Supplementary Materials

Preclinical efficacy of immune-checkpoint monotherapy does not recapitulate corresponding biomarkers-based clinical predictions in glioblastoma

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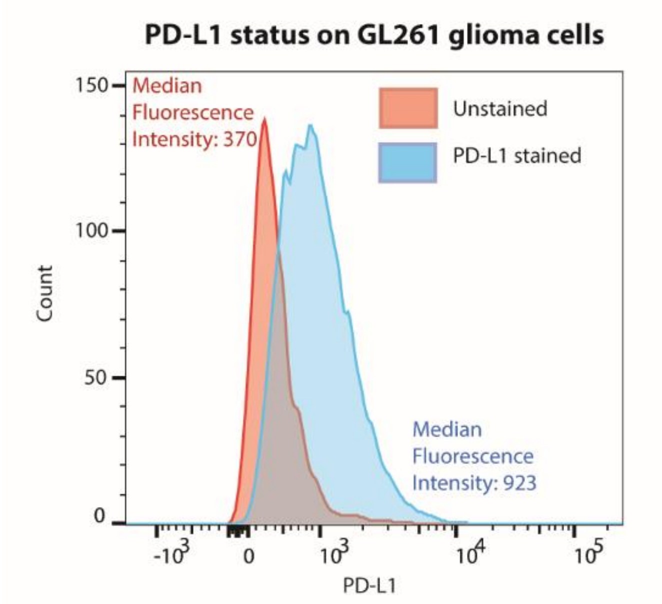
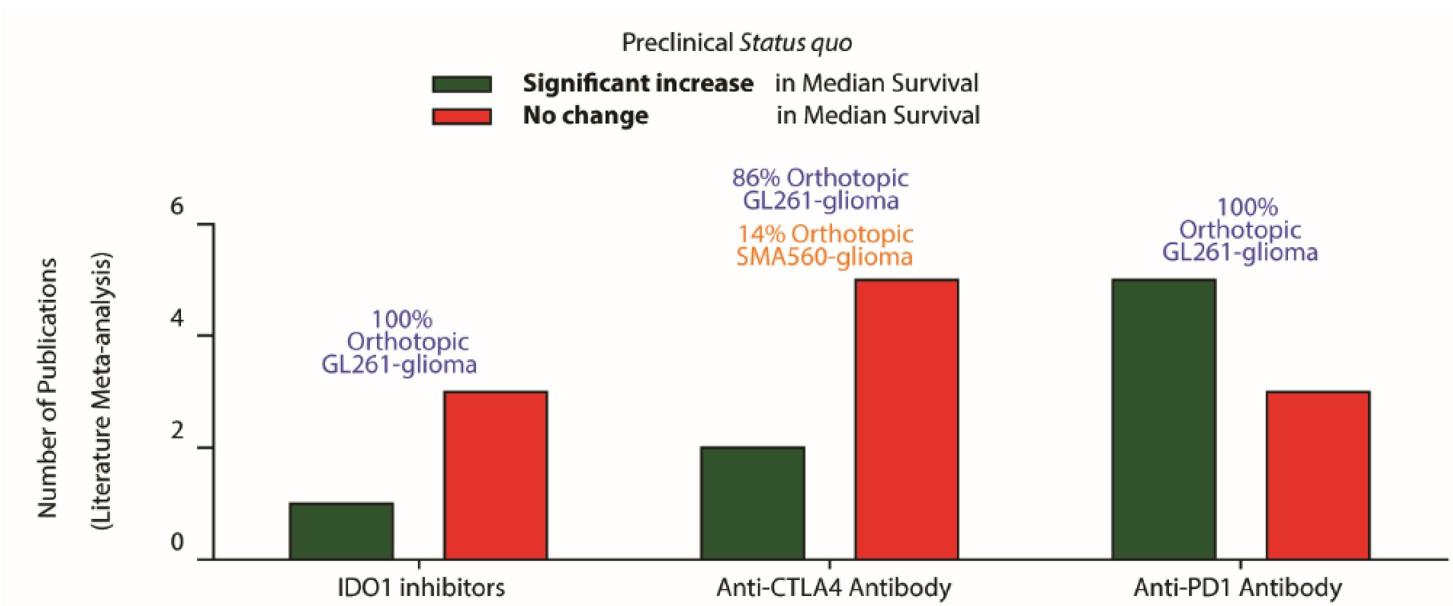
Supplementary Figures



Supplementary Figure S1. GL261 cells exhibit surface expression of PD-L1. GL261 cells were either left unstained or stained with anti-PD-L1 antibody followed by FACS-based scoring of PD-L1 positive GL261 cells (the median fluorescence intensity of different samples has been indicated).



Supplementary Figure S2. Anti-PD1 mono-immunotherapy exhibits the highest therapeutic efficacy against preclinical glioma. Analysis of 15 research articles studying the preclinical therapeutic efficacy of anti-CTLA4, anti-PD1 or IDO1 blockade in syngeneic mice models bearing orthotopic glioma (Suppl. Box S1, see next page) was analyzed. Significant change (green) or null/non-significant change (red) in median overall survival of the mice are denoted.

Supplementary Box S1

The following research articles[1-15] were short-listed for literature meta-analysis of preclinical efficacy of immune-checkpoint inhibitors in orthotopic murine glioma model:

1. Hanihara M, Kawataki T, Oh-Oka K, Mitsuka K, Nakao A, Kinouchi H. Synergistic antitumor effect with indoleamine 2,3-dioxygenase inhibition and temozolomide in a murine glioma model. Journal of neurosurgery 2016; 124:1594-601.
2. Li M, Bolduc AR, Hoda MN, Gamble DN, Dolisca SB, Bolduc AK, Hoang K, Ashley C, McCall D, Rojiani AM, et al. The indoleamine 2,3-dioxygenase pathway controls complement-dependent enhancement of chemo-radiation therapy against murine glioblastoma. Journal for immunotherapy of cancer 2014; 2:21.
3. Wainwright DA, Chang AL, Dey M, Balyasnikova IV, Kim CK, Tobias A, Cheng Y, Kim JW, Qiao J, Zhang L, et al. Durable therapeutic efficacy utilizing combinatorial blockade against IDO, CTLA-4, and PD-L1 in mice with brain tumors. Clinical cancer research : an official journal of the American Association for Cancer Research 2014; 20:5290-301.
4. Belcaid Z, Phallen JA, Zeng J, See AP, Mathios D, Gottschalk C, Nicholas S, Kellett M, Ruzevick J, Jackson C, et al. Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model. PLoS One 2014; 9:e101764.
5. Cockle JV, Rajani K, Zaidi S, Kottke T, Thompson J, Diaz RM, Shim K, Peterson T, Parney IF, Short S, et al. Combination viroimmunotherapy with checkpoint inhibition to treat glioma, based on location-specific tumor profiling. Neuro-oncology 2016; 18:518-27.
6. Vom Berg J, Vrohlings M, Haller S, Haimovici A, Kulig P, Sledzinska A, Weller M, Becher B. Intratumoral IL-12 combined with CTLA-4 blockade elicits T cell-mediated glioma rejection. The Journal of experimental medicine 2013; 210:2803-11.
7. Agarwalla P, Barnard Z, Fecci P, Dranoff G, Curry WT, Jr. Sequential immunotherapy by vaccination with GM-CSF-expressing glioma cells and CTLA-4 blockade effectively treats established murine intracranial tumors. J Immunother 2012; 35:385-9.
8. Reardon DA, Gokhale PC, Klein SR, Ligon KL, Rodig SJ, Ramkissoon SH, Jones KL, Conway AS, Liao X, Zhou J, et al. Glioblastoma Eradication Following Immune Checkpoint Blockade in an Orthotopic, Immunocompetent Model. Cancer Immunol Res 2016; 4:124-35.
9. Fecci PE, Ochiai H, Mitchell DA, Grossi PM, Sweeney AE, Archer GE, Cummings T, Allison JP, Bigner DD, Sampson JH. Systemic CTLA-4 blockade ameliorates glioma-induced changes to the CD4+ T cell compartment without affecting regulatory T-cell function. Clinical cancer research : an official journal of the American Association for Cancer Research 2007; 13:2158-67.
10. Hardcastle J, Mills L, Malo CS, Jin F, Kurokawa C, Geekiyanage H, Schroeder M, Sarkaria J, Johnson AJ, Galanis E. Immunovirotherapy with measles virus strains in combination with anti-PD-1 antibody blockade enhances antitumor activity in glioblastoma treatment. Neuro-oncology 2016.
11. Antonios JP, Soto H, Everson RG, Orpilla J, Moughon D, Shin N, Sedighim S, Yong WH, Li G, Cloughesy TF, et al. PD-1 blockade enhances the vaccination-induced immune response in glioma. JCI insight 2016; 1.
12. Kim JE, Patel MA, Mangraviti A, Kim ES, Theodros D, Velarde E, Liu A, Sankey E, Tam A, Xu H, et al. Combination therapy with anti-PD-1, anti-TIM-3, and focal radiation results in regression of murine gliomas. Clinical cancer research : an official journal of the American Association for Cancer Research 2016.
13. Mathios D, Park CK, Marcus WD, Alter S, Rhode PR, Jeng EK, Wong HC, Pardoll DM, Lim M. Therapeutic administration of IL-15 superagonist complex ALT-803 leads to long-term survival and durable antitumor immune response in a murine glioblastoma model. Int J Cancer 2016; 138:187-94.
14. Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, Durham N, Meyer C, Harris TJ, Albesiano E, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. Int J Radiat Oncol Biol Phys 2013; 86:343-9.
15. Mathios D, Kim JE, Mangraviti A, Phallen J, Park CK, Jackson CM, Garzon-Muvdi T, Kim E, Theodros D, Polanczyk M, et al. Anti-PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM. Sci Transl Med 2016; 8:370ra180.