

SUPPLEMENTARY MATERIALS

Any Grade Adverse Events

Two (1, 2), one (3), and two studies (2, 4) reported any grade adverse event rates when using immune checkpoint inhibitor (ICI) monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. The pooled any grade adverse event rates were 49% (30–69%; $I^2 = 82\%$), 77% (48–92%; I^2 not estimable), and 97% (95% confidence interval [CI], 92–99%; $I^2 = 0\%$) when using ICI monotherapy, ICI combined with radiotherapy, and ICI combination therapy, respectively. The overall any grade adverse event rate was 81% (95% CI, 52–94%), with a substantial heterogeneity ($I^2 = 93\%$; $p < 0.01$) (Supplementary Fig. 2). There was a significant publication bias observed in the Deeks funnel plot ($p = 0.03$).

Any Grade CNS-Related Adverse Events

Three (1, 2, 5) and two studies (2, 4) reported any grade central nervous system (CNS)-related adverse event rates when using ICI monotherapy and ICI combination therapy, respectively. There were no studies reporting any grade CNS-related adverse event rates when using ICI combined with radiotherapy. The pooled any grade CNS-related adverse event rates were 18% (6–43%; $I^2 = 85\%$) and 33% (95% CI, 24–43%; $I^2 = 19\%$) when using ICI monotherapy and ICI combination therapy, respectively. The overall any grade CNS-related adverse event rate was 23% (95% CI, 11–40%), with a substantial heterogeneity ($I^2 = 86\%$; $p < 0.01$) (Supplementary Fig. 2). There was no significant publication bias observed in the Deeks funnel plot ($p = 0.71$).

REFERENCES

1. Queirolo P, Spagnolo F, Ascierto PA, Simeone E, Marchetti P, Scoppola A, et al. Efficacy and safety of ipilimumab in patients with advanced melanoma and brain metastases. *J Neurooncol* 2014;118:109-116
2. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol* 2018;19:672-681
3. Trommer-Nestler M, Marnitz S, Kocher M, Rueß D, Schlaak M, Theurich S, et al. Robotic stereotactic radiosurgery in melanoma patients with brain metastases under simultaneous anti-PD-1 treatment. *Int J Mol Sci* 2018;19:2653
4. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 2018;379:722-730
5. Weber JS, Amin A, Minor D, Siegel J, Berman D, O'Day SJ. Safety and clinical activity of ipilimumab in melanoma patients with brain metastases: retrospective analysis of data from a phase 2 trial. *Melanoma Res* 2011;21:530-534
6. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol* 2012;13:459-465
7. Kluger HM, Chiang V, Mahajan A, Zito CR, Sznol M, Tran T, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *J Clin Oncol* 2019;37:52-60
8. Anderson ES, Postow MA, Wolchok JD, Young RJ, Ballangrud Å, Chan TA, et al. Melanoma brain metastases treated with stereotactic radiosurgery and concurrent pembrolizumab display marked regression; efficacy and safety of combined treatment. *J Immunother Cancer* 2017;5:76
9. Nardin C, Mateus C, Texier M, Lanoy E, Hibat-Allah S, Ammari S, et al. Tolerance and outcomes of stereotactic radiosurgery combined with anti-programmed cell death-1 (pembrolizumab) for melanoma brain metastases. *Melanoma Res* 2018;28:111-119
10. Tawbi HA, Forsyth PA, Hodi FS, Lao CD, Moschos SJ, Hamid O, et al. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). *J Clin Oncol* 2019;37:9501
11. Silk AW, Bassetti MF, West BT, Tsien CI, Lao CD. Ipilimumab and radiation therapy for melanoma brain metastases. *Cancer Med* 2013;2:899-906