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CURRENT TRENDS ON A MONOCLONAL ANTIBODY THERAPY

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ABSTRACT

Mononoclonal antibodies have been found to be more effective in treating various types of diseases because they are more targeted than some other forms of medications. The use of mAbs in cancer, autoimmune disorders, chronic illnesses, and a number of other conditions has previously been authorised. Numerous biopharmaceutical firms attempt to compete by creating monoclonal antibodies and moving them forward into clinical trials due to their extensive potential as immunotherapeutics. Some monoclonal antibodies are also used in immunotherapy to aid the immune system's fight against cancer. Some monoclonal antibodies, for example, mark cancer cells so that the immune system can detect and kill them more effectively. In a recent clinical experiment, it was discovered that Dostarlimab completely cured all CRC patients who received it, with no patients experiencing any grade 3 or above side effects. A humanised monoclonal antibody called dostarlimab (Jemperli) or dostarlimab-gxly functions as an antagonist for programmed death-1 (PD-1) receptors. Moreover, clinical trial data showed dostarlimab is more effective than other PD-1 inhibitors and no significant adverse effects in any of the research participants, The purpose of this study is to summarise current evidence about monoclonal antibodies for cancer treatment and New drug Dostarlimab and to assess the possibility for Novel and Combination therapy.

Keyword: Monoclonal antibody therapy, PD1 anatgonist , Immunotherapy , Dostarlimab, Endometrial cancer

INTRODUCTION

Since its effective introduction into clinical practise more than 25 years ago, therapeutic monoclonal antibodies (mAbs) have grown to become one of the foundational elements of the healthcare system. Due to their ability to target certain molecular elements, they brought about a therapeutic revolution. A significant number of mAbs have already been approved for use in oncology, autoimmune disorders, chronic diseases, and a variety of other problems. Currently, in Europe and/or the US, over 80 antibody therapies have received regulatory approval, and just in 2017, sales of therapeutic antibodies exceeded $100 billion globally **[1]**. The main disadvantage of creating mAbs as therapeutic agents was the emergence of an immunological response in patients, which resulted in the rapid inactivation of mouse antibodies. To avoid this difficulty, technical development in antibody synthesis was regarded as critical. The use of monoclonal antibodies (mAbs) against a diverse variety of antigenic compounds is one of the most essential aspects of modern immunotherapy technology **[2]**. Furthermore, recent developments in molecular biology have defined a number of cell surface receptors that are by-products of cellular oncogenes and are essential for the development of tumour cells. Such receptors present themselves for antibody targeting, including the PDGF and EGF receptors **[3]**. The use of monoclonal antibodies in diagnosis is by far the most sophisticated, particularly for procedures involving bodily fluids like blood and urine. Antigen detection can be done using monoclonal antibodies. ELISA, western blot, immunoblot blot, flow cytometry, immunohistochemistry, radioimmunology assay, electron microscopy, fluorescence microscopy, and confocal microscopy are just an a number of the techniques that can employ them. Additionally, monoclonal antibodies are employed for the diagnosis of parasite diseases, the detection of antigen and antibodies against bacterial, fungal, viral, and viral-like diseases in livestock, as well as the detection of antigen and antibodies against fungal diseases in cattle **[4, 5]**.

Man-made proteins known as antibody treatments imitate or enhance the body's natural immune response by functioning like human antibodies. In a lab, scientists can create several copies (clones) of an antibody they have designed to recognise and target a particular pathogen. These are called monoclonal antibodies (mAbs) **[6]**.

A huge number of diseases, including different cancers, autoimmune and metabolic diseases, are being treated or prevented with monoclonal antibody therapy. Some examples include Crohn's disease, asthma, rheumatoid arthritis and bladder cancer. Infectious diseases such the respiratory syncytial virus, anthrax, and Clostridioides difficile are also treated or prevented with them. The death rate from the Ebola virus disease has also been shown to be decreased by two monoclonal antibody treatments **[7, 8]**.

Cancer treatment based on monoclonal antibodies

Many monoclonal antibodies are useful in cancer treatment. They are a kind of targeted cancer therapy, which means they bind with particular targets. Some monoclonal antibodies are also used in immunotherapy because they helps the immune system against cancer. Some monoclonal antibodies, for example, mark cancer cells so that the immune system can better detect and kill them **[9]**.

The term "mABs" refers to multiple copies of a single antibody isotype that are "all for just one" specific kind of antibody and are intended to target a single antigen. While all of the existing mABs for the treatment of cancer work via separate routes, some of them may also function via several processes. Since unmodified murine mAbs were initially evaluated as anticancer agents, mAB treatment for cancer has advanced significantly. Numerous mAB-based treatments for cancer patients have shown to have high potential. They work by using unlabeled IgG that particularly binds to tumour cells or by changing the host's active defence against the tumour. These mABs can change the specificity of mABs to retarget cellular immunity by serving as immunoconjugates to deliver cytotoxic moieties to malignant locations. The following mechanisms are involved in the process: (a) ADCC, which consists of targeted mABs made from human or chimeric antibody components that are intended to bind tumor-associated antigens; (b) CDC, which, as its name suggests, depicts complement activation; (c) and factor and receptor inhibition, which involves limiting the receptors that are involved in the activation of signal pathways for cancer cell proliferation or in the process of angiogenesis **[10]**.

it is a time of incredible success in mAb-based therapy, With new therapeutic agents and constructs being created quickly, improved knowledge of their biological effects, and expanding clinical experience

based on both clinical trials and the widespread use of FDA-approved medications. For the first time in anticancer therapy, diligent research in the translational and clinical fields of mABs has produced spectacular outcomes. Dostarlimab was examined on 12 patients who had colorectal cancer, and all of the patients recovered completely. Despite the fact that this study is in its phase II stage and was only conducted on a small number of people, the world looks at this drug with great hope because it has been proven to be a complete cure for cancer **[11]**.

Dostarlimab

Dostarlimab was discovered by AnaptysBio and licenced to TESARO, Inc. in March 2014 under a Collaboration and Exclusive License Agreement. Three monospecific antibody drugs have developed to the clinic as a result of the collaboration. Dostarlimab (GSK4057190), a PD-1 antagonist, cobolimab (GSK4069889), a TIM-3 antagonist, and GSK4074386, a LAG-3 antagonist, are among them. Under the terms of the Agreement, GSK is responsible for the ongoing research, development, commercialization, and manufacturing of each of these products **[12]**.

Dostarlimab-gxly (Jemperli, GlaxoSmithKline LLC) was granted accelerated approval by the Food and Drug Administration on August 17, 2021, for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumours, as determined by an FDA-approved test **[13]**.

Jemperli is a cancer drug used to treat specific forms of endometrial cancer (womb cancer) that have progressed or returned and gotten worse despite treatment with a platinum-based cancer drug. Jemperli is used to treat endometrial cancer, in which the cancer cells lack the genetic machinery to fix mistakes made during cell division (mismatch repair deficit and high microsatellite instability).

The active substance in jemperli is dostarlimab **[14]**.

Dostarlimab, the active substance in Jemperli, is a monoclonal antibody, a protein that has been developed to block the PD-1 receptor on specific immune system cells, the body's natural defences. Some tumours can produce the proteins PD-L1 and PD-L2, which when combined with PD-1 turn off the immune cells' function and stop them from attacking the malignancy. Dostarlimab prevents the tumour from turning off these immune cells by blocking PD-1, enhancing the immune system's capacity to destroy cancer cells **[15]**.

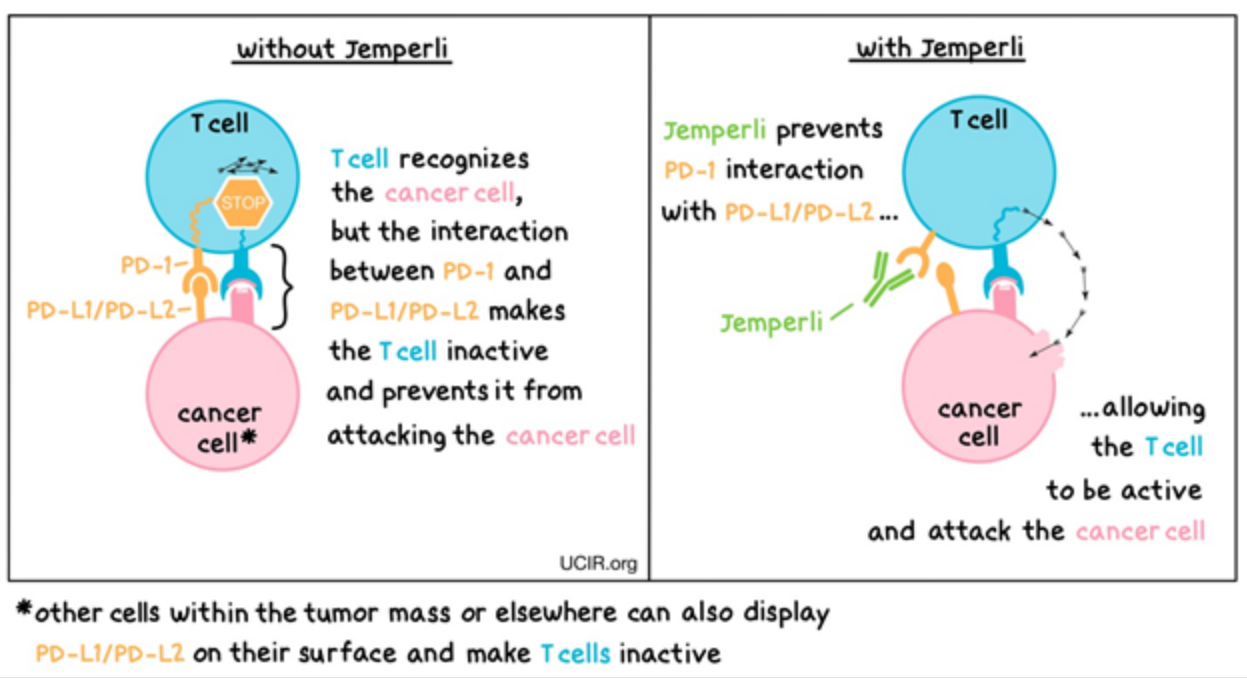

Figure 1: Mechanism of Dostarlimab

In dMMR advanced endometrial cancers, dostarlimab is more effective than other PD-1 inhibitors like avelumab and durvalumab. The drug's effectiveness is determined by the response rate, which for dostarlimab is 47% **[16]**.

Dostarlimab is a humanised IgG4 monoclonal antibody that was created by grafting a mouse complementarity determining region (CDR) onto a human antibody. Its 25.4-day serum half-life. Other PD-1 antibodies include nivolumab (Opdivo) and pembrolizumab (Keytruda), which are used to treat a wide range of cancers such as Hodgkin lymphoma, renal cell carcinoma, and breast cancer. Cemiplimab (Libtayo) is another PD-1 antibody that has been approved for the treatment of squamous cell carcinoma, basal cell carcinoma, and non-small cell lung cancer **[17]**.

Table 1: Previously found monoclonal antibodies for cancer treatment and their efficacy as follows:

Drug	Mode Of Action	Uses (Year Of Approval)	Efficacy	Side Effect
Transtuzumab (Herceptin)	**Binds to an extracellular domain of this receptor and inhibit HER_2 Homodemerization**	**Breast cancer. Stomach/esophagus Cancer(2019)**	**80-85%**	**Fever, Nausea, Vomiting, Diarrhea, infection, cough, headache,fatigue, dyspnea rash, neutropenia, anemia,myalegia.**
Bevacizumab (Avastin)	**Humanized IgG_1 MAB Binds to VEGF and block Its binding to VEGF receptor**	**Metastatic Colon Cancer, Metastatic kidney cancer and non-small cell lung cancer and glioblastoma.(2018)**	**43-50%**	**Black/tarry stools body aches/pain cloudy urine. Chest pain decrease urine output.**

Rituximab (Rituxan)	**Binds to protein called CD_{20} (located on surface of B cell) causes destruction of B cell.**	**Non Hodkin's lymphoma and lymphocytic leukemia. Lupus erythematosus (2021)**	**50-80%**	**Infusion related reaction, heart and heart rhythm problem.**
Brentuximab (ADCETRIS)	**Binds to CD_{30} receptor and is internalized via endocytosis.**	**Hodkin's lymphoma, systemic anaplastic large cell lymphoma, peripheral T cell lymphoma (2018)**	**75%**	**Neutropenia, peripheral sensory neuropathy and fatigue**
Alemtuzumab (campath)	**Selectively binds to CD52, highly expressed on lymphocytes (T and B cell) depleting these cells from circulation in the periphery.**	**Chronic lymphocytic leukemia (2007)**	**67.8%**	**Rash, headache, thyroid problem, fever, swelling of your nose and throat, nausea.**
Panitumumab (vectibix)	**Binding to the extracellular domain of the EGFR expressing tumor cells.**	**Metastatic colorectal cancer (2006)**	**56.4%**	**Skin reaction, diarrhea, nausea, vomiting, tiredness, constipation, stomach and abdominal pain.**
Cetuximab (Erbitux)	**Inhibiting the growth and survival of EGFR expressing tumor cells.**	**Head and neck cancer EGFR positive colon cancer (2021)**	**46-56%**	**Itching/rash, headache, diarrhea,infection dry cracked skin, changes in fingernails.**
Olfatumumab (Arzerra)	**Binding to and blocking the action of CD_{20} a molecule expressed on the surface of both healthy and leukemic B lymphocytes.**	**Chronic lymphocytic leukemia (2009)**	**_**	**Chest pain, fever, chills, itching, hives, flushing of face, rash, dizziness, fainting, trouble breathing swelling of face tongue and throat**
Ipilimumab (yervay)	**Binds to the cytotoxic T-lymphocytic associated antigen 4 (CTLA-4) a molecule on T cells that supresses the immune response**	**Melanoma in the skin and lymph nodes (2011)**	**_**	**Feeling tired, diarrhea, nausea, itching, rash, vomiting, weight loss, fever, decreased appetite.**
Pembrolimab (KEYTRUDA)	**Inhibiting lymphocytes PD-1 receptors, blocking the ligands that would deactivate it and prevent on immune response**	**Gastric cancer melanoma and non-small cell lung cancer (2014)**	**73.83%**	**Feeling tired, pain in muscle, rash, diarrhea, fever, cough, decreased appetite, itching, shortness of breath, constipation**

CONCLUSION

From the above data we can predict that monoclonal antibody is more effective and widely used Target specific treatment for cancer and other diseases. The past few year history we can conclude that all the other drugs are less effective than dostarlimab. Dostarlimab is one of the drug having 100% efficiency for colorectal cancer and dmmR deficient. The review also discuss the history of monoclonal antibodies and their recent uses in various diseases. for further more study it can be also used for other disease treatment.

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