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Review Article

Atezolizumab Is A Humanized Igg1 Monoclonal Antibody That Targets Pd-L1

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Abstract

TECENTRIQ can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during your treatment or even after your treatment has ended.

Tecentriq has some adverse problems. Lung problems: cough, shortness of breath, chest pain. Intestinal problems: diarrhea [loose stools] or more frequent bowel movements than usual, stools that are black, tarry, sticky, or have blood or mucus, severe stomach-area [abdomen] pain or tenderness. Liver problems: yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of your stomach area [abdomen], dark urine [tea colored], bleeding or bruising more easily than normal. Hormone gland problems: headaches that will not go away or unusual headaches, eye sensitivity to light, eye problems, rapid heartbeat, increased sweating, extreme tiredness, weight gain or weight loss, feeling more hungry or thirsty than usual, urinating more often than usual, hair loss, feeling cold, constipation, voice gets deeper, dizziness or fainting, changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness. Kidney problems: decrease in your amount of urine, blood in urine, swelling of ankles, loss of appetite. Skin problems: rash, itching, skin blistering or peeling, painful sores or ulcers in mouth or nose, throat, or genital area, fever or flu-like symptoms, swollen lymph nodes. Chest pain, irregular heartbeat, shortness of breath, or swelling of ankles, Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs, Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight

Persistent or severe muscle pain or weakness, muscle cramps, Low red blood cells, bruising, Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include: chills or shaking, itching or rash, flushing, shortness of breath or wheezing, dizziness, feeling like passing out, fever, back or neck pain. Complications, including graft-versus-host disease [GVHD], in people who have received a bone marrow [stem cell] transplant that uses donor stem cells [allogeneic]. These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with TECENTRIQ. Your healthcare provider will monitor you for these complications. Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with TECENTRIQ if you have severe side effects. Before you receive TECENTRIQ, tell your healthcare provider about all of your medical conditions, including if you: have immune system problems such as Crohn's disease, ulcerative colitis, or lupus; have received an organ transplant; have received or plan to receive a stem cell transplant that uses donor stem cells [allogeneic]; have received radiation treatment to your chest area; have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barre syndrome; are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with TECENTRIQ. Females who are able to become pregnant: Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ. You should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ. You are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breast milk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ. Tell your healthcare provider about all

about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. The most common side effects of TECENTRIQ when used alone include: feeling tired or weak, decreased appetite, nausea, cough, shortness of breath. The most common side effects of TECENTRIQ when used in lung cancer with other anti-cancer medicines include: feeling tired or weak, nausea, hair loss, constipation, diarrhea, decreased appetite.

Keywords: Monoclonal antibody, Urothelial carcinoma, Immunoglobulin

Chemistry: Atezolizumab is a solid [CAS: 1380723-44-3, MW: 33275.095 Da] It is used as injection is in a class of medications called monoclonal antibodies. It works by blocking the action of a certain protein in cancer cells. This helps the person's immune system to fight against the cancer cells, and helps to slow tumor growth. Experimental Properties: Melting Point: 78°C, Water solubility: 50mg/mL, Isoelectric point: 6.6-7.2]. Atezolizumab has a half-life of 27 days with a clearance that non-significantly decreases at steady state. The pharmacokinetic profile is linear between doses ranging from 1 to 20 mg/kg. No dose-exposure relationship has been shown for efficacy or safety in the different types of cancer evaluated. Cycle length: 21 days. Duration of therapy: Four cycles plus maintenance atezolizumab monotherapy. [1] Dilute in 250 mL NS* and administer first dose over 60 minutes; if first infusion is tolerated, then administer subsequent doses over 30 minutes. Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter [pore size of 0.2–0.22 micron].It is a monoclonal antibody used to treat advanced or metastatic urothelial carcinoma with disease progression during or up to 12 months after platinum-containing chemotherapy. Atezolizumab is a humanized monoclonal antibody used to prevent the interaction of PD-L1 and PD-1, removing inhibition of immune responses seen in some cancers. Normally, PD-L1 is found on certain healthy cells. It acts as a kind of "brake" to stop cells in your immune system, called T cells, from attacking healthy cells in your body. The recommended dosage of TECENTRIQ is 1200 mg as an intravenous infusion over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. No dose reductions of TECENTRIQ are recommended [2].

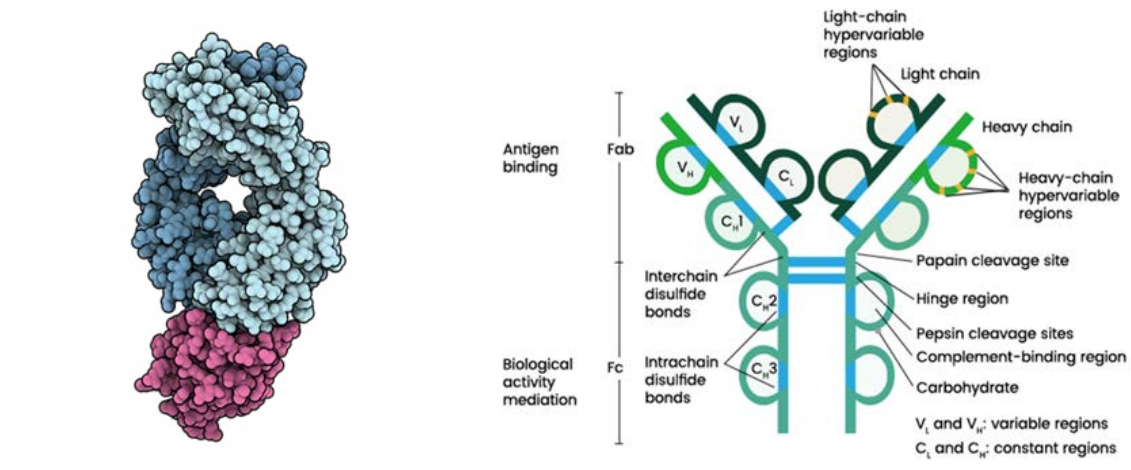

Figure 1: Monoclonal antibody

Atezolizumab is considered a hazardous drug because it can cause embryo-fetal toxicity and may impair fertility in females of reproductive potential. If cancer cells have high amounts of PD-L1, they can turn your T cells off so they can't attack the cancer cells. PD-L1 [programmed cell death ligand 1] is a protein that plays a role in the body's immune system. It can bind to another protein called PD-1. When this happens, the two proteins block the immune system from killing cancer cells. This medication is reserved for patients whose tumors express PD-L1, cannot receive platinum-based chemotherapy, or whose tumors do not respond to platinum-based chemotherapy. Atezolizumab was granted FDA approval on 18 October 2016. In November 2022, the manufacturer [Genentech] voluntarily withdrew the use of atezolizumab for the treatment of urothelial carcinoma, previously approved under the FDA's Accelerated Approval Program. The rest of atezolizumab indications remain unaffected. Urothelial carcinoma [also called transitional cell carcinoma] is cancer that begins in the urothelial cells, which line the urethra, bladder, ureters, renal pelvis, and some other organs. Almost all bladder cancers are urothelial carcinomas.

Atezolizumab is a humanized monoclonal antibody used to prevent the interaction of PD-L1 and PD-1, removing inhibition of immune responses seen in some cancers. This drug has a long duration of action as it is usually given every 3-4 weeks. Atezolizumab should not be used in patients with immune mediated pneumonitis, hepatitis, colitis, and some endocrinopathies [3].

Mechanism of action: Atezolizumab is a humanized IgG antibody that binds PD-L1, preventing its interaction with PD-1 and B7-1. Preventing the interaction of PD-L1 and PD-1 removes inhibition of immune responses such as the anti-tu-

mor immune response but not antibody dependent cellular cytotoxicity. Atezolizumab, sold under the brand name Tecentriq, is a monoclonal antibody medication used to treat urothelial carcinoma, non-small cell lung cancer [NSCLC], small cell lung cancer [SCLC], hepatocellular carcinoma and alveolar soft part sarcoma, but discontinued for use in triple-negative breast cancer [TNBC]. It is a fully humanized, engineered monoclonal antibody of IgG1 isotype against the protein programmed cell death-ligand 1 [PD-L1]. The most common side effects when used on its own include tiredness, reduced appetite, nausea, vomiting, cough, difficulty breathing, diarrhea, rash, fever, pain in the back, joints, muscles and bones, weakness, itching and urinary tract infection. The most common side effects when used with other cancer medicines include peripheral neuropathy [nerve damage in the hands and feet], nausea, anemia [low red blood cell counts], neutropenia [low white blood cell counts], thrombocytopenia [low platelet counts], rash, tiredness, constipation, reduced appetite, diarrhea, and cough. Atezolizumab is the first PD-L1 inhibitor approved by the U.S. Food and Drug Administration [FDA].

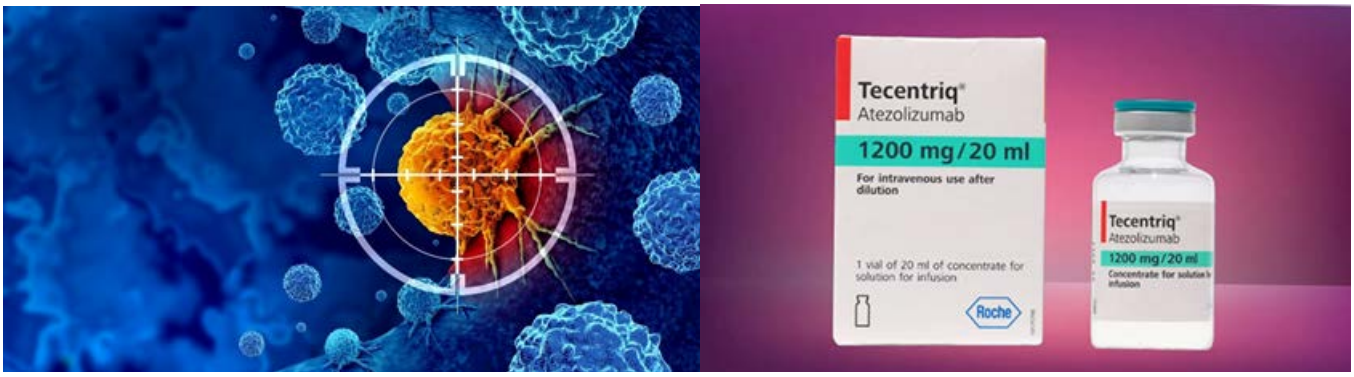

Figure 2: Atezolizumab Target

Medical uses: In the European Union, atezolizumab is indicated for the treatment of urothelial carcinoma, non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, urothelial carcinoma, and triple-negative breast cancer. It is no longer indicated for triple-negative breast cancer [4].

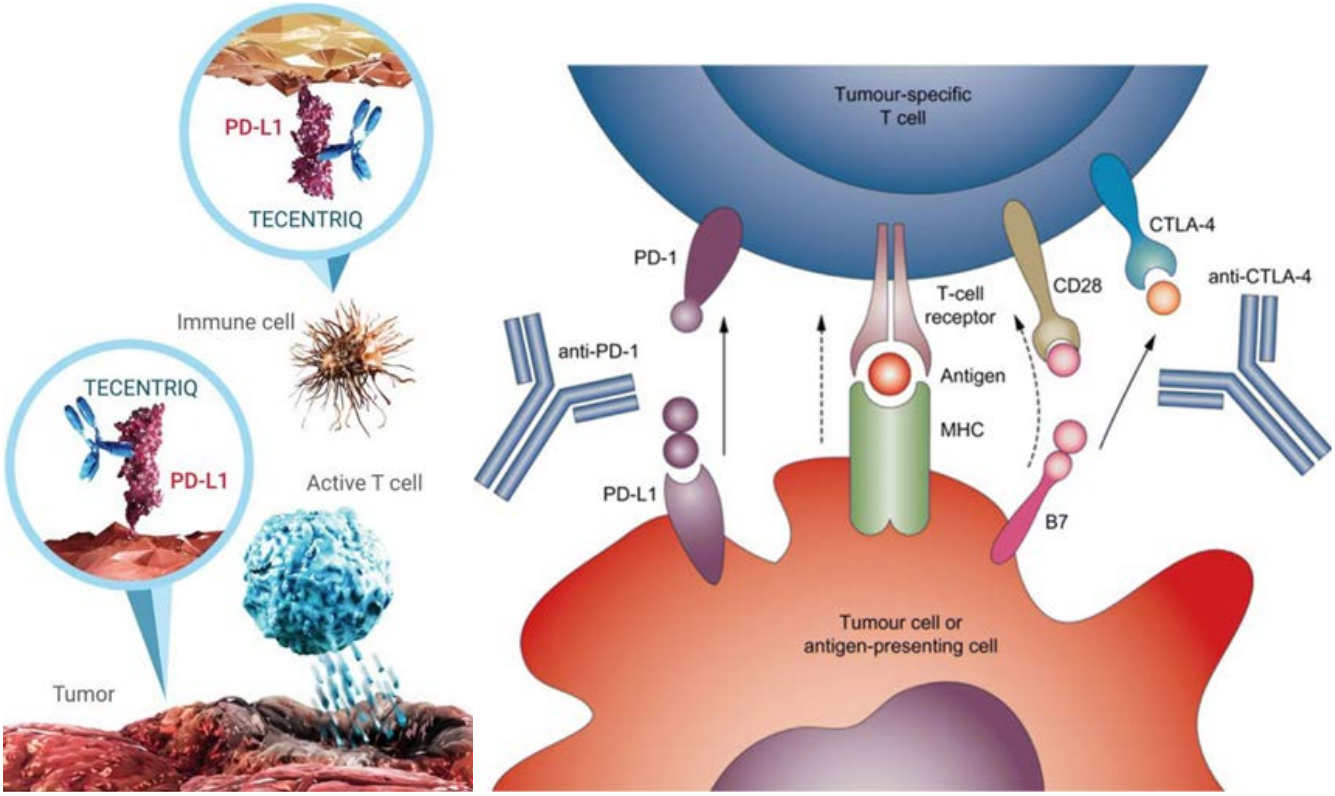

Figure 3: Mode Of Action

In the United States, atezolizumab is indicated for the treatment of non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, melanoma, and alveolar soft part sarcoma. Its indication for urothelial carcinoma was withdrawn in November 2022.

Adverse Effects: The most common adverse effects in studies were fatigue, decreased appetite, nausea, and infections. Urinary tract infection was the most common severe adverse effect.

Pharmacology-Mechanism Of Action: Non-small cell lung cancer [NSCLC] cells expressing programmed death-ligand 1 [PD-L1] could interact with programmed death receptor 1 [PD-1] expressed on the surface of T cells, and result in decreased tumor cell kill by the immune system. Atezolizumab is an anti PD-L1 monoclonal antibody. Nivolumab and pembrolizumab are anti PD-1 monoclonal antibodies. Ipilimumab is a monoclonal antibody that targets cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] on the surface of T cells. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor [VEGF] in the circulation and functions as an angiogenesis inhibitor. Atezolizumab blocks the interaction of PD-L1 with programmed cell death protein 1 [PD-1] and CD80 receptors [B7-1Rs]. PD-L1 can be highly expressed on certain tumors, which is thought to lead to reduced activation of immune cells [cytotoxic T-cells in particular] that might otherwise recognize and attack he cancer. Inhibition of PD-L1 by atezolizumab can remove this inhibitor effect and thereby engender an anti-tumor response. It is one of several ways to block inhibitory signals related to T-cell activation, a more general strategy known as “immune checkpoint inhibition.”

For some cancers [notably bladder] the probability of benefit is related to PD-L1 expression, but most cancers with PD-L1 expression still do not respond, and many [about 15%] without PD-L1 expression do respond [5].

Conclusion: Atezolizumab [Tecentriq™]-a monoclonal antibody targeting programmed death ligand 1 [PD-L1 or CD274 antigen]-is being developed by Genentech as treatment for a variety of haematological malignancies and solid tumours. It been approved in the US as a second-line therapy for urothelial carcinoma and is awaiting approval as a second-line therapy for non-small cell lung cancer. This article summarizes the milestones in the development of atezolizumab leading to this first approval for urothelial carcinoma. The structure shows that atezolizumab binds the front beta-sheet of PD-L1 through three CDR loops from the heavy chain and one CDR loop from the light chain. The binding involves extensive hydrogen-bonding and hydrophobic interactions. Atezolizumab works by targeting the immune checkpoint protein PD-L1 on cancer cells.

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