

## Clinical Efficacy of Nivolumab and Ipilimumab Combination Therapy for the Treatment of Advanced Melanoma: A Systematic Review and Meta-Analysis of Clinical Trials

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**Abstract :** Background: Advanced melanoma accounts for the majority of skin cancer death due to its poor prognosis. Nivolumab and ipilimumab are monoclonal antibodies targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocytes antigen 4 (CTLA-4). Nivolumab and ipilimumab combination therapy has been proven to be effective for advanced melanoma. This systematic review and meta-analysis are to evaluate its clinical efficacy and adverse events. Method: A systematic search was done on databases (Pubmed, Embase, Medline, Cochrane) on 21 June 2020. Search keywords were nivolumab, ipilimumab, melanoma, and randomised controlled trials. Clinical trials fulfilling the inclusion criteria were selected to evaluate the efficacy of combination therapy in terms of prolongation of progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). The odd ratios and distributions of grade 3 or above adverse events were documented. Subgroup analysis was performed based on PD-L1 expression-status and BRAF-mutation status. Results: Compared with nivolumab monotherapy, the hazard ratios of PFS, OS and odd ratio of ORR in combination therapy were 0.64 (95% CI, 0.48-0.85; p=0.002), 0.84 (95% CI, 0.74-0.95; p=0.007) and 1.76 (95% CI, 1.51-2.06; p < 0.001), respectively. Compared with ipilimumab monotherapy, the hazard ratios of PFS, OS and odd ratio of ORR were 0.46 (95% CI, 0.37-0.57; p < 0.001), 0.54 (95% CI, 0.48-0.61; p < 0.001) and 6.18 (95% CI, 5.19-7.36; p < 0.001), respectively. In combination therapy, the odds ratios of grade 3 or above adverse events were 4.71 (95% CI, 3.57-6.22; p < 0.001) compared with nivolumab monotherapy, and 3.44 (95% CI, 2.49-4.74; p < 0.001) compared with ipilimumab monotherapy, respectively. High PD-L1 expression level and BRAF mutation were associated with better clinical outcomes in patients receiving combination therapy. Conclusion: Combination therapy is effective for the treatment of advanced melanoma. Adverse events were common but manageable. Better clinical outcomes were observed in patients with high PD-L1 expression levels and positive BRAF-mutation.

**Keywords :** nivolumab, ipilimumab, advanced melanoma, systematic review, meta-analysis

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