Clinical efficacy of Nivolumab monotherapy, Ipilimumab monotherapy, and combined Nivolumab and Ipilimumab therapy in BRAF-mutant vs BRAF wild-type melanoma, a meta-analysis

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Abstract

Nivolumab and Ipilimumab are immune checkpoint inhibitors (ICIs) widely used in the treatment of Melanoma. Nivolumab binds to the programmed death-1 (PD-1) receptor on T-cells preventing interaction with the PD-1 ligands, while ipilimumab binds to cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), blocking its interaction with B7 molecules on antigen-presenting cells. By preventing inhibitory signals that suppress T cell activity, these mechanisms promote T cell activation, resulting in a sustained anti-tumor response. BRAF is a serine/threonine-protein kinase involved in the regulation of cell growth and survival. Mutations in BRAF are seen in many malignancies, including melanoma. To investigate the clinical efficacy of nivolumab monotherapy, ipilimumab monotherapy, and combined nivolumab and ipilimumab therapy in patients with BRAF-mutant and BRAF-wild type melanoma, a meta-analysis was conducted on published studies containing clinical outcomes of these treatments. Published studies of the clinical efficacy of nivolumab monotherapy, ipilimumab monotherapy, and combined nivolumab with ipilimumab were collected through PubMed. Studies focusing on a specific melanoma subtype or brain metastasis were excluded. Objective response rate (ORR), progression free survival (PFS), and overall survival (OS) were assessed to determine clinical efficacy. After screening for studies with similar methodologies, a total of 18 studies were included. BRAF mutation status significantly improved ORR only in patients treated with ipilimumab monotherapy, with an odds ratio of 1.78 (95% CI: 1.15-2.77, p=0.01). However, BRAF mutation status did not significantly affect PFS or OS at 6 months and 12 months for patients treated with ipilimumab monotherapy. Similarly, in patients treated with nivolumab monotherapy or combined nivolumab and ipilimumab, BRAF status did not significantly impact ORR, PFS, or OS at 6 months and 12 months. These findings suggest that routine BRAF mutation testing may not be necessary for patients receiving immunotherapy and that immunotherapy may potentially benefit patients with failed therapy targeting BRAF.

Introduction

- Nivolumab and Ipilimumab are immune checkpoint inhibitors (ICIs) widely used in the treatment of Melanoma. Nivolumab binds to the programmed death-1 (PD-1) receptor on T- cells preventing interaction with the PD-1 ligands, while ipilimumab binds to cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), blocking its interaction with B7 molecules on antigen-presenting cells. By preventing inhibitory signals that suppress T cell activity, these mechanisms promote T cell activation, resulting in a sustained anti-tumor response. BRAF is a serine/threonine-protein kinase involved in the regulation of cell growth and survival. Mutations in BRAF are seen in many malignancies, including melanoma.
- To investigate the clinical efficacy of nivolumab monotherapy, ipilimumab monotherapy, and combined nivolumab and ipilimumab therapy in patients with BRAF-mutant and BRAF-wild type melanoma, a meta-analysis was conducted on published studies containing clinical outcomes of these treatments.

Methodology

- Published studies of the clinical efficacy of nivolumab monotherapy, ipilimumab monotherapy, and combined nivolumab with ipilimumab were collected through PubMed.
- Various combinations of key words of nivolumab, ipilimumab, melanoma, survival, and response were used.
- Reviews, preclinical studies, case reports, studies limited to specific melanoma subtype or brain metastasis, and studies lacking clinical outcomes were excluded.
- The full text of included studies were reviewed. Objective response rate (ORR), progression free survival (PFS), and overall survival (OS) were stratified by BRAF mutation status (mutant vs wild-type) and subsequently assessed to determine clinical efficacy.
- Odds ratios were calculated using findings from relevant publications.
- Meta-analysis was conducted using RevMan5.

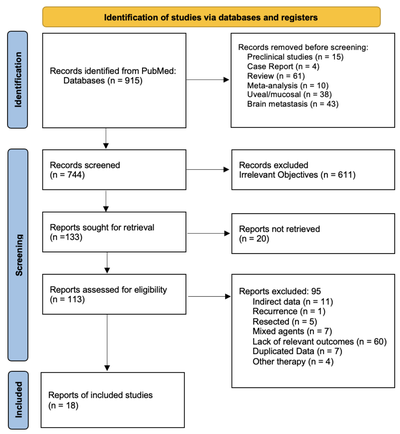

Figure 1. PRISMA 2020 flow diagram for systematic reviews which included searches of databases and registers only.

Results

Overall Response Rate (ORR)

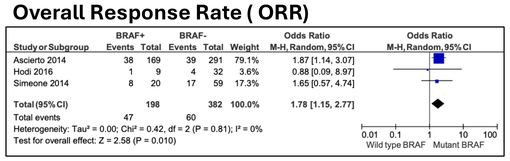

Figure 2. ORR to Ipilimumab monotherapy by BRAF mutation status. Meta-analysis of three studies demonstrates higher ORR in BRAF-mutant compared to BRAF wild-type patients (OR 1.78; 95% CI, 1.15-2.77; p = 0.01)

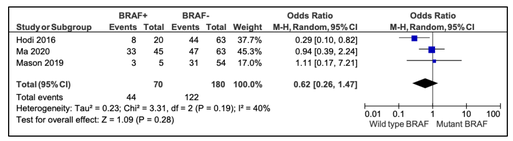

Figure 3. ORR to combined Nivolumab and Ipilimumab therapy by BRAF mutation status. Meta-analysis of three studies shows no significant difference in ORR between BRAF-mutant and BRAF wild-type patients (OR 0.62; 95% CI, 0.26-1.47; p = 0.28)

Progression Free Survival (PFS)

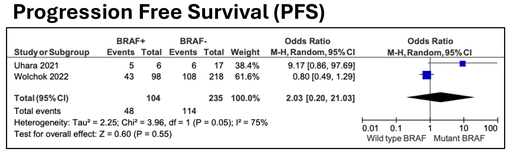

Figure 4. PFS at 6 months with Nivolumab monotherapy by BRAF mutation status. Meta-analysis of two studies shows no significant difference in 6-month PFS between BRAF-mutant and BRAF wild-type patients (OR 2.03; 95% CI, 0.20-21.03; p = 0.55)

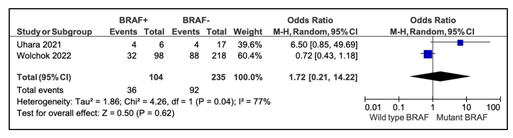

Figure 5. PFS at 12 months with Nivolumab monotherapy by BRAF mutation status. Meta-analysis of two studies shows no significant difference in 12-month PFS between BRAF-mutant and BRAF wild-type patients (OR 1.72; 95% CI, 0.21-14.22; p = 0.62)

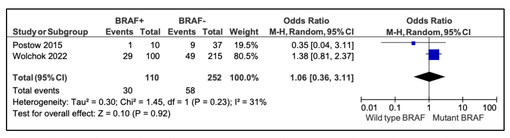

Figure 6. PFS at 6 months with Ipilimumab monotherapy by BRAF mutation status. Meta-analysis of two studies shows no significant difference in 6-month PFS between BRAF-mutant and BRAF wild-type patients (OR 1.06; 95% CI, 0.36-3.11; p = 0.92)

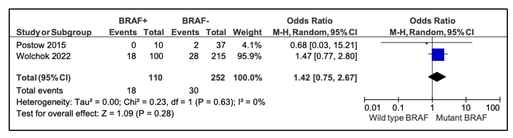

Figure 7. PFS at 12 months with Ipilimumab monotherapy by BRAF mutation status. Meta-analysis of two studies shows no significant difference in 12-month PFS between BRAF-mutant and BRAF wild-type patients (OR 1.42; 95% CI, 0.75-2.67; p = 0.28)

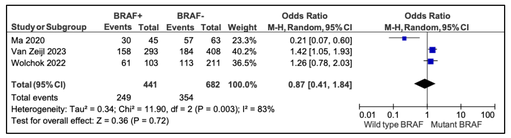

Figure 8. PFS at 6 months with combined Nivolumab and Ipilimumab therapy by BRAF mutation status. Meta-analysis of three studies shows no significant difference in 6-month PFS between BRAF-mutant and BRAF wild-type patients (OR 0.87; 95% CI , 0.41-1.84; p = 0.72)

Overall survival (OS)

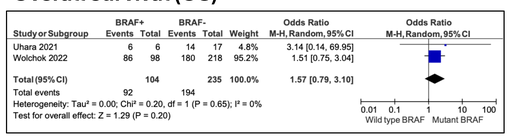

Figure 10. OS at 6 months with Nivolumab monotherapy by BRAF mutation status. Meta-analysis of two studies shows no significant difference in 6-month OS between BRAF-mutant and BRAF wild-type patients (OR 1.57; 95% CI, 0.79-3.10; p = 0.20)

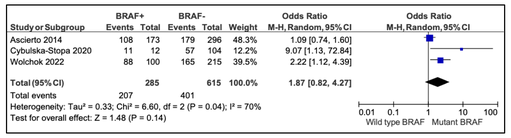

Figure 12. OS at 6 months with Ipilimumab monotherapy by BRAF mutation status. Meta-analysis of three studies shows no significant difference in 6-month OS between BRAF-mutant and BRAF wild-type patients (OR 1.87; 95% CI, 0.82-4.27; p = 0.14)

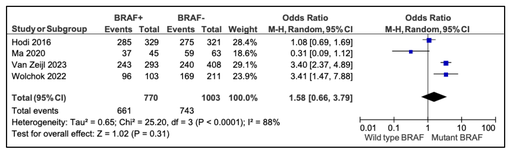

Figure 14. OS at 6 months with combined Nivolumab and Ipilimumab therapy by BRAF mutation. Meta-analysis of four studies shows no significant difference in 6-month OS between BRAF-mutant and BRAF wild-type patients (OR 1.58; 95% CI, 0.66-3.79; p = 0.31)

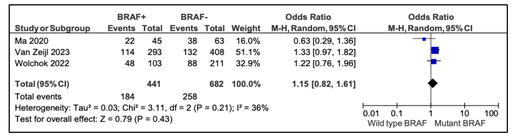

Figure 9. PFS at 12 months with combined Nivolumab and Ipilimumab therapy by BRAF mutation status. Meta-analysis of three studies shows no significant difference in 12-month PFS between BRAF-mutant and BRAF wild-type patients (OR 1.15; 95% CI, 0.82-1.61; p = 0.43)

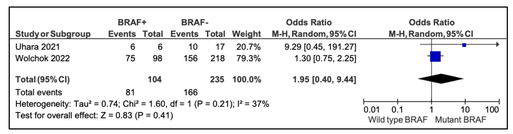

Figure 11. OS at 12 months with Nivolumab monotherapy by BRAF mutation status. Meta-analysis of two studies shows no significant difference in 12-month OS between BRAF-mutant and BRAF wild-type patients (OR 1.95; 95% CI, 0.82-1.61; p = 0.41)

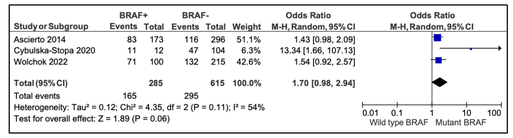

Figure 13. OS at 12 months with Ipilimumab monotherapy by BRAF mutation status. Meta-analysis of three studies shows no significant difference in 12-month OS between BRAF-mutant and BRAF wild-type patients (OR 1.70; 95% CI, 0.98-2.94; p = 0.06)

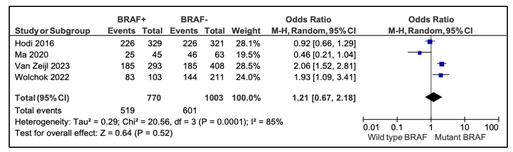

Figure 15. OS at 12 months with combined Nivolumab and Ipilimumab therapy by BRAF mutation. Meta-analysis of four studies shows no significant difference in 12-month OS between BRAF-mutant and BRAF wild-type patients (OR 1.21; 95% CI, 0.67-2.94; p = 0.52)

Conclusion

1. BRAF mutation status is associated with improved ORR only in patients treated with Ipilimumab monotherapy, favoring BRAF-mutant patients.
2. BRAF mutation status did not significantly affect PFS or OS at 6 or 12 months in patients treated with Ipilimumab monotherapy.
3. No significant differences in ORR, PFS, or OS at 6 or 12 months were observed between BRAF-mutant and BRAF wild-type patients treated with Nivolumab monotherapy or Nivolumab + Ipilimumab combination therapy.
4. No significant differences in differences in ORR, PFS, or OS at 6 or 12 months, were observed between BRAF-mutant and BRAF wild-type patients treated with Nivolumab monotherapy or Nivolumab + Ipilimumab combination therapy.
5. Overall, BRAF status does not appear to be a necessary biomarker for guiding immunotherapy selection, and immunotherapy may still provide benefit in patients with prior failure of BRAF-targeted therapy.

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