PD-L1 Expression in Gliomas: A Potential Immunotherapeutic Target in High-grade Tumours

Ayushi Agarwal[1], Charanjeet Ahluwalia[1], Kepeemadam Balasubramanyam Shankar[2], Sana Ahuja[1]

[1] Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India;
[2] Department of Neurosurgery, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Received June 24, 2025; Accepted February 26, 2026.

Key words: PD-L1 – Gliomas – Immunotherapy – Grade

Abstract: Gliomas are the most common primary tumours of the central nervous system, with glioblastoma (grade 4 glioma) being the most malignant form. Despite standard therapy, patient survival remains poor. Immune checkpoint blockade targeting the PD-1/PD-L1 axis has shown promise in other cancers, but its role in gliomas remains under investigation. This study evaluates PD-L1 expression in gliomas and its correlation with tumour grade. A total of 50 histologically confirmed glioma cases were studied. Tumours were graded according to WHO 2021 CNS classification, and immunohistochemistry (IHC) was performed using antibodies for IDH, ATRX, TP53, Ki67, and PD-L1. PD-L1 expression was scored using an immunoreactivity scale, and its association with tumour grade was analysed using ordinal regression. A p-value < 0.05 was considered statistically significant. Among the 50 gliomas, the majority were astrocytoma, IDH-mutant (54%) followed by glioblastoma, IDH-wild type (26%). Most tumours were grade 4 (44%), grade 2 (34%), or grade 3 (18%). PD-L1 expression was detected exclusively in grade 4 tumours, with 6 of 22 (27.27%) cases showing positive expression. No expression was noted in grade 1–3 tumours. The association between PD-L1 expression and tumour grade was statistically significant (p=0.007). PD-L1 expression is limited to high-grade (grade 4) gliomas, suggesting a role in immune evasion. These findings support the potential utility of PD-L1 as a biomarker to identify glioma patients who may benefit from anti-PD-1/PD-L1 immunotherapy.

Mailing Address: Dr. Sana Ahuja, Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, Ansari Nagar, 110029 New Delhi, India; Phone: +91 995 818 86 32; e-mail: sanaahuja11@yahoo.com

https://doi.org/10.14712/23362936.2026.3

Prague Medical Report / Vol. 127 (2026) No. 1, p. 21–26

Introduction

Gliomas are the most common primary tumour of the central nervous system, comprising over 40–50% of primary brain tumours (Smith et al., 2022). In the United States (between 2012 and 2016), the overall incidence rate of all primary brain and other central nervous system (CNS) tumours was 23.41 per 100,000 of which 30.2% were malignant and 69.8% were non-malignant. Gliomas accounted for about 80.8% of the malignant tumours and about 25.5% of all the CNS tumours with the majority of them being formed by the glioblastoma (57.3%) (Ostrom et al., 2019).

Gliomas form a heterogeneous group of neoplasms with multiple histologic types and malignancy grades. Most gliomas, the diffuse gliomas, show extensive infiltration within the brain parenchyma. Diffuse gliomas were traditionally typed as astrocytic, oligodendroglial, or rare mixed oligodendroglial-astrocytic of World Health Organization (WHO) grade II (low grade), III (anaplastic), or IV (glioblastoma). Since many decades the histologic diagnosis formed a useful basis for the assessment of prognosis and therapeutic management of the glial tumours. But recently, molecular biomarkers have gained importance in providing both ancillary and defining diagnostic information. WHO 2021 classification, therefore, incorporates numerous molecular changes with clinicopathologic utility that are important for the most accurate classification of CNS tumours (Perry and Wesseling, 2016; Louis et al., 2021).

In the WHO 2021 classification, the adult-type diffuse gliomas, includes only three types: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wild type.

All IDH-mutant diffuse astrocytic tumours are considered a single type (astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3 and 4. For the diagnosis of glioblastoma, IDH-wild type, the fifth edition of WHO incorporates three genetic parameters – TERT promoter mutation, EGFR amplification or +7/–10 chromosome copy-number alteration (Brat et al., 2021).

An immunohistochemistry panel of IDH, ATRX, TP53 and Ki67 is used to confirm the diagnosis of gliomas and grade the tumour.

The conventional therapy for gliomas includes surgical intervention, chemotherapy and radiotherapy for low-grade gliomas, its median survival time in about 85% patients is nearly 5 years starting from the diagnosis, which reflects that the overall survival of glioma patients remains dismal. The most frequent but unfortunately the most malignant of all gliomas is the grade 4 glioma – glioblastoma (Wen and DeAngelis, 2007; Pouratian and Schiff, 2010; Schiff, 2011). It constitutes a universally lethal diagnosis and is characterized by highly aggressive behaviour and a high recurrence rate. Despite the conventional standard of care (surgery, chemotherapy and radiotherapy), glioblastoma is associated with a median survival of only 14.6 months and less than 10% of the treated patients are alive after 5 years of diagnosis (Stupp et al., 2009). In contrast to many other tumours, molecularly targeted therapies for glioblastoma (GBM) produced very limited advances in prolonging life expectancies of the patients, which can be attributable to the poor penetration of the blood brain barrier by therapeutic agents or the rapidly developing drug resistance (Schlageter et al., 1999; Ramirez et al., 2013).

Thus, there is a clinical need for new treatment strategies. In the past two decades, our understanding of pathology and the molecular details of cancer has improved. Basic research has provided scientific support towards immunotherapy as a potentially promising treatment approach (Preusser et al., 2011).

Programmed cell death-1(PD-1)/program death ligand 1(PD-L1) pathway is a classic immune checkpoint of a promising therapeutic approach. Programmed death ligand 1 (PD-L1) expression is upregulated in human tumour cell lines, which suggests that it has a close relationship with tumour growth and development. Several studies have focused on PD-L1 expression in many malignancies such as cancers of the breast, pancreas, lung, renal and stomach (Flies and Chen, 2007; Zou and Chen, 2008). However, the expression of PD-L1 on glioma cells has been documented recently (Berghoff et al., 2015; Heiland et al., 2017).

Immunotherapy targeting the PD-L1/PD-1 pathway has made a series of remarkable breakthroughs in the clinical treatment of a variety of cancers, showing response rates of 20–40%. Nivolumab, Pemrolizumab (anti-PD1 antibodies), Atezolizumab, Avelumab (anti-PD-L1 antibodies) are approved drugs in the treatment of melanoma, non-small cell lung carcinoma and some breast cancers (Gandini et al., 2016). This has led to the generation of increasing interest in the use of this therapy in the treatment of gliomas as well, particularly glioblastomas.

In our study, we have used PD-L1 monoclonal antibody immunohistochemically to study its expression in gliomas and also to compare its expression with varying grades of the tumour. If these gliomas are shown to express PD-L1, it will open avenues for cancer immunotherapy in these patients.

Material and Methods

This cohort study included 50 histologically confirmed cases of gliomas. The haematoxylin and eosin sections were evaluated for the histological type and grade of the tumour. Immunohistochemistry for IDH, ATRX, TP53 and Ki67 was performed using their respective antibodies to confirm the diagnosis and grade the tumour.

Immunohistochemistry (IHC) for PD-L1 was performed and expression was assessed according to the immunoreactivity score (Table 1 [Di Bonito et al., 2016]). The association of this score with tumour grade was determined.

Data analysis was done using licensed SPSS software version 21.0. A p-value of < 0.05 was considered statistically significant. Ordinal regression analysis was used to evaluate the correlation of immunohistochemical marker (PD-L1) with the different grades of glioma.

Ethical approval

The study was done in accordance with the Helsinki Declaration. The study was approved by Institutional Ethics committee (IEC/VMMC/SJH/Thesis/2020-11/CC-241). Written informed consent was taken from all patients included in the study.

Results

50 histologically confirmed cases of gliomas were included in the study. In the majority (27 [54%]) of patients, diagnosis was astrocytoma, IDH-mutant type, followed by glioblastoma, IDH-wild type (13 [26%]) and oligodendroglioma, not otherwise specified (NOS) (8 [16%]). Pilocytic astrocytoma was diagnosed only in 2 out of 50 patients (4%). In 22 (44%) of patients, the tumour was grade 4, followed by grade 2 (17 [34%]) and grade 3 (9 [18%]).

Table 1: Scoring system for interpretation of immunohistochemistry for PD-L1

Extent of cell stained	Intensity of staining	Final score
0 (absence of membranous immunoreactivity or mild/moderate cytoplasmic positivity)	negative	0
1 (incomplete but moderate/intense membranous positivity, with/without cytoplasmic positivity, in ≥ 10% of tumour cells)	weak positive	1+
2 (complete and moderate/intense membranous positivity, with/without cytoplasmic positivity, in ≥ 10% of tumour)	strong positive	2++

PD-L1 score was assigned to every case based on the following immunoreactivity score

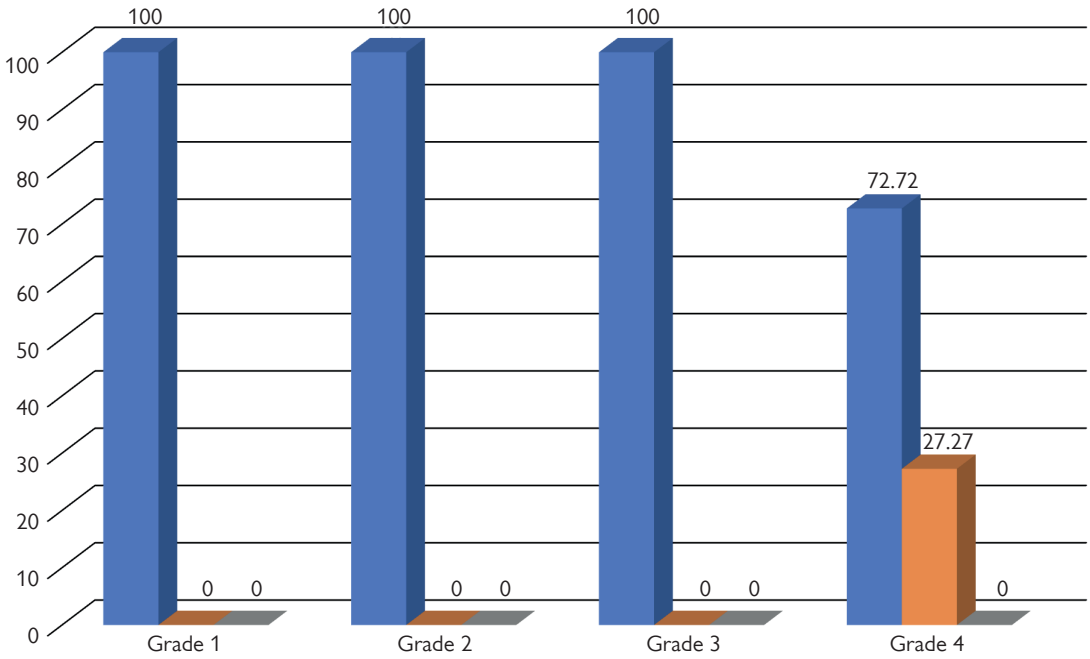

Figure 1: Expression of PD-L1 in the tumour in different grades.

Prague Medical Report / Vol. 127 (2026) No. 1, p. 21–26

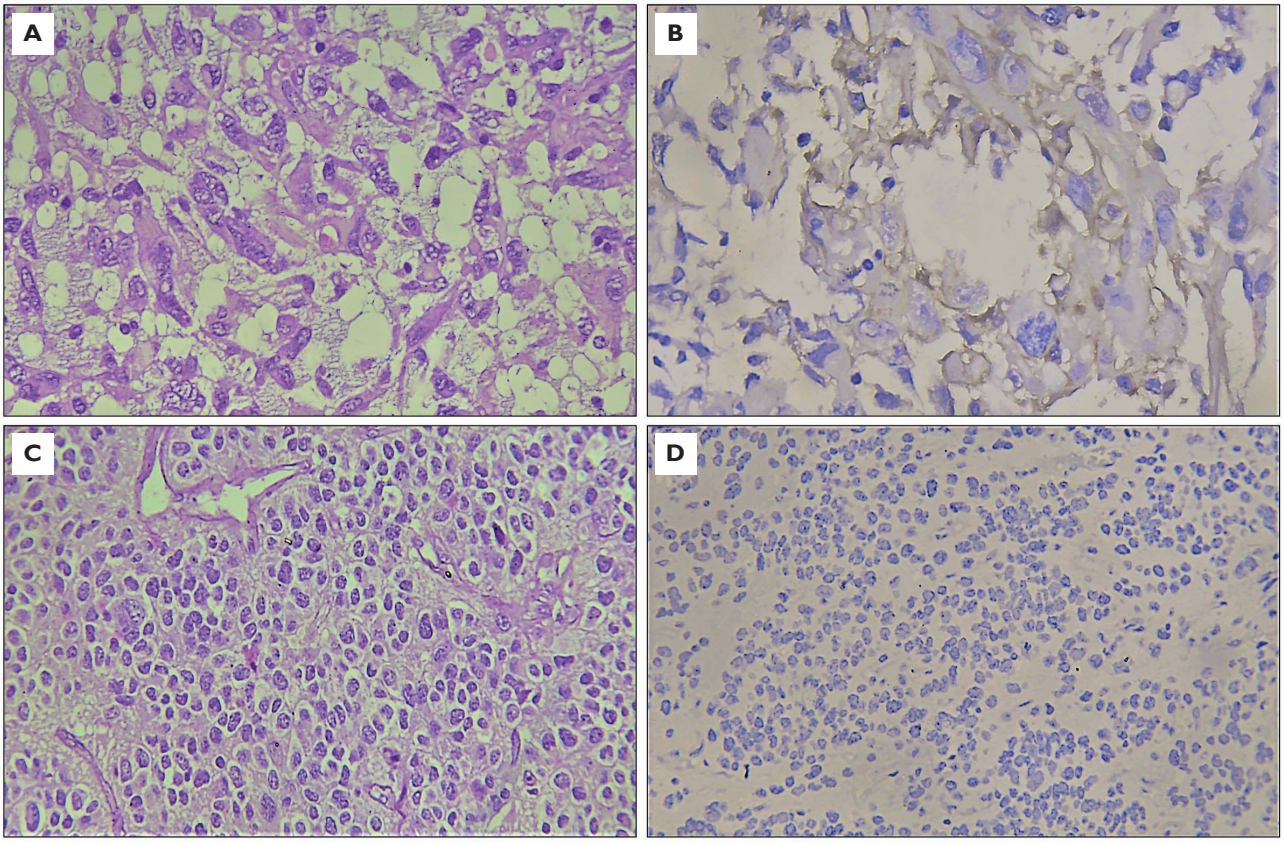

Figure 2: (A) Haematoxylin and eosin (H and E) stained section of grade 4 glioma (glioblastoma) in 100× magnification. (B) Immunohistochemistry (IHC) – positive expression of PD-L1 in tumour cells seen in a case of grade 4 glioma (glioblastoma) in 400× magnification. Membranous positivity of PD-L1 is seen in the tumour cells. (C) H and E stained section of grade 4 glioma (astrocytoma, IDH mutant) in 100× magnification. (D) IHC – negative expression of PD-L1 in tumour cells seen in a case of grade 4 glioma (astrocytoma, IDH mutant) in 100× magnification.

Table 2: Expression of PD-L1 in the tumour in different grades

WHO tumour grade	Score 0	Score 1	Score 2	Statistical significance (p-value)
Grade 1	02 (100%)	0 (0%)	0 (0%)	
Grade 2	17 (100%)	0 (0%)	0 (0%)	
Grade 3	9 (100%)	0 (0%)	0 (0%)	0.007*
Grade 4	16 (72.72%)	6 (27.27%)	0 (0%)	
Total	44	06	0	

*Fisher's exact test; WHO – World Health Organization

The tumour was grade 1 only in 2 out of 50 patients (4%). The mean value of age (years) of study subjects was 42.62 years with a standard deviation of 12.52. The male-to-female ratio was 2.1:1.

PD-L1 was not expressed in grade 1, grade 2 and grade 3 tumours. However, the expression of PD-L1 was observed in 6 (27.27%) of 22 cases of grade 4 tumour. P-value was found to be 0.007, which was statistically significant ($p<0.05$) (Figures 1 and 2, Table 2).

Discussion

The present study was designed to assess the immunohistochemical expression of PD-L1 in gliomas and to correlate its expression with the grade of the tumour. We aimed to find out if there was any association between the expression of PD-L1 and the grades of gliomas.

Among the 50 cases of gliomas included in our study, 6 cases (12%) expressed PD-L1. It was shown

to have a statistically insignificant association (p-value = 0.007) between the expression of PD-L1 and the grade of the tumour (Table 2). However, the expression rate of PD-L1 in our study was much lower than the expression rates found in other studies. Shukla et al. (2021) in their study to analyse the expression of PD-L1 in adult diffuse gliomas in WHO grade II, III, and IV glioma found that PD-L1 was expressed in 33.3% (n=10/30) cases (20% [n=2]) grade II tumours, 30% [n=3] grade III tumours, and 50% [n=5] GBMs]. The p-value was found to be 0.013. Another study done by Zeng et al. (2016) found that the tumour cell PD-L1 expression rate was 51.1% (117/229) in all patients with gliomas. The PD-L1 expression rates were 49.2, 53.7 and 68.8% for grade II, III and IV samples, respectively. The difference in the expression rates of PD-L1 between the various studies could be attributed to the differences in the monoclonal antibody used and the scoring and interpretation of results. In the present study, none of the grade 1, grade 2 and grade 3 tumours expressed PD-L1. PD-L1 was found to be expressed in only 6 cases out of the 22 cases (27.27%) of grade 4 glioma (glioblastoma) (score 1). The expression of PD-L1 with the tumour grade was found to be statistically significant (p-value = 0.007). This result was found to be comparable to the previously conducted studies, which had also shown a statistically significant association between PD-L1 expression and the grades of glioma, with the grade 4 gliomas expressing higher scores of PD-L1 as compared to grade 2 and grade 3 gliomas. Our study suggested that the expression of PD-L1 is increased in the higher grade of the tumour (grade 4) in comparison to the lower grades of the tumour (grade 1, 2 and grade 3). Furthermore, in the study by Kumar et al. (2025) the majority of grade I and II gliomas showed no or low PD-L1 expression, whereas grade III and IV gliomas demonstrated increasing levels of moderate to strong expression. A statistically significant association was observed between PD-L1 expression and glioma grade (p=0.019), with higher expression correlating with higher tumour grade. They also reported a significant association between PD-L1 expression and tumour grade, with higher expression observed in grade III and IV gliomas compared to grade I and II tumours. Their findings further support the correlation between PD-L1 expression and increasing glioma aggressiveness.

The current study highlights the fact that the expression of PD-L1 increases with the grade of the tumour. A statistically significant association was observed between the expression of PD-L1 and the grade of the tumour. The expression of PD-L1 by the tumour could be used to identify those cases of glioma which could benefit from targeted chemotherapy using anti-PD-1/anti-PD-L1 monoclonal antibodies.

Conclusion

In our study, PD-L1 was expressed only by the high grade gliomas (grade 4).

This suggests that it could be one of the possible mechanisms of tumour evasion from host immunity. PD-L1 testing may be useful in identifying glioma patients who could benefit from targeted therapy.

References

Berghoff, A. S., Kiesel, B., Widhalm, G., Rajky, O., Ricken, G., Wöhrer, A., Dieckmann, K., Filipits, M., Brandstetter, A., Weller, M., Kurscheid, S., Hegi, M. E., Zielinski, C. C., Marosi, C., Hainfellner, J. A., Preusser, M., Wick, W. (2015) Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. *Neuro Oncol*. **17**, 1064–1075.

Brat, D., Ellison, D., Louis, D. (2021) *WHO Classification of Tumours. Central Nervous System Tumors*, 5th Edition. International Agency for Research on Cancer, Lyon.

Di Bonito, M., Scognamiglio, G., Collina, F., Liguori, G., Cantile, M., Botti, G. (2016) Programmed death ligand 1 (PDL-1) expression in triple negative breast cancer cells: New proposal for a "tumor score" definition. *Int. J. Clin. Exp. Pathol*. **9**, 11693–11696.

Flies, D. B., Chen, L. (2007) The new B7s: Playing a pivotal role in tumor immunity. *J. Immunother*. **30**, 251–260.

Gandini, S., Massi, D., Mandalà, M. (2016) PD-L1 expression in cancer patients receiving anti PD-1/PD-L1 antibodies: A systematic review and meta-analysis. *Crit. Rev. Oncol. Hematol*. **100**, 88–98.

Heiland, D. H., Haaker, G., Delev, D., Mercas, B., Masalha, W., Heynckes, S., Gäbelein, A., Pfeifer, D., Carro, M. S., Weyerbrock, A., Prinz, M., Schnell, O. (2017) Comprehensive analysis of PD-L1 expression in glioblastoma multiforme. *Oncotarget* **8**, 42214–42225.

Kumar, V., Raghuvanshi, S., Bhalla, S., Rawat, S., Ojha, B. K., Srivastava, C., Goel, M. M. (2025) Immunohistochemical expression of PDL1 and Ki67 in glioma and its correlation with treatment and overall survival. *J. Cancer Res. Ther*. **21**, 145–150.

Louis, D., Perry, A., Wesseling, P., Brat, D., Cree, I., Figarella-Branger, D., Hawkins, C., Ng, H. K., Pfister, S. M., Reifenberger, G., Soffietti, R., von Deimling, A., Ellison, D. W. (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. *Neuro Oncol*. **23**, 1231–1251.

Ostrom, Q. T., Cioffi, G., Gittleman, H., Patil, N., Waite, K., Kruchko, C., Barnholtz-Sloan, J. S. (2019) CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012–2016. *Neuro Oncol*. **21(Suppl. 5)**, v1–v100.

Perry, A., Wesseling, P. (2016) Histologic classification of gliomas. *Handb. Clin. Neurol*. **134**, 71–95.

Pouratian, N., Schiff, D. (2010) Management of low-grade glioma. *Curr. Neurol. Neurosci. Rep*. **10**, 224–231.

Preusser, M., de Ribaupierre, S., Wöhrer, A., Erridge, S. C., Hegi, M., Weller, M., Stupp, R. (2011) Current concepts and management of glioblastoma. *Ann. Neurol*. **70**, 9–21.

Ramirez, Y., Weatherbee, J., Wheelhouse, R., Ross, A. (2013) Glioblastoma multiforme therapy and mechanisms of resistance. *Pharmaceuticals (Basel)* **6**, 1475–1506.

Schiff, D. (2011) Editorial: Low-grade gliomas. *J. Neurosurg*. **115**, 945–947.

Schlageter, K., Molnar, P., Lapin, G., Groothuis, D. (1999) Microvessel organization and structure in experimental brain tumors: Microvessel populations with distinctive structural and functional properties. *Microvasc. Res*. **58**, 312–328.

Shukla, S., Husain, N., Kaif, M., Awale, R., Mishra, S., Malhotra, K. (2021) Programmed death ligand-1 expression in gliomas: A study of histopathological and molecular associations. *Neurol. India* **69**, 1005–1009.

Smith, H. L., Wadhwani, N., Horbinski, C. (2022) Major features of the 2021 WHO classification of CNS tumors. *Neurotherapeutics* **19**, 1691–1704.

Stupp, R., Hegi, M. E., Mason, W. P., van den Bent, M. J., Taphoorn, M. J. B., Janzer, R. C., Ludwin, S. K., Allgeier, A., Fisher, B., Belanger, K., Hau, P., Brandes, A. A., Gijtenbeek, J., Marosi, C., Vecht, C. J., Mokhtari, K., Wesseling, P., Villa, S., Eisenhauer, E., Gorlia, T., Weller, M., Lacombe, D., Cairncross, J. G.,Mirimanoff, R. O.; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. **10**, 459–466.

Wen, P. Y., DeAngelis, L. M. (2007) Chemotherapy for low-grade gliomas: Emerging consensus on its benefits. *Neurology* **68**, 1762–1763.

Zeng, J., Zhang, X. K., Chen, H. D., Zhong, Z. H., Wu, Q. L., Lin, S. X. (2016) Expression of programmed cell death-ligand 1 and its correlation with clinical outcomes in gliomas. *Oncotarget* **7**, 8944–8955.

Zou, W., Chen, L. (2008) Inhibitory B7-family molecules in the tumour microenvironment. *Nat. Rev. Immunol*. **8**, 467–477.