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Letters to the Editor

The best dosage of nivolumab plus ipilimumab combination for melanoma brain metastases

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ABSTRACT

Tawbi et al. (2021) have recently reported that nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses (N1I3) provided durable survival for patients with active melanoma brain metastases without symptoms as first-line regimen. While we believe in the usefulness of the regimen proposed by Tawbi et al. (2021) we sought to investigate whether the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses (N3I1) regimen might lead to better safety profile. To compare the risk of adverse events caused by these two regimes, we have recently conducted a meta-analysis using the data of patients with both melanoma and the other malignancies. N1I3 regimen, compared to N3I1 regimen, more frequently induced any adverse events (N1I3, 96%; N3I1, 85%; $P = 0.003$), grade III or higher adverse events (N1I3, 64%; N3I1, 36%; $P < 0.001$; Fig. 1), and serious adverse events (N1I3, 61%; N3I1, 48%; $P = 0.004$). In terms of organ specific side effects, the N1I3 regimen also caused significantly more hepatic dysfunction, diarrhea, colitis, and pyrexia. We hope that there will be further discussion on the best dosage of the combination therapy.

Tawbi et al. have recently reported that nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses (N1I3) provided durable survival for patients with active melanoma brain metastases without symptoms as first-line regimen [1]. While we believe in the usefulness of the regimen proposed by Tawbi et al., we thought to investigate whether the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for four doses (N3I1) regimen might lead to better safety profile. This is because Tawbi et al. stated, in their previous report of CheckMate 204, that "the currently available evidence does not suggest that lower doses of ipilimumab are superior to the doses used in our study" [2].

To compare the risk of adverse events caused by these two regimes, we have recently conducted a random-model meta-analysis using a generic inverse variance method and the data of patients with both melanoma and the other malignancies (RevMan ver 5.4. Cochrane Collaboration, London, UK) [3]. This analysis suggested that N3I1 regimen caused less adverse events [3]. We performed additional subgroup analyses limited to advanced melanoma cases, who were treated with four doses of N1I3 regime every 3 weeks, which we considered satisfactory homogeneous to evaluate adverse events. N1I3 regimen, compared to N3I1 regimen, more frequently induced any adverse events (N1I3, 96%; N3I1, 85%; $P = 0.003$), grade III or higher adverse events (N1I3, 64%; N3I1, 36%; $P < 0.001$; Fig. 1), and serious adverse events (N1I3, 61%; N3I1, 48%; $P = 0.004$). In terms of organ specific side effects, the N1I3 regimen also caused significantly more hepatic dysfunction, diarrhea, colitis, and pyrexia.

To our knowledge, CheckMate 511 trial is the only phase III trial that compared N1I3 and N3I1 regimens for advanced melanoma [4]. According to this trial, response and survival at a minimum follow-up of 1 year were compatible in both arms; however, of note that this trial did not include melanoma brain metastasis [4]. OpACIN-neo study assessed safety and efficacy of two different doses of the combined regimens in neoadjuvant setting [5]. Two cycles of the high nivolumab (3mg/kg) and low ipilimumab (1mg/kg) led to the higher pathological complete response rate [5].

According to the CheckMate 511 and OpACIN-neo, the N3I1 regimen is sufficiently effective for melanoma. Besides, our analyses revealed safety superiority of the N3I1 regimen (Fig. 1) [3]. The data from Tawbi et al. are valuable in demonstrating the efficacy of the nivolumab plus ipilimumab combination [1], and we appreciate the authors for their contribution. We hope that there will be further discussion on the best dosage of the combination therapy.

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CRediT authorship contribution statement

Takeshi Fukumoto: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nobuyuki Horita:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

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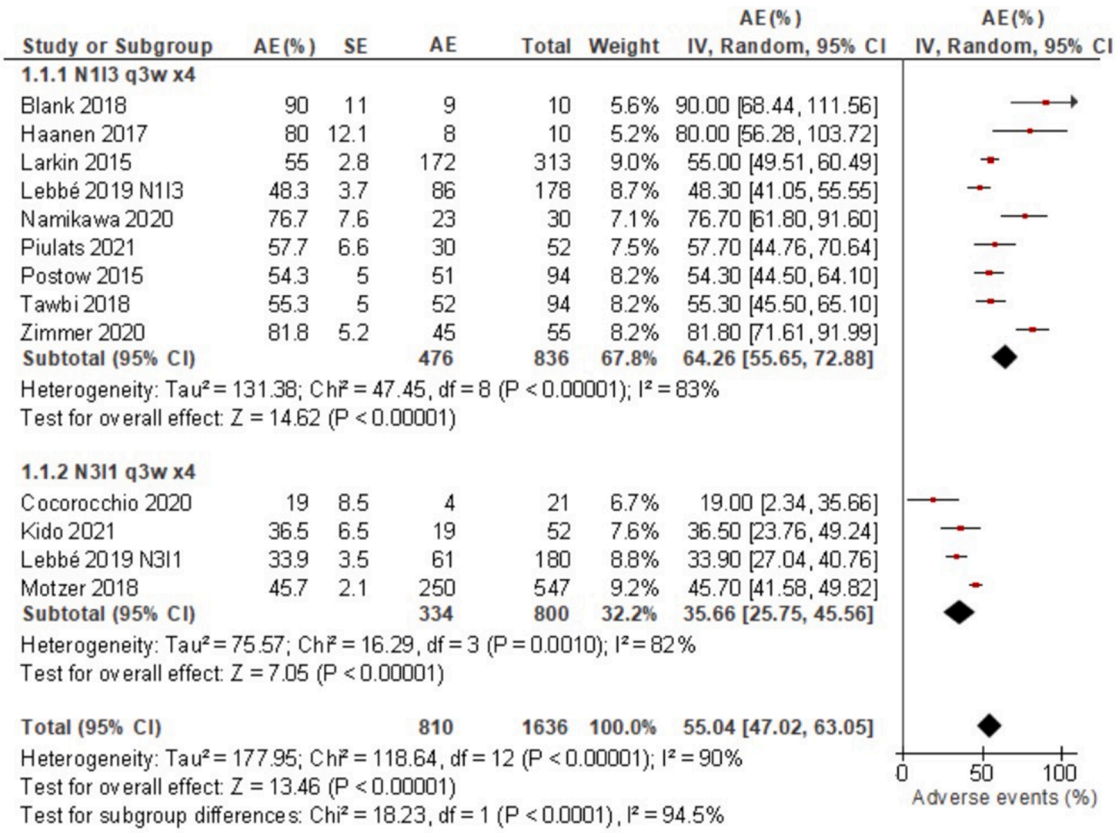

Fig. 1. Forest plot for grade III or higher adverse events.
AE, adverse events; SE, standard error; IV, inverse variance; 95% CI, 95% confidence interval.
N1I3, Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg; N3I1, Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; q3w x4, every 3 weeks for four doses.

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