# Pembrolizumab for glioblastoma

Immune analyses indicated that pembrolizumab anti-programmed cell death 1 (PD-1) monotherapy alone can't induce effector immunologic response in most GBM patients, probably owing to a scarcity of T cells within the tumor microenvironment and a CD68+ macrophage preponderance [1].

## Case series

Blumenthal et al. retrospectively reviewed the charts of 22 patients (17 adults and 5 children) with recurrent central nervous system tumors treated with PBL. We analyzed prior antineoplastic therapies, steroid usage, and outcomes. Patients received a median of two neoplastic therapies prior to PBL, and a median of three infusions of PBL in adults and four in children. Twelve patients (9 adults and 3 children) started PBL on steroids (median dose in adults 4 mg; range 2-8, and in children 1.5 mg, range 0.5-4) and five patients received steroids later during PBL treatment. Twelve patients (10 adults and 2 children) received concomitant bevacizumab with PBL. Side effects were minimal. All patients showed progressive tumor growth during therapy. Median OS from the start of PBL was 2.6 months in adults and 3.2 months in children. Two GB patients underwent tumor resection following treatment with PBL. Tumor-lymphocytic response in these cases was unremarkable, and PD-L1 immuno-staining was negative. In this series of 22 patients with recurrent primary brain tumors, PBL showed no clinical or histologic efficacy. They do not recommend further use of PBL for recurrent PBT unless convincing prospective clinical trial data are published [2].

## Unclassified

2: Sinigaglia M, Assi T, Besson FL, Ammari S, Edjlali M, Feltus W, Rozenblum-Beddok L, Zhao B, Schwartz LH, Mokrane FZ, Dercle L. Imaging-guided precision medicine in glioblastoma patients treated with immune checkpoint modulators: research trend and future directions in the field of imaging biomarkers and artificial intelligence. EJNMMI Res. 2019 Aug 20;9(1):78. doi: 10.1186/s13550-019-0542-5. Review. PubMed PMID: 31432278; PubMed Central PMCID: PMC6702257.

3: Wang X, Guo G, Guan H, Yu Y, Lu J, Yu J. Challenges and potential of PD-1/PD-L1 checkpoint blockade immunotherapy for glioblastoma. J Exp Clin Cancer Res. 2019 Feb 18;38(1):87. doi: 10.1186/s13046-019-1085-3. Review. PubMed PMID: 30777100; PubMed Central PMCID: PMC6380009.

4: Cloughesy TF, Mochizuki AY, Orpilla JR, Hugo W, Lee AH, Davidson TB, Wang AC, Ellingson BM, Rytlewski JA, Sanders CM, Kawaguchi ES, Du L, Li G, Yong WH, Gaffey SC, Cohen AL, Mellinghoff IK, Lee EQ, Reardon DA, O'Brien BJ, Butowski NA, Nghiemphu PL, Clarke JL, Arrillaga-Romany IC, Colman H, Kaley TJ, de Groot JF, Liau LM, Wen PY, Prins RM. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med. 2019 Mar;25(3):477-486. doi: 10.1038/s41591-018-0337-7. Epub 2019 Feb 11. PubMed PMID: 30742122; PubMed Central PMCID: PMC6408961.

5: Zhao J, Chen AX, Gartrell RD, Silverman AM, Aparicio L, Chu T, Bordbar D, Shan D, Samanamud J, Mahajan A, Filip I, Orenbuch R, Goetz M, Yamaguchi JT, Cloney M, Horbinski C, Lukas RV, Raizer J, Rae AI, Yuan J, Canoll P, Bruce JN, Saenger YM, Sims P, Iwamoto FM, Sonabend AM, Rabadan R. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. Nat Med. 2019

Mar;25(3):462-469. doi: 10.1038/s41591-019-0349-y. Epub 2019 Feb 11. Erratum in: Nat Med. 2019 Apr 17;:. PubMed PMID: 30742119; PubMed Central PMCID: PMC6810613.

6: Baldini C, Romano PM, Varga A, Champiat S, Dumont S, Dhermain F, Louvel G, Marabelle A, Postel-Vinay S, Angevin E, Gazzah A, Ribrag V, Bahleda R, Michot JM, Hollebecque A, Soria JC, Massard C. Immunothérapie des glioblastomes. Bull Cancer. 2018 Dec;105 Suppl 1:S59-S67. doi: 10.1016/S0007-4551(18)30391-6. Review. French. PubMed PMID: 30595200.

7: Schwartz C, Romagna A, Machegger L, Weiss L, Huemer F, Fastner G, Kleindienst W, Weis S, Greil R, Winkler PA. Extensive Leptomeningeal Intracranial and Spinal Metastases in a Patient with a Supratentorial Glioblastoma Multiforme, IDH-Wildtype. World Neurosurg. 2018 Dec;120:442-447. doi: 10.1016/j.wneu.2018.09.082. Epub 2018 Sep 22. PubMed PMID: 30253992.

8: Reiss SN, Yerram P, Modelevsky L, Grommes C. Retrospective review of safety and efficacy of programmed cell death-1 inhibitors in refractory high grade gliomas. J Immunother Cancer. 2017 Dec 19;5(1):99. doi: 10.1186/s40425-017-0302-x. PubMed PMID: 29254497; PubMed Central PMCID: PMC5735528.

9: Lakin N, Rulach R, Nowicki S, Kurian KM. Current Advances in Checkpoint Inhibitors: Lessons from Non-Central Nervous System Cancers and Potential for Glioblastoma. Front Oncol. 2017 Jul 6;7:141. doi: 10.3389/fonc.2017.00141. eCollection 2017. Review. PubMed PMID: 28730140; PubMed Central PMCID: PMC5498463.

10: Qin L, Li X, Stroiney A, Qu J, Helgager J, Reardon DA, Young GS. Advanced MRI assessment to predict benefit of anti-programmed cell death 1 protein immunotherapy response in patients with recurrent glioblastoma. Neuroradiology. 2017 Feb;59(2):135-145. doi: 10.1007/s00234-016-1769-8. Epub 2017 Jan 9. PubMed PMID: 28070598; PubMed Central PMCID: PMC6097616.

11: Snyder A, Wolchok JD. Successful Treatment of a Patient with Glioblastoma and a Germline POLE Mutation: Where Next? Cancer Discov. 2016 Nov;6(11):1210-1211. PubMed PMID: 27807100; PubMed Central PMCID: PMC5109825.

12: Johanns TM, Miller CA, Dorward IG, Tsien C, Chang E, Perry A, Uppaluri R, Ferguson C, Schmidt RE, Dahiya S, Ansstas G, Mardis ER, Dunn GP. Immunogenomics of Hypermutated Glioblastoma: A Patient with Germline POLE Deficiency Treated with Checkpoint Blockade Immunotherapy. Cancer Discov. 2016 Nov;6(11):1230-1236. Epub 2016 Sep 28. PubMed PMID: 27683556; PubMed Central PMCID: PMC5140283.

13: Garber ST, Khoury L, Bell D, Schomer DF, Janku F, McCutcheon IE. Metastatic Adenoid Cystic Carcinoma Mimicking Butterfly Glioblastoma: A Rare Presentation in the Splenium of the Corpus Callosum. World Neurosurg. 2016 Nov;95:621.e13-621.e19. doi: 10.1016/j.wneu.2016.07.111. Epub 2016 Aug 10. PubMed PMID: 27521725.

15: Neagu MR, Reardon DA. An Update on the Role of Immunotherapy and Vaccine Strategies for Primary Brain Tumors. Curr Treat Options Oncol. 2015 Nov;16(11):54. doi: 10.1007/s11864-015-0371-3. Review. PubMed PMID: 26454859.

16: Preusser M, Lim M, Hafler DA, Reardon DA, Sampson JH. Prospects of immune checkpoint modulators in the treatment of glioblastoma. Nat Rev Neurol. 2015 Sep;11(9):504-14. doi: 10.1038/nrneurol.2015.139. Epub 2015 Aug 11. Review. PubMed PMID: 26260659; PubMed Central PMCID: PMC4782584.

1)
de Groot J, Penas-Prado M, Alfaro-Munoz KD, Hunter K, Pei B, O'brien B, Weathers SP, Loghin M, Kamiya Matsouka C, Yung WKA, Mandel J, Wu J, Yuan Y, Zhou S, Fuller GN, Huse J, Rao G, Weinberg JS, Prabhu SS, McCutcheon IE, Lang FF, Ferguson SD, Sawaya R, Colen R, Yadav SS, Blando J, Vence L, Allison J, Sharma P, Heimberger AB. Window-of-opportunity clinical trial of pembrolizumab in patients with recurrent glioblastoma reveals predominance of immune-suppressive macrophages. Neuro Oncol. 2019 Nov 22. pii: noz185. doi: 10.1093/neuonc/noz185. [Epub ahead of print] PubMed PMID: 31755915.
2)
Blumenthal DT, Yalon M, Vainer GW, Lossos A, Yust S, Tzach L, Cagnano E, Limon D, Bokstein F. Pembrolizumab: first experience with recurrent primary central nervous system (CNS) tumors. J Neurooncol. 2016 Sep;129(3):453-460. doi: 10.1007/s11060-016-2190-1. Epub 2016 Jul 4. PubMed PMID: 27377654.