

# Immune checkpoint inhibitors may work in brain cancers

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New evidence that immune checkpoint inhibitors may work in glioblastoma and brain metastases was presented today by Dr Anna Sophie Berghoff at the ESMO Symposium on Immuno-Oncology 2014 in Geneva, Switzerland.

The novel research shows that [brain metastases](#) have dense concentrations of tumour infiltrating lymphocytes, providing an immunoactive environment. Moreover, both primary and secondary brain cancers often exhibit high expression of the immunosuppressive factor programmed cell death ligand 1 (PDL1), which can be inhibited by new treatments, thus activating the immune system.

Berghoff, resident at the Department of Medicine I, Comprehensive Cancer Centre-CNS Tumours Unit, Medical University of Vienna, Austria, said: "Patients with [glioblastoma](#) and brain metastases have very few treatment options and usually die within a short period of time."

Immune checkpoint inhibitors are a new group of cancer treatments that work by boosting the patient's [immune response](#) to the tumour. The immune system operates differently in the brain in comparison to other organs. "Our study was designed to find out whether the immune system is activated and working in [brain tumours](#), which would provide the foundation for immune checkpoint inhibitors to work," Berghoff explained.

The study included 117 patients with glioblastoma and 116 patients with

brain metastases. Using immunohistochemistry the researchers looked for the presence of T-cells —also called tumour infiltrating lymphocytes— in the tumours and whether they were accentuated in different areas of the tumour. T-cells are the main effector cells of the immune response and can be boosted by immune checkpoint inhibitors. They also looked for PDL1 —an immunosuppressive protein that influences responses to immune checkpoint inhibitors.

The researchers found that patients with glioblastoma had fewer T-cells, and therefore less activation of the immune system, than patients with brain metastases who had high concentrations of T-cells. They also found that PDL1 was common in both glioblastoma and brain metastases, with glioblastoma showing particularly high PDL1 positivity.

Berghoff said: "We saw that these brain tumour types have a different interaction with the immune system. The glioblastoma actively suppresses the immune system and there is little immune response. In contrast the brain metastases do a little less suppression of the immune system and there are a lot more tumour infiltrating lymphocytes."

Berghoff said the findings demonstrate that the immune system interacts with glioblastoma and brain metastases, which is evidence that immune checkpoint inhibitors may work: "We have arguments for conducting clinical studies with immune checkpoint inhibitors in patients with glioblastoma and brain metastases. In both tumour types we commonly see high expression of PDL1, an immunosuppressive factor which can be inhibited with new treatments. By inhibiting the suppression you can activate the immune system which in theory would work in brain cancers."

She continued: "We know that immune checkpoint inhibitors are more effective in immunoactive microenvironments. In brain metastases we see dense infiltration with T-cells which provides a good background for

immune checkpoint inhibitors."

Small preliminary studies have shown efficacy of immune checkpoint inhibitors in melanoma brain metastases. However, melanoma is only the third most common brain metastases, the most common being non-small-cell lung cancer. Immune checkpoint inhibitors are active in extracranial metastasised lung cancer but it is unknown whether this holds true for patients with brain metastases. Data on immune checkpoint inhibitors in glioblastoma exists only in mice.

Berghoff said: "Our study shows that T-cells and PDL1 expression are present in glioblastoma and brain metastases. This means that the targets for novel drugs that activate the immune system against cancer cells are present and brain tumours may be effectively treatable with such drugs."

She concluded: "Our data strongly support the launch of clinical trials with immune checkpoint inhibitors, especially the ones targeting the PD1/PDL1 axis, in patients with glioblastoma and brain metastases. Indeed, some early studies are being designed and started at the moment. In addition, profiling of other immune checkpoint molecules and modes of immune escape in brain tumours need to be identified to prepare for the development of next generation immunomodulators."

Commenting on the implications of the findings for patients with glioblastoma and brain metastases, Professor Martin J. van den Bent, of the Neuro-Oncology Unit, Erasmus Medical Centre, Rotterdam, the Netherlands, said: "The investigators found different immune reactions to the malignant process in the brain that were related to the type of cancer. It is quite interesting that the immune system does play a role in brain metastases as well. The findings indicate that therapeutic interventions for brain cancers that use the [immune system](#) should be explored."

Van den Bent noted that brain metastases are not a homogenous group but vary depending on the primary tumour. He said: "I would guess that the type of immune reaction to brain metastases will differ between the various tumour types. We know that the mechanism with which metastases arise can be completely different between the various diseases."

"The debate on the penetration through the intact blood brain barrier and how significant that is for treatment effectiveness is still on the table," continued van den Bent. "But the general understanding is that any therapy that works for a specific type of cancer will also work if it has metastasised to the brain provided the access is good."

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