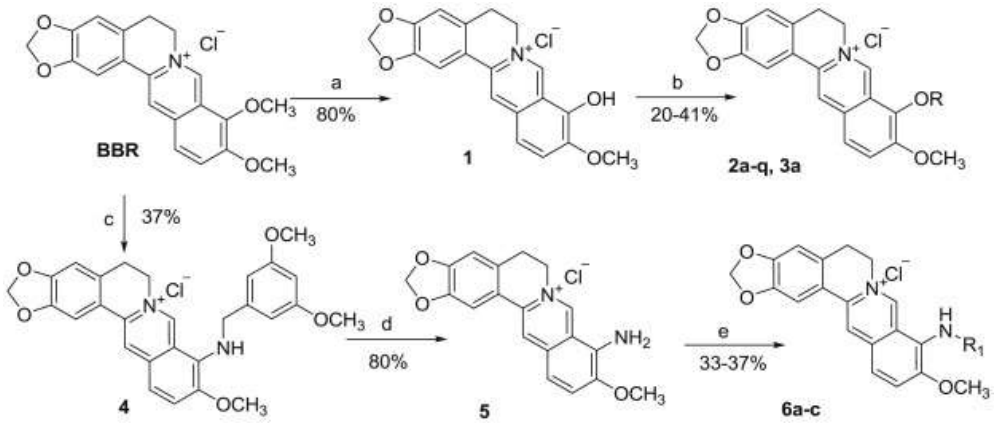

Figure 2 Method of synthesis of pembrolizumab[8]

MEDICINAL USES OF PEMBROLIZUMAB

Pembrolizumab is a type of immune checkpoint inhibitor that's making waves in cancer treatment. It functions by blocking the PD-1 receptor on T-cells, which boosts the immune system's power to identify and fight off cancer cells.

Pembrolizumab combined with lenvatinib is the first treatment that's been approved for women dealing with endometrial carcinoma, especially those with recurrent or metastatic disease who have already been treated with carboplatin and paclitaxel.[9]

Non-Small Cell Lung Cancer (NSCLC): Pembrolizumab is utilized for treating advanced or metastatic non-small cell lung cancer, frequently alongside chemotherapy or as a first-line option in specific situations.

Melanoma: This medication is effective for advanced melanoma, whether used alone (as a single treatment) or in conjunction with other therapies like ipilimumab, which is another type of immune checkpoint inhibitor.

Chemotherapy can actually boost immune activation in a few key ways, enhancing the immune system's ability to fight tumors and improving the effectiveness of immune checkpoint inhibitors. It triggers a significant number of immunogenic deaths in tumor cells within a short period, which releases tumor antigens and helps lift the immune system's suppression caused by those tumor cells.[10]

Pembrolizumab is a PD-1 inhibitor that focuses on immune checkpoint proteins, and it has really changed the game for treating **metastatic melanoma**, non-small cell lung cancer, and various other cancers. That said, the outcomes of clinical trials using immunotherapy for pancreatic ductal adenocarcinoma (PDAC) have not lived up to expectations.[11]

Esophageal Cancer: This treatment is intended for patients dealing with advanced esophageal or gastroesophageal junction cancers that show PD-L1 expression.

Cervical Cancer: Pembrolizumab is utilized for treating recurrent or metastatic cervical cancer, especially when the disease has advanced following chemotherapy.

SYSTEMIC ADVERSE EFFECTS

The reasons behind cardiotoxicity linked to immunotherapy are still being explored. When it comes to immune checkpoint inhibitors, researchers believe that the similarity in T-cell receptor sequences found in both tumors and cardiac muscle might be what triggers inflammation in the heart and surrounding areas. This theory is further supported by histopathological evidence showing fibrinous exudates along with infiltration of lymphocytes, plasma cells, and macrophages in patients suffering from pericarditis.[12]

Autoimmune Conditions: Pembrolizumab can trigger autoimmune diseases, where the immune system attacks the body's own tissues. This can affect many different organs.

Lung Inflammation: Pneumonitis can sometimes develop slowly and worsen if untreated.

The patient was given four doses of pembrolizumab but is currently facing some health challenges, reflected in a prognosis index of 3 on the Eastern Cooperative Oncology Group performance status (ECOG). As a result, the decision was made to halt the immunotherapy.[13]

CARDIOVASCULAR ADVERSE EFFECTS

In the heart, tyrosine kinase inhibitors (TKIs) can have a negative impact on vascular endothelial cells and cardiac postmitotic cells, especially cardiomyocytes (CMs). These TKIs, particularly those that target multiple kinases, influence various signaling pathways. The ones that are most significantly affected include cardiotrophin and its receptor gp130, the epidermal growth factor receptor (EGFR, ErbB2, or HER2), phosphoinositide 3-kinase (PI3K), AMP-activated protein kinase (AMPK), the ubiquitin-proteasomal system, and the pathways involved in lysosomal autophagy.[14]

Dermatologic Toxicities

The initial clinical trial revealed that about 89% of patients experienced skin toxicities, while cetuximab was associated with a rash in 27.85% of patients during its second clinical trial. This was observed in the context of erbitux being used as a first-line treatment for recurrent or metastatic head and neck cancer in the EXTREME study.[15]

Gastrointestinal

After dermatitis, gastrointestinal (GI) tract toxicity ranks as the second most common immune-related adverse event (irAE) in patients undergoing treatment with immune checkpoint inhibitors (ICIs). This issue tends to be more prevalent and severe, especially in those receiving anti–CTLA-4 antibodies (30–40%) or a mix of different ICIs (10%) .Inflammation related to ICIs can affect any part of the digestive system, from the mouth all the way to the rectum. This means that inflammation in the upper GI tract can lead to conditions like esophagitis, gastritis, and duodenitis . When it comes to upper GI adverse events, which are often linked to PD-1 inhibitors, they tend to be less common and not well-documented in existing literature. On the other hand, lower GI adverse events are reported in nearly one-third of patients treated with CTLA-4 inhibitors.[16]

When it comes to pembrolizumab, patients are kept under careful watch during their treatment due to the risk of serious side effects. If you notice any severe or unusual symptoms, it's essential to reach out to your healthcare provider right away. Often, side effects can be handled with medications such as steroids or other immune-suppressing therapies, but there might be times when the treatment plan needs to be modified or even halted. It's really important to let your doctor know about any new or unexpected symptoms as soon as possible to make sure you get the right care in a timely manner.

TREATMENT OF OVERDOSE

If someone takes too much of an anticancer drug, it can lead to serious complications and needs urgent medical help. The effects and risks of an overdose can differ based on the specific medication, since various anticancer drugs operate in unique ways and have their own toxicity levels.

It turns out that about 90% (16 out of 18) of the Accelerated Approvals (AAs) for new indications were grounded in objective response rate (ORR) and duration of response (DOR) data from single-arm trials or those that didn't have a randomized control group. Interestingly, around 75% of these AAs were aimed at treating patients with metastatic or locally advanced disease who had already seen their condition progress after previous treatments. These figures make sense, especially since ORR and DOR in later treatment lines have historically been the backbone of most oncology AAs.[17]

In clinical trials, patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) are often left out due to the potential risk of worsening graft versus host disease (GVHD). However, as we gain more experience, we've started treating patients with lymphomas that relapse after allogeneic HSCT using pembrolizumab.[18]

Steps in Managing an Overdose of Pembrolizumab

IMMEDIATE MEDICAL ATTENTION:

If a patient has received too much pembrolizumab, it's crucial to keep a close eye on them for any serious immune-related side effects, like inflammation in organs such as the liver, lungs, or intestines. Regular blood tests might be necessary to check for any changes in how the organs are functioning like the liver, kidneys, and heart—as well as to monitor immune system activity, including inflammation markers.

If someone has taken too much pembrolizumab, it's crucial to seek medical help right away. Treatment typically includes supportive care and addressing any immune-related side effects, which may involve using corticosteroids or other immunosuppressive medications. Since there isn't a specific antidote for this situation, healthcare professionals will concentrate on managing symptoms and any complications that come up. If you think an overdose has occurred, don't hesitate to reach out to healthcare providers or emergency services.

CONTRAINDICATION:

Pregnancy:

When it comes to pregnancy, Keytruda can pose risks to an unborn baby. That's why your healthcare provider will conduct a pregnancy test to ensure you're not pregnant before starting treatment. It's important to use reliable birth control while you're on Keytruda and for at least four months after your last dose. If you suspect you might be pregnant or if you do become pregnant during your treatment, make sure to inform your healthcare provider immediately.[18]

Pediatric patients:

We still need to determine the safety and effectiveness of pembrolizumab for pediatric patients. **Geriatric use** Out of 411 patients with relapsed unresectable or metastatic melanoma who were treated with pembrolizumab, 39% were 65 years or older. There were no significant differences in efficacy noted between the different age groups.[20]

DRUG INTERACTION

DRUG INTERACTIONS BETWEEN LENALIDOMIDE AND PEMBROLIZUMAB

When it comes to treating multiple myeloma, using medications like pembrolizumab alongside lenalidomide and dexamethasone could raise the chances of experiencing serious and potentially life-threatening side effects, even leading to death, compared to just using lenalidomide and dexamethasone on their own. This conclusion comes from findings in two investigational studies. If you have any questions or concerns, don't hesitate to reach out to your doctor. It's really important to keep your doctor informed about all the other medications you're taking, including any vitamins or herbal supplements. And remember, never stop taking any medications without first discussing it with your doctor.[23]

DRUG INTERACTIONS BETWEEN PEMBROLIZUMAB AND THALIDOMIDE

When it comes to treating multiple myeloma, using medications like pembrolizumab alongside thalidomide and dexamethasone could raise the chances of experiencing serious, even life-threatening side effects, as well as an increased risk of death, compared to just using thalidomide and dexamethasone on their own. This conclusion comes from findings in two investigational studies. If you have any questions or concerns, don't hesitate to reach out to your doctor. It's really important to keep your doctor informed about all the other medications you're taking, including vitamins and herbal supplements. And remember, never stop taking any medications without first discussing it with your doctor.[21]

CONVENTION MARKETED FORMULATION:

Type: Injectable solution

- **100mg/4mL (25mg/mL)**
- Indicated for treatment of unresectable or metastatic melanoma
- 200 mg IV q3Weeks OR 400 mg q6Weeks until disease progression or unacceptable toxicity

Non-Small Cell Lung Cancer

Single-agent for localized disease

- Indicated as adjuvant treatment following resection and platinum-based chemotherapy for Stage IB (T2a ≥4 cm), II, or IIIA NSCLC
- 200 mg IV q3Weeks OR 400 mg q6Weeks until disease progression or unacceptable toxicity, or up to 12 months without disease progression

NOVAL MARKETED FORMULATION:

Brand Name: Keytruda

Company Name: Merck & Co

Dose: **200 mg IV q3Weeks** OR 400 mg q6Weeks until disease progression, unacceptable toxicity, or up to 24 months without disease progression.

Prize: 2,00,000 to 4,00,000 per vial

CONCLUSION:

Keytruda (pembrolizumab) has made waves as a revolutionary immunotherapy in the battle against different forms of cancer. By focusing on the PD-1/PD-L1 pathway, Keytruda helps the immune system spring back to life, enabling it to spot and eliminate cancer cells. Both clinical trials and real-world evidence have shown its effectiveness in tackling a range of cancers, such as melanoma, non-small cell lung cancer, head and neck squamous cell carcinoma, and beyond.

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