# Immunotherapy Effects on Meningioma

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Cancer is when abnormal or mutated cells grow rapidly and uncontrollably. The immune system is a network of cells, organs, tissues, and chemicals which help defend the body from harmful substances. Ideally, the immune system would send out T-cells (a type of white blood cell, also known as a lymphocyte) to attack and destroy cancerous cells, but unfortunately, certain cancerous cells have mechanisms to avoid T-cells. Two of the main ways cancer cells can avoid detection from the T-cells is by downregulating the major histocompatibility complex (MHC) and blocking the co-stimulation. Downgrading the MHC can cause the T-cells to not recognize the cancer cells, but NK cells will kill the cancer cell if it lacks MHC. Cancer cells block co-stimulation through the CTLA-4 molecule, which then inhibits the T-cell from becoming fully activated. One of the most attractive treatments for cancer is immunotherapy. Immunotherapy is a type of drug therapy which uses a person's own immune system to fight cancer. This makes it an attractive option because unlike other treatments it has very few side effects which can vary depending on the cancer being treated. In this review we will talk about immunotherapy treatments for meningioma.

Meningioma is a central nervous system tumor (CNS). It is the most common primary intracranial tumor and can also be found anywhere in the dura, including the spinal membrane. There is no known cause of meningioma, the only known environmental factor of meningioma is exposure to radiation of 21 Gy or more. People with neurofibromatosis type 2 (*NF2* gene) are more susceptible to meningioma. The *NF2* gene is a genetic condition associated with acoustic neuromas. Meningioma can occur at any age but are more common in people 65 years or older. In fact, women are twice as likely to develop meningioma than men. Like other cancers, meningioma is caused by a mutation of the *KLF4* and *AKT1* genes. According to the National Institute of Health, *KLF4* helps regulate centrosome duplication following DNA damage", it also regulates the chromosome number, which inhibits the progression of colorectal, gastric, and hepatocellular carcinomas. The mutation *AKT1* belongs to a group called oncogenes; these have the "potential to cause normal cells to become cancerous." 90% of people between the ages of 20 and 44 survive for at least 5 years after being diagnosed with meningioma. Most patients with meningioma are treated with surgery; however, new evidence supports immunotherapy as a form of treatment for meningioma. but there is evidence supporting immunotherapy as a form of treatment for people with meningioma, although there are no confirmed tests.

Like other cancers, meningioma has certain mechanisms to avoid being detected by T-cells. The main way meningioma avoids detection is through the PD-L1 protein. PD-L1 is expressed through the surface of tumor cells, they inhibit T-cell activation by binding to the T-cells and B-cells. Unfortunately, research shows that drug therapy is not effective against meningioma and can only delay cranial and spinal tumors instead of treating them. Instead of

immunotherapy, Pembrolizumab (Keytruda) is the immune checkpoint inhibitor used against high grade meningiomas. It is a humanized monoclonal antibody, meaning, the original antibody does not come from humans, but was altered to be functional in the human body. But like all treatments, Pembrolizumab (Keytruda) has its limits. Pembrolizumab (Keytruda) can only be used on patients with high-grade meningiomas, which means that patients with grade 1 meningiomas cannot be treated. Currently, there are no FDA approved therapies for high grade meningioma.

An ongoing phase 2 clinical trial is occurring in San Francisco, California about the effects of Pembrolizumab (Keytruda) on meningioma (NCT04659811). NCT04659811 is a phase trial that studies the effect of stereotactic radiosurgery and Pembrolizumab (Keytruda) on recurring meningioma. There are currently 37 people enrolled in the trial. The trial includes people who have a grade II or grade III meningioma, they must be eligible for radiation treatments, have absolute neutrophil count, and must not be pregnant or planning to become pregnant within 180 days (about 6 months) before and after the treatment. Some of the exclusions are, having a known metastasis outside the CNS, received a live vaccine 30 days (about 4 and a half weeks) prior to the treatment, participating in another clinical trial 4 weeks before and after the trial (these are only some of the exclusions and inclusions for the trial). The trial is treating a recurring high-grade meningioma with radiosurgery and Pembrolizumab. Another trial which explored immunotherapy was trial NCT03267836. This was a phase 1 trial which focused on neoadjuvant avelumab, and hypofractionated proton radiation therapy followed by surgery for recurrent radiation-refractory meningioma. This trial had nine volunteers and some of the inclusion criteria included, being diagnosed with grade I-III meningioma, Prior treatment must include external beam radiation, radiosurgery, or combination of both, and they must be deemed eligible for additional partial resection by treating physician and determined to be safe to receive 3 months of neoadjuvant therapy before planned surgery. Some of the exclusion criteria include previous treatment with PD-1 or PD-L1 therapy, an active infection requiring systemic therapy, and having a history of AIDS or HIV. The trial was, unfortunately, terminated. Both trials do not directly address these limitations.

Meningioma is the most common CNS; it cannot be treated fully through immunotherapy since immunotherapy can only delay cranial and spinal tumors. Meningioma uses the PD-L1 protein to avoid detection of the T-cells, The drug Pembrolizumab (Keytruda) is the most effective drug against meningioma and often used along with another form of treatment such as surgery. The main obstacle scientists and doctors in this field are trying to solve is getting the drugs used in cranial tumors to only affect the tumor and not the brain and spine. Sadly, the future for immunotherapy in meningioma is not as bright as other treatment options because immunotherapy is not effective on cranial or spinal cancers.

## References

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