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Research Article

# Evaluation of Immunotherapy and Targeted Therapies in the Treatment of Metastatic Malignant Melanoma

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## Abstract

**Objectives:** The prognosis of metastatic malignant melanoma is poor. In this study, we aim to evaluate the response rates, PFS and OS times obtained with Nivolumab, Ipilimumab and Dabrafenib plus Trametinib in the treatment of advanced malignant melanoma, as well as the side effect profiles of these three agents.

**Methods:** This study included 58 patients diagnosed with advanced malignant melanoma who received Nivolumab, Ipilimumab or Dabrafenib plus Trametinib therapy between January 2010 - March 2021 and had follow-up at our clinic. Response rates, survival times and side effects associated with each of the three treatment arms were evaluated. Nivolumab, Ipilimumab and Dabrafenib plus Trametinib were compared with regard to effectiveness and tolerability.

**Results:** The Nivolumab, Ipilimumab and Dabrafenib plus Trametinib treatment arms, included 34 (58.6%), 13 (22.4%) and 11 (19%) patients, respectively. The comparison of Nivolumab, Ipilimumab and Dabrafenib plus Trametinib yielded, respectively; ORR (53%, 38.5%, 72.8%), mPFS (7 months, 3 months, 9 months) (p=0.57), mOS (12 months, 16 months, 15 months) (p=0.85).

**Conclusion:** In this study that we conducted with real life data, we confirmed that Nivolumab, Ipilimumab and Dabrafenib plus Trametinib have different effectiveness adn manageable side effect profiles in the treatment of advanced malignant melanoma.

**Keywords:** Dabrafenib plus trametinib, malignant melanoma, nivolumab, ipilimumab

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The incidence of malignant melanoma has shown a rise in the last decade and, as the primary cause of skin cancer-related mortality, it represents approximately 2.3% of all skin cancers.[1] According to data from the US National Cancer Institute's SEER 2020, the statistics of the most prevalent cancers in 2020 indicated malignant melanoma to be the fifth, with 6850 patients losing their lives due to the disease, which corresponds to 1.1% of cancer-related deaths.[2] Research has determined melanoma to be a highly immunogenic tumor and immunotherapy was introduced to the treatment of metastatic melanoma.[3] In advanced malignant melanoma, BRAF mutations are encountered at a rate of approximately 50% and the most common mutation is V600E.[4] In BRAF-positive advanced malignant melanoma patients, BRAF inhibitors are utilized in the first-line treatment and a prolonged survival could be achieved by combination therapy (Dabrafenib plus Trametinib) including an added MEK inhibitor to forestall early developing resistance mechanisms.[5,6] Prior to immune checkpoint inhibitors and targeted therapies, advanced melanoma had a

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poor prognosis and a five-year survival rate of <10%.[7] Currently, the five-year survival rates for advanced melanoma varies between 15-23% as a result of these effective therapies, and survival rates have increased.[8,9] In our study, response rates and PFS, OS times obtained with Nivolumab, Ipilimumab and Dabrafenib plus Trametinib were evaluated. It was investigated whether these three agents are different in terms of response rates, survival times and side effect profiles.

## Methods

Our study included 58 patients who were diagnosed with metastatic malignant melanoma in the Medical Oncology Center of Dicle University, Faculty of Medicine between January 2010 - March 2021 and received Dabrafenib plus Trametinib in the first-line treatment or Nivolumab, Ipilimumab after first-line chemotherapy and their data were retrospectively evaluated from hospital records (In our country, the use of immunotherapy in metastatic melanoma is recommended after temozolamide treatment). Patients aged 18 years or older with a histopathologically confirmed diagnosis of malignant melanoma who were de-novo metastatic or developed metastasis during follow-up and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 01 or ≥2 were included in the study. From patient files; patients' demographic characteristics (age, gender, ECOG PS, metastasis sites, BRAF mutation status, treatment options they received, treatment responses, treatment-related side effects were recorded. An approval (date and approval number: 06.05.2021/356) was obtained for this study from the Ethics Committee of Dicle University, Faculty of Medicine.

### Procedure

Nivolumab (3 mg/kg/day), administered as a 90-minute infusion every 14 days (until unacceptable toxicity or progression). Ipilimumab (3 mg/kg/day) was administered as a 90-minute infusion every 21 days. (up to 4 cycles). Dabrafenib (150 mg/day, orally, 2x daily) plus Trametinib (2 mg/day, orally, 1x daily) was administered (until unacceptable toxicity or progression).

### Assessment

All patients underwent radiological evaluation with computerized tomography prior to the treatment. Disease response status was assessed after every 6 cycles in patients on Nivolumab, after every 3 cycles in patients on Ipilimumab, every 3 months or in case of clinical progression in patients on Dabrafenib plus Trametinib. Treatment response status was determined according to Recist 1.1 (Response Evaluation Criteria in Solid Tumors). The sum of patients with complete response and partial response was expressed as the objective response rate (ORR). The evaluation of toxicity followed the US National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0. Overall survival was defined as the time from the date of metastatic disease to death. Progression-free survival was defined as the time from initiation of treatment to progression or thedate of last follow-up.

### Statistical Analysis

The SPSS 22.0 software was used. Differences between the characteristics of two groups were analyzed using the chi-square or Fisher's exact tests, Survival analysis was conducted with the Kaplan-Meier method. Survival times were analyzed within a 95% confidence interval. Cox regression analysis was used for multivariate analyses. Two tailed p significance values were accepted as <0.05.

## Results

Fifty eight patients were included in the study. Of these, 32 (55.2%) were male, 26 (44.8%) were female. The median age of the patients was 55 (18-88) years. The Nivolumab, Ipilimumab and Dabrafenib plus Trametinib treatment groups included 34, 13 and 11 patients, respectively. The most common primary tumor site was the lower extremities (37.9%). Detailed features of the patients are summarized in Table 1.

When the initial treatment responses of all patients were examined at 3 months, there was complete response in 8 (13.8%) patients, partial response in 23 (39.7%) patients, stable disease in 12 (20.6%) patiegrapnts and progression in 15 (25.9%) patients. In the nivolumab arm there was CR in 4 (11.8%) patients, PR in 14 (41.2%) patients, in the Ipilumumab arm there was CR in 3 (23.1%) patients, PR in 2 (15.4%) patients. In the Dabrafenib plus Trametinib arm, there was CR in 1 (10%) patients, PR in 7 (70%) patients. Overall, PD was found in 15 (26.3%) patients; 11 of these were in the Nivolumab arm and 4 were in the Ipilimumab arm, with no PD encountered in the Dabrafenib plus Trametinib arm. Objective response was obtained in 31 of all patients, and ORR was determined as (53%, 38.5%, 72.8%) in the Nivolumab, Ipilimumab, Dabrafenib plus Trametinib arms, respectively (Table 2).

Mean duration of follow-up was 16.6 months in our study. In the analyses performed with regard to survival, median PFS was, respectively, 7 months, 3 months, 9 months for Nivolumab, Ipilimumab, Dabrafenib plus Trametinib, and no statistically significant difference was found (p=0.57). Median OS was, respectively, 12 months, 16 months, 15 months for the group that received Nivolumab, the group

**Table 1.** Basal characteristics of patients

| | All patients (n,%) | Nivolumab (n,%) | İpilimumab (n,%) | Dabrafenib+Trametinib (n,%) |
|---|---|---|---|---|
| Total | 58 (100) | 34 (58.6) | 13 (22.4) | 11 (19) |
| Age median (min - max) | 55 (18-88) | 60 (18-88) | 49 (18-66) | 56 (25-86) |
| Gender | | | | |
| Male | 32 (55.2) | 18 (52.9) | 7 (53.8) | 7 (63.6) |
| Famale | 26 (44.8) | 16 (47.1) | 6 (46.2) | 4 (36.4) |
| ECOG PS | | | | |
| 0-1 | 53 (91.4) | 32 (94.1) | 11 (84.6) | 10 (91.4) |
| ≥2 | 5 (8.6) | 2 (5.9) | 2 (15.4) | 1 (8.6) |
| BRAF V600E Mutation | | | | |
| Yes | 14 (24.1) | 2 (5.9) | 1 (7.7) | 11 (100) |
| No | 44 (75.9) | 32 (94.1) | 12 (92.3) | 0 (0) |
| Liver metation status | | | | |
| Yes | 19 (32.8) | 11 (32.4) | 5 (38.5) | 3 (27.3) |
| No | 39 (67.2) | 23 (67.6) | 8 (61.5) | 8 (72.7) |
| Bone metation status | | | | |
| Yes | 25 (43.1) | 14 (41.2) | 9 (69.2) | 2 (18.2) |
| No | 33 (56.9) | 20 (58.8) | 4 (30.8) | 9 (81.8) |
| Lung metation status | | | | |
| Yes | 21 (36.2) | 14 (41.2) | 3 (23.1) | 4 (36.4) |
| No | 37 (63.8) | 20 (58.8) | 10 (76.9) | 7 (63.6) |
| Brain metation status | | | | |
| Yes | 11 (19) | 6 (17.6) | 3 (23.1) | 2 (18.2) |
| No | 47 (81) | 28 (82.4) | 10 (76.9) | 9 (81.8) |
| Primary tumor localizations | | | | |
| Head-neck | 8 (13.8) | | | |
| Uper extremity | 4 (6.9) | | | |
| Lower extremity | 22 (37.9) | | | |
| Body | 8 (13.8) | | | |
| Others | 16 (27.6) | | | |

ECOG PS; Eastern Cooperative Oncology Group performance status.

that received Ipilimumab, the group that received Dabrafenib plus Trametinib, and no statistically significant difference was found (p=0.85) (Table 2, Figs. 1 and 2).

When the factors that could influence PFS were evaluated in univariate and multivariate analyses in patients who received any first-line treatment (age at diagnosis, gender, ECOG PS, metastasis sites, BRAF mutation status, treatment options), lung metastasis status was statistically significant, with a PFS of 3 months in the arm with lung metastasis as opposed to 12 months in the arm without lung metasta-

**Table 2.** Response rates and survival times of treatment options

| | All patients (n,%) | Nivolumab (n,%) | İpilimumab (n,%) | Dabrafenib + Trametinib (n,%) | p |
|---|---|---|---|---|---|
| CR | 8 (14) | 4 (11.8) | 3 (23.1) | 1 (9.2) | |
| PR | 23 (40.4) | 14 (41.2) | 2 (15.4) | 7 (63.6) | |
| SD | 11 (19.3) | 5 (14.7) | 4 (30.8) | 3 (27.2) | |
| PD | 15 (26.3) | 11 (32.4) | 4 (30.8) | 0 (0) | |
| ORR | 31 (54.4) | 28 (53) | 5 (38.5) | 8 (72.8) | |
| mOS (mo) | 15 | 12 | 16 | 15 | 0.85 |
| mPFS (mo) | 7 | 7 | 3 | 9 | 0.57 |

*Log Rank P value, CR; complete remission, PR; partial response, SD; stable disease, PD; progressive disease, ORR: objective response rate, mPFS; median progression-free survival, mOS; median overall survival, mo.; month.

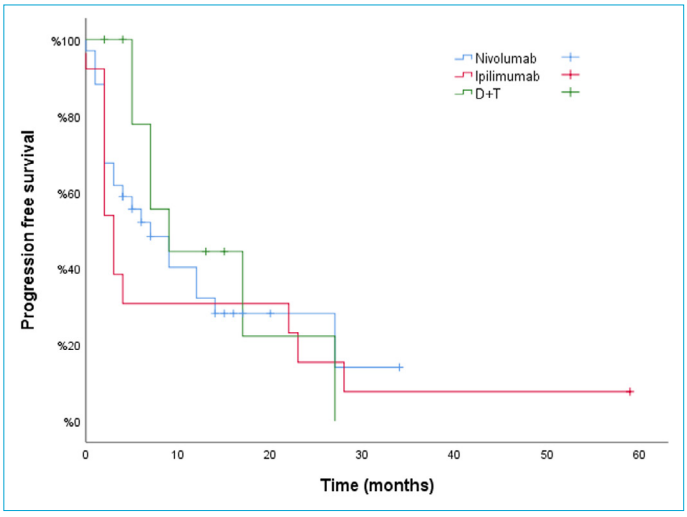


**Figure 1.** Progression free survival outcomes according to the agents used. D+T: Dabrafenib plus Trametinib.

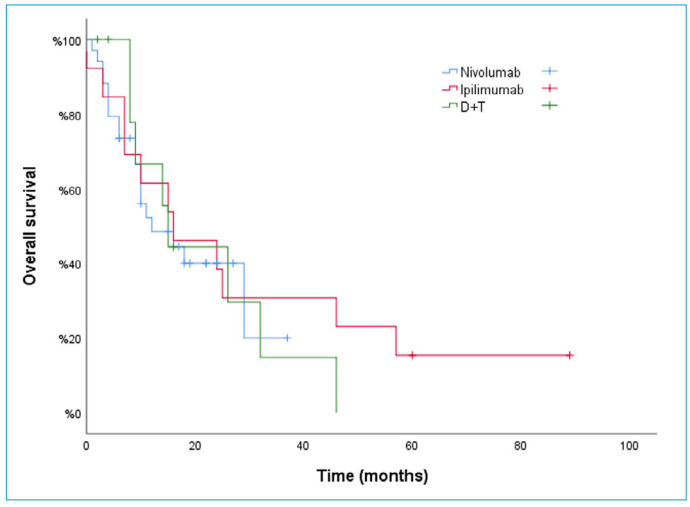


**Figure 2.** Overall survival outcomes according to the agents used. D+T: Dabrafenib plus Trametinib.

sis (p=0.019). Median PFS was significantly shorter in those with brain metastasis in univariate analysis (4 months versus 9 months, Log Rank p=0.27); however, this was not significant in multivariate analysis (p=0.06) (Table 3). When considered in terms of overall survival, mOS was 10 months in those with lung metastasis and 25 months in those without lung metastasis. Those without lung metastasis had a statistically longer mOS (p=0.047). mOS was 9 months in patients with brain metastasis as opposed to 25 months in those without brain metastasis (p=0.007).

The most common side effects associated with treatment in all patients were anemia in 19 (32.8%), fatigue in 17 (29.1%), skin toxicity in 10 (17.2%) and nausea-vomiting in 6 (10.3%) of the patients, other side effects and the associated grades are specified in Table 4.

**Table 3.** Univariate and multivariate analysis of factors affecting progression-free survival

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p | HR | 95% CI | p |
| Age | 1.00 | 0.98-1.02 | 0.80 | | | |
| Gender | 1.71 | 0.90-3.24 | 0.09 | | | |
| Female* vs. Male | | | | | | |
| ECOG PS | 1.26 | 0.38-4.15 | 0.69 | | | |
| 0-1* vs. ≥2 | | | | | | |
| BRAF mutation status | 0.74 | 0.35-1.56 | 0.43 | | | |
| No* vs. Yes | | | | | | |
| Lung metastasis status | 1.98 | 1.07-3.68 | 0.029 | 2.14 | 1.13-4.05 | 0.018 |
| No* vs. Yes | | | | | | |
| Liver metastasis status | 1.86 | 0.99-3.48 | 0.051 | | | |
| No* vs. Yes | | | | | | |
| Bone metastasis status | 1.70 | 0.91-3.16 | 0.09 | 1.80 | 0.96-3.37 | 0.06 |
| No* vs. Yes | | | | | | |
| Brain metastasis status | 2.08 | 1.03-4.20 | 0.041 | | | |
| No* vs. Yes | | | | | | |
| Treatment options | | | 0.61 | | | |
| Nivolumab | Reference | | | | | |
| Ipilimumab | 1.20 | 0.58-2.48 | 0.61 | | | |
| Dabrafenib plus Trametinib | 0.74 | 0.31-1.74 | 0.49 | | | |

*Reference category, HR; hazard ratio, CI; confidence interval, ECOG PS; Eastern Cooperative Oncology Group performance status.

**Table 4.** Treatment-related side effects

| | Nivolumab (n,%) | | Ipilimumab (n,%) | | Dabrafenib + Trametinib (n,%) | |
|---|---|---|---|---|---|---|
| | **Grade 1-2** | **Grade 3-4** | **Grade1-2** | **Grade3-4** | **Grade 1-2** | **Grade 3-4** |
| Anemia | 6 (17.6) | 0 (0) | 7 (53.9) | 0 (0) | 6 (54.5) | 0 (0) |
| Neutropenia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Thrombocytopenia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Fatigue | 7 (20.6) | 0 (0) | 6 (46.2) | 1 (7.7) | 3 (27.3) | 0 (0) |
| Dermatitis | 4 (11.7) | 1 (2.9) | 2 (15.4) | 0 (0) | 3 (27.3) | 0 (0) |
| Nausea-vomiting | 2 (5.9) | 0 (0) | 2 (15.4) | 1 (7.7) | 1 (9.1) | 0 (0) |
| Pneomonitis | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Colitis | 1 (2.9) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Arthritis | 1 (2.9) | 0 (0) | 1 (7.7) | 0 (0) | 0 (0) | 0 (0) |
| Hepatitis | 3 (8.8) | 0 (0) | 1 (7.7) | 1 (7.7) | 0 (0) | 0 (0) |
| Hypothyroidism | 2 (5.8) | 0 (0) | 1 (7.7) | 1 (7.7) | 1 (9.1) | 0 (0) |
| Hyperthyroidism | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (18.2) | 0 (0) |

## Discussion

In this study, the effectiveness and tolerability of Nivolumab, Ipilimumab and Dabrafenib plus Trametinib therapies were compared in the treatment of metastatic malignant melanoma. In a study where Nivolumab and dacarbazine were compared, median PFS was found as 2.2 months in the dacarbazine arm and, 5.1 months in the Nivolumab arm and while median OS could not be obtained for the Nivolumab arm, ORR was determined as 40%.[10] Another study evaluated Nivolumab in advanced melanoma and found a median OS of 32.9 months, median PFS of 5.9 months and ORR of 34.8%.[11] In our study, the Nivolumab arm demonstrated a median OS of 12 months, median PFS of 7 months and ORR of 53%. Although the median PFS and ORR were higher when compared with the literature, the median OS was shorter. Since clinical trials include selected patients without major comorbidities, results from real life data are expected to be lower than the results of clinical trials. In the first of two important studies that have investigated Ipilimumab monotherapy in treatment-naive patients diagnosed with metastatic melanoma, a median OS of 10.1 months, a median PFS of 2.8 months and an ORR of 15% were found in the Ipilimumab arm, which was compared with the glycoprotein 100 peptide vaccine.[12] In the other study, Ipilimumab plus dacarbazine was compared with dacarbazine alone and the group with Ipilimumab showed superior survival (11.2 months versus 9.4 months) with an ORR of 14.2%, which was higher than in the dacarbazine group.[13] In the Ipilimumab arm of our study, median PFS was 3 months, median OS was 16 months, and ORR was 38.2%. Our results were consistent with the literature in terms of PFS, however, our OS outcomes were higher when compared with the literature. In the COMBI-d study that compared Dabrafenib plus Trametinib with Dabrafenib in the first-line treatment of BRAF-mutated unresectable advanced melanoma, median OS was 25.1 months in the combination arm as opposed to 18.7 months in the other arm, median PFS was (11 months versus 8.8 months) and ORR was 69%.[6] In the DESCRIBE II study, the use of Dabrafenib plus Trametinib in patients with BRAF-mutated advanced melanoma yielded an OS of 20 months, median PFS of 7.5 months and ORR of 67.3%.[14] The median OS, median PFS and ORR in our study were, respectively, 15 months, 9 months, 72.8%, and were not consistent with the literature. For all treatment arms, our survival rates and treatment response rates were, albeit not identical, comparable to the literature. We reason that this can be attributed to the lower number of our patients in all three treatment arms.

According to the results of a recent metaanalysis, Dabrafenib plus Trametinib was found to provide a better PFS than Ipilimumab and Nivolumab; in terms of OS, Dabrafenib plus Trametinib was better than Ipilimumab, and while Nivolumab was numerically better in comparison to Dabrafenib plus Trametinib, the difference was not statistically significant.[15] The median PFS in the Nivolumab, Ipilimumab, and Dabrafenib plus Trametinib treatment arms was 7 months, 3 months, and 9 months, respectively. Among the three regimens used in our study median PFS was the longest in the Dabrafenib plus Trametinib arm. In our study, the longest median OS was found in the Ipilimumab arm, and while there were numerical differences across the three treatment arms in terms of PFS and OS, PFS and OS were not significantly different between these arms.

When the factors that could affect PFS and OS were investigated in all patient groups, presence of lung metastasis

was found to be independent unfavorable prognostic factor that influenced both median PFS and OS in univariate and multivariate analyses; patients with lung metastasis had shorter PFS and OS. In a study by Sandru A. and colleagues, lung metastasis was linked to a poor prognosis and the median OS was determined as 13 months[16]; median OS was 10 months in our study.

In a study by Davies MA and colleagues, the occurrence of brain metastasis indicated a poor prognosis and the OS was around 4 months.[17] In our study, presence of brain metastasis was a factor influencing the median OS in all patients groups, and survival was poorer in patients with brain metastasis (9 months versus 25 months, p=0.007).

A study by Topalian and colleagues showed the common treatment-related side effects that occurred in ≥%5 of the patients on Nivolumab to include infusion reaction (10%), fatigue (16%), diarrhea (9%), arthralgia (7%), skin rash (7%), nausea (6%) and pruritus (6%).[18] In our study, Nivolumab-related side effects were, in order of frequency, fatigue, anemia, dermatitis, nausea, hepatitis and hypothyroidism; dermatitis was encountered in 14.6% of the patients and was grade-3 in one patient. In the 4-year updated safety analysis of the CheckMate 067 study, the most common side effects in the Ipilimumab arm were diarrhea in 34%, fatigue in 29%, nausea-vomiting in 17% of the patients; grade-3 fatigue developed in 3 patients and grade-3 nausea developed in 2 patients. In the same study, hypothyroidism and hepatitis developed at a rate of 5% each.[19] In the Ipilimumab arm of our study, anemia occurred at a rate of 53.9%, fatigue at a rate of 53%, nausea-vomiting at a rate of 23.1%, dermatitis at a rate of 15%, with grade-3 fatigue in one patient, grade-3 nausea in one patient, grade-3 hepatitis in one patient, grade-3 hypothyroidism in 1 patient. In a study conducted by Long G.V. and colleagues, the side effects encountered in patients in the Dabrafenib plus Trametinib arm included pyrexia in 69%, chills in 60%, fatigue in 59%, nausea-vomiting in 45% and diarrhea in 35%.[20] Meanwhile, our study was not consistent with the literature, with anemia in 54.5%, fatigue in 27%, dermatitis in 23%, hyperthyroidism in 18.2%, nausea-vomiting in 9.1% of the patients, and this difference resulted from the limited number of patients in our study.

The limitations of our study; It was a retrospective design, single-center, heterogeneous patient population and small number of patients.

## Conclusion

There has been a dramatic rise in the survival rates in metastatic melanoma with immunotherapy and the development of targeted therapies. In our study, the survival times (OS, PFS) and response rates obtained with the use of Nivolumab, Ipilimumab, Dabrafenib plus Trametinib in the treatment of metastatic melanoma differed from the results previously reported in the literature. The three treatment arms were not different in terms of OS and PFS. In the overall patient population, the presence of brain metastasis was associated with a shorter OS, while both mOS and median PFS were shorter in patients with lung metastasis. Side effects were consistent with the literature and at manageable levels in all of the three treatment arms.

### Disclosures

**Acknowledge:** This article has not previously been published elsewhere as a partial or complete text and article is not under review or publication in any other journal.

**Ethics Committee Approval:** The study was conducted based on the rules of Declaration of Helsinki and approved by the Institutional Ethics Committee of Dicle University, Faculty of Medicine (Document number: 06.05.2021-356).

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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