REVIEW ARTICLE

Comparative Effectiveness of Nivolumab Plus Ipilimumab Versus Nivolumab Monotherapy in BRAF-Mutated Unresectable Stage III–IV Melanoma: A Systematic Review

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Abstract

Introduction: Skin cancer is among the most prevalent malignancies worldwide, with melanoma being the most aggressive because of its invasive and metastatic potential. Advanced melanoma (unresectable stage III/IV) carries a high mortality rate, and although targeted therapy benefits patients with BRAF mutations, immunotherapy remains central across mutation statuses. However, the optimal strategy for BRAF-mutated disease, particularly the survival benefit of dual checkpoint blockade versus anti-programmed cell death protein 1 monotherapy, remains uncertain. This systematic review evaluated the survival and outcomes of adults with BRAF-mutated advanced melanoma treated with nivolumab plus ipilimumab versus nivolumab alone, using literature published from 2017 to 2024. **Methods:** Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and a Patient/population; Intervention; Comparison; Outcome-defined question, PubMed/MEDLINE, Scopus, and Web of Science were searched, and eligible trials and observational cohorts reporting BRAF-mutant subgroup outcomes were selected for inclusion. Two reviewers conducted screening and extraction, quality was assessed using the Jadad scale or Newcastle-Ottawa Scale, and findings were synthesized qualitatively due to the design heterogeneity. Five studies met the inclusion criteria (one phase II, three phase III, and one retrospective cohort), with high methodological quality and low-to-moderate risk of bias. **Results:** Across trials, combination therapy generally improved objective response, progression-free survival, treatment-free interval, and overall survival (OS) compared to nivolumab monotherapy, with long-term follow-up suggesting a durable benefit. Estimates also indicated a longer median OS with combination therapy, although several studies were not powered for formal subgroup comparisons; one retrospective analysis found no statistically significant differences after adjustment, with potential residual confounding and selection bias. **Conclusion:** Overall, dual blockade appears to be beneficial despite its higher toxicity in this setting.

Key words: BRAF mutation, immunotherapy, ipilimumab, melanoma, nivolumab, targeted therapy

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INTRODUCTION

Skin cancer, a malignant growth from skin cells, is among the most prevalent cancers globally.[1] There are two primary types of skin cancer: Melanoma, which arises from melanocytes, and non-melanoma skin cancer, which develops from keratinocytes. Non-melanoma skin cancer includes basal cell carcinoma, squamous cell carcinoma, and other variants.[2] Melanoma is aggressive, invasive, and metastatic, whereas basal cell carcinoma usually grows slowly and rarely spreads. Some malignant squamous cell carcinoma subtypes can be highly invasive and metastatic.[3]

Globally, non-melanoma skin cancer is the most common malignant tumor among Caucasians, and its incidence is increasing. It is much more common than melanoma and poses a challenge to global healthcare and well-being.[4] Global Cancer 2020 data reported 1,198,073 new non-melanoma skin cancer cases (excluding basal cell carcinoma), representing 6.2% of all cancer cases, and 63,731 deaths, accounting for 0.6% of all cancer cases. For melanoma, there were 324,635 new cases and 57,043 deaths, representing 1.7% and 0.6% of the total, respectively.[5]

It is typically diagnosed in middle age and is twice as prevalent in women than in men.[6] Melanoma often arises on healthy skin (*de novo*), and ultraviolet radiation exposure, especially childhood sunburns, is the main modifiable risk factor.[7] The tumor has radial and vertical growth phases; the vertical phase, which involves dermal infiltration, is key to distant metastasis because cells access blood and lymphatic vessels.[7] Advanced melanoma spreads to the lymph nodes (stage III) or organs (stage IV) and has a high mortality rate.[7] Several mutations have been identified, especially mutated BRAF, present in 50–60% of melanomas, with targeted therapies available.

The treatment approach for melanoma depends on the disease progression. From stage III onward, adjuvant therapy with BRAF and MEK inhibitors is recommended.[7] For widespread disease, two strategies improve the long-term survival of patients with advanced disease: Targeted therapy and immunotherapy. Targeted therapy acts on melanomas with BRAF mutations, particularly V600E mutations. BRAF inhibitors, such as vemurafenib, dabrafenib, and encorafenib, are generally combined with MEK inhibitors, such as trametinib, cobimetinib, and binimetinib.

Immunotherapy enhances antitumor responses and can be used regardless of BRAF mutation status. Options include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, such as ipilimumab, and programmed cell death protein 1 (PD-1) inhibitors, such as nivolumab and pembrolizumab. Both CTLA-4 and PD-1 are receptors on T lymphocytes.[7]

Ipilimumab blocks CTLA-4, which reduces helper T lymphocyte responses and increases regulatory T lymphocyte activity; thus, CTLA-4 blockade activates the immune response against tumors.[8] Nivolumab inhibits PD-1, a receptor that suppresses T lymphocyte activity and promotes an immunosuppressive tumor environment through interaction with PD-L1 and PD-L2 on tumor cells, induced by inflammatory cytokines. PD-1 inhibition bolsters the T lymphocyte response to tumors.[9]

With more treatment options available, identifying the best survival outcomes remains difficult. Evidence on the use of drugs alone or in combination is insufficient; therefore, the most suitable treatment for each case remains unclear. Ipilimumab and nivolumab are also less often used and studied in patients with BRAF mutations. Therefore, a systematic review is warranted to address this issue.

This study aimed to evaluate the survival of patients with advanced melanoma with a BRAF mutation by comparing combined ipilimumab and nivolumab therapy with nivolumab monotherapy, based on literature from the past 5 years.

METHODS

This systematic review assessed the prognostic outcomes of nivolumab plus ipilimumab versus nivolumab alone in patients with BRAF-mutated advanced melanoma, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[10,11]

Using the PICO framework, the population (P) was adults with unresectable stage III or IV BRAF-mutated melanoma. The Intervention (I) was nivolumab plus ipilimumab, the comparator (C) was nivolumab alone, and the outcomes (O) were overall survival (OS), progression-free survival (PFS), objective response rate, treatment-free interval (TFI), disease control rate, and treatment-related adverse events.

A literature search of PubMed/MEDLINE, Scopus, and Web of Science identified studies published from January 1, 2017 to December 31, 2024. Reference lists were also manually searched. The strategy was tailored for each database: (“Melanoma” AND “ipilimumab” AND “nivolumab” AND “BRAF” AND [“mutation” OR “mutant”] AND [“advanced” OR “metastatic”] AND “survival”). Medical Subject Headings and database-specific terms were used in the search. Searches were limited to human subjects and English language articles.

The included studies enrolled adults (≥18 years) with histologically confirmed advanced melanoma, reported outcomes for BRAF mutations, compared nivolumab plus ipilimumab with nivolumab monotherapy, reported at least one survival outcome, and were randomized trials, prospective clinical trials, or observational cohort studies. Studies were excluded if they included non-human data, reviews, editorials, conference abstracts, letters, case reports,

expert opinions, studies lacking separate data for BRAF-mutated patients, or those lacking survival-related endpoints.

Records were entered into a reference management system, and duplicates were removed. Two reviewers independently screened the titles and abstracts and then evaluated the full-text articles. Disagreements were resolved through discussion or by a third reviewer. The selection process was documented using a PRISMA flowchart.

Data were independently extracted using a standardized form: Author, year, design, country, setting, sample size, demographics, BRAF status, regimens, follow-up, survival outcomes, response rate, TFI, adverse events, and hazard ratios (HRs) with 95% confidence intervals (CIs). Discrepancies were resolved through consensus.

The methodological quality was assessed using the Jadad Scale for randomized trials and the Newcastle-Ottawa Scale (NOS) for observational studies.[12,13] Studies scoring ≥3 (Jadad) or ≥7 (NOS) were deemed high quality, and disagreements were resolved by discussion.

Given the variability in study designs, a qualitative synthesis was performed. The findings were summarized descriptively, focusing on survival and toxicity. Where available, HRs, median survival, and Kaplan-Meier outcomes were compared to evaluate whether combination immunotherapy offered benefits over nivolumab monotherapy in BRAF-mutated melanoma. Evidence strength was assessed based on design, quality, consistency, and bias, prioritizing the robustness of long-term survival and the efficacy-toxicity balance.

RESULTS

The initial search yielded 19 results from Medline, 31 from Scopus, and 36 from Web of Science. Ultimately, five articles were selected [Figure 1]: One phase II trial,[14] three phase III trials,[15-17] and one retrospective cohort study.[18] Quality was assessed using the Jadad scale or NOS; all studies achieved satisfactory scores. Table 1 summarizes these results.

Long *et al*. reported that combining nivolumab and ipilimumab improved response rates, progression-free survival, and overall survival compared with nivolumab alone.[14] However, the study lacked sufficient statistical power to confirm definitive associations due to toxicity and sample size limitations (76 patients). Furthermore, a lower initial intracranial disease burden correlated with longer PFS, potentially introducing selection bias.

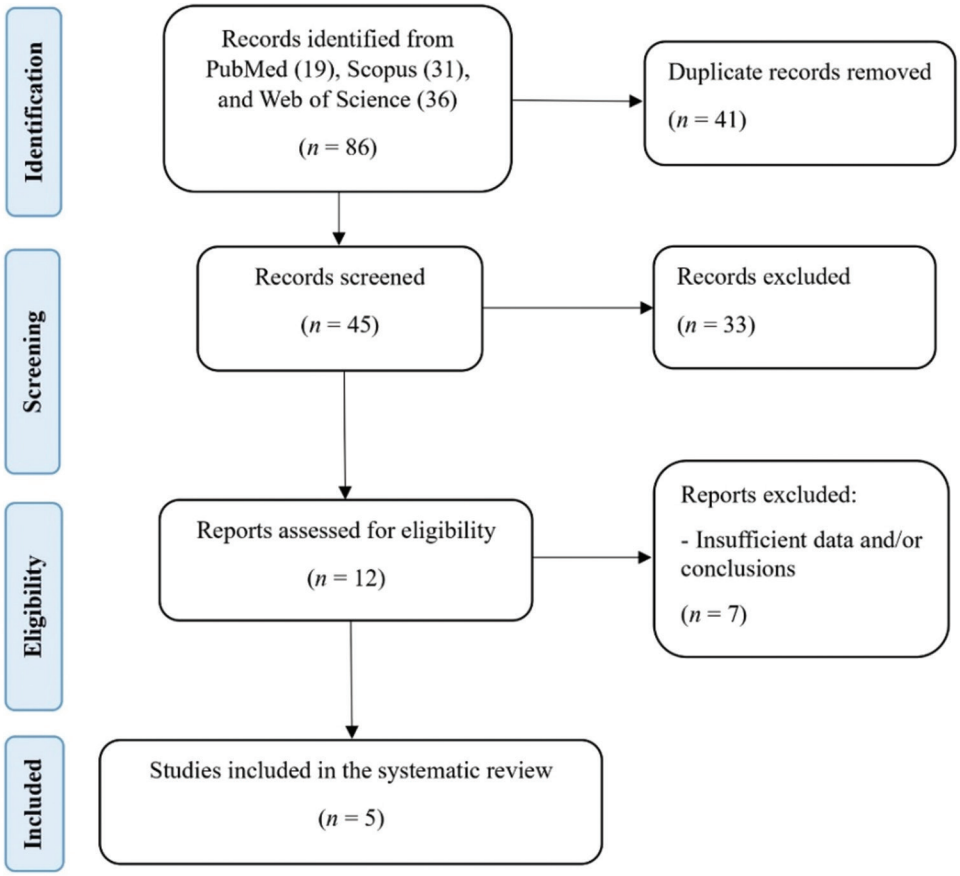

Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow diagram of the literature search and study selection for the systematic review

Table 1: Summary characteristics of included patients

Study	Study design	Population	Intervention	Comparator	Follow- up	Primary outcomes	Key findings
Long *et al*.[14]	Phase II clinical trial	76 patients diagnosed with melanoma with brain metastases and BRAF mutation	Combined therapy: nivolumab 1 mg/kg IV+ipilimumab 3 mg/kg	Nivolumab 3 mg/kg	Until diseases progression or death	Disease improvement	The combination treatment improved survival more than the monotherapy treatment, but without statistical significance.
Hodi *et al*.[17]	Phase III clinical trial	630 patients with unresectable melanoma in stage III or IV without prior treatment.	Combination therapy of nivolumab 1 mg/kg IV+ipilimumab 3 mg/kg IV.	Nivolumab 3 mg/kg with placebo.	4 years	Increased survival in response to combination therapy of nivolumab and ipilimumab.	Combination therapy shows better median survival and PFS results, as well as longer treatment-free intervals compared to nivolumab monotherapy.
Larkin *et al*.[16]	Phase III clinical trial	630 patients with previously untreated, unresectable or histologically confirmed stage III or IV melanoma with BRAF mutation.	Combination therapy: nivolumab 1 mg/kg+ipilimumab 3 mg/kg.	Nivolumab 3 mg/kg+ ipilimumab placebo	5 years	Increased global survival.	Combination therapy shows better median survival and PFS results, as well as longer treatment-free intervals compared to nivolumab monotherapy.
Wolchok *et al*.[15]	Phase III clinical trial	630 patients with unresectable stage III–IV melanoma not previously treated.	Combined therapy: nivolumab 1 mg/kg IV+ipilimumab 3 mg/kg	Nivolumab 3 mg/kg	6.5 years	Increased survival	The combination treatment improved survival more than the monotherapy treatment, but without statistical significance.
Ma *et al*.[18]	Retrospective cohort study	Patients diagnosed with stage III or IV melanoma, never previously treated. 51 with BRAF mutation (45 Ipi/Liv, 6 Lv) and 90 BRAF WT (63 Ipi/Niv, 27 Niv)	Combination therapy: nivolumab 1 mg/kg+ipilimumab 3 mg/kg	Nivolumab 3 mg/kg	Mean 14.9 months	Increased survival	There were no significant differences between BRAF mutants and wild-type patients in treatment application. Patients with BRAF mutations showed a trend, not statistically significant, toward survival with combination therapy.

PFS: Progression-free survival

Hodi *et al*. observed that over half of the patients receiving combination therapy survived beyond four years, whereas nivolumab monotherapy had a median survival of 19.9 months (95% CI: 16.9-24.6).[17] Combination therapy yielded longer PFS (11.5 months) and TFIs (15.4 months) than monotherapy (2.9 and 1.7 months, respectively). Comparisons with other trials suggest that combination therapy may enhance survival in patients with BRAF mutations.

Larkin *et al.,*[16] updating the trial evaluated by Hodi *et al.,*[17] reported that median survival for the combination cohort was not reached after five years, compared to 36.9 months for the nivolumab cohort. Combination therapy showed PFS and TFIs of 11.5 and 18.1 months, respectively, versus 6.9 and 1.8 months for nivolumab alone.

Wolchok *et al*. found an investigator-assessed median long-term survival of 11.5 months (95% CI: 8.7-19.3) with combination therapy versus 6.9 months (95% CI: 5.1-10.2) with nivolumab.[15] The median OS was 72.1 months (95% CI: 38.2–NR) with combination therapy and 36.9 months (95% CI: 28.2–58.7) with nivolumab alone, indicating an advantage, with OS nearly double that of nivolumab monotherapy. Nonetheless, the study was not structured or powered to formally compare the nivolumab treatment groups with ipilimumab and nivolumab.

Ma *et al*. showed in univariate and multivariate analyses, adjusted for known prognostic factors, no definitive association in PFS (HR: 0.61, 95% CI: 0.32-–1.16, $P = 0.127$) or OS (HR: 0.71, 95% CI: 0.26–1.93, $P = 0.500$) between combination therapy with ipilimumab and nivolumab and monotherapy with nivolumab or pembrolizumab.[18] Efficacy was not affected by BRAF mutation status, with those lacking the mutation showing a beneficial response. The results were obtained from a combined nivolumab and pembrolizumab monotherapy cohort. The study relied on multivariate Cox regression, excluding variables, such as patient comorbidities and metastatic sites, suggesting a selection bias.

The methodological quality was evaluated using the Jadad Scale for randomized controlled trials and the NOS for observational studies [Tables 2 and 3]. The quality of evidence was high. Long *et al*. and Hodi *et al*. attained perfect Jadad scores of 5/5, reflecting excellent randomization, blinding, and reporting quality.[14,17] Wolchok *et al.* and Larkin *et al.* received Jadad scores of 3/5, indicating moderate-to-high quality, with lower scores due to unblinding during follow-up.[15,16] The cohort study by Ma *et al*. earned an NOS score of 8/9, demonstrating high quality in terms of selection and outcome evaluation.[18] Overall, the studies met rigorous thresholds, providing a dependable basis for comparing nivolumab plus ipilimumab with nivolumab alone in BRAF-mutated advanced melanoma.

The risk of bias assessment indicated satisfactory quality, with most domains showing a low risk [Figure 2]. Trials by Long et al. and Hodi et al. showed a low risk across all domains.[14,17] Wolchok *et al*. and Larkin *et al*. also showed low risk, though moderate concerns arose regarding performance bias from unblinding during extended follow-up.[15,16] The study by Ma *et al*. exhibited moderate risk due to its observational nature and potential confounding factors.[18] No study was deemed to be at a high risk. The evidence, considered to be of low-to-moderate risk, supports the reliability of the survival benefits reported for combination therapy over monotherapy in BRAF-mutated advanced melanoma.

DISCUSSION

This systematic review's findings indicated that ipilimumab plus nivolumab improved PFS and OS compared with nivolumab alone but caused higher toxicity. Compared with similar studies, Postow *et al*. showed that nivolumab combined with ipilimumab was more effective than ipilimumab alone in patients with advanced melanoma.[19] Chen *et al*. reported comparable results when comparing ipilimumab plus nivolumab with nivolumab alone, showing survival benefits regardless of BRAF mutation status.[20] Although the

Table 2: Quality assessment of randomized controlled trials using the Jadad scale

Study	Randomization (0–2)	Blinding (0–2)	Withdrawals/ Dropouts (0–1)	Total score (0–5)	Quality
Long *et al*.[14]	2	2	1	5	High
Hodi *et al*.[17]	2	2	1	5	High
Larkin *et al*.[16]	2	0	1	3	Moderate-High
Wolchok *et al*.[15]	2	0	1	3	Moderate-High

Table 3: Quality assessment of observational study using the Newcastle-Ottawa Scale

Study	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total score (0–9)	Quality
Ma *et al*.[18]	4	2	2	8	High

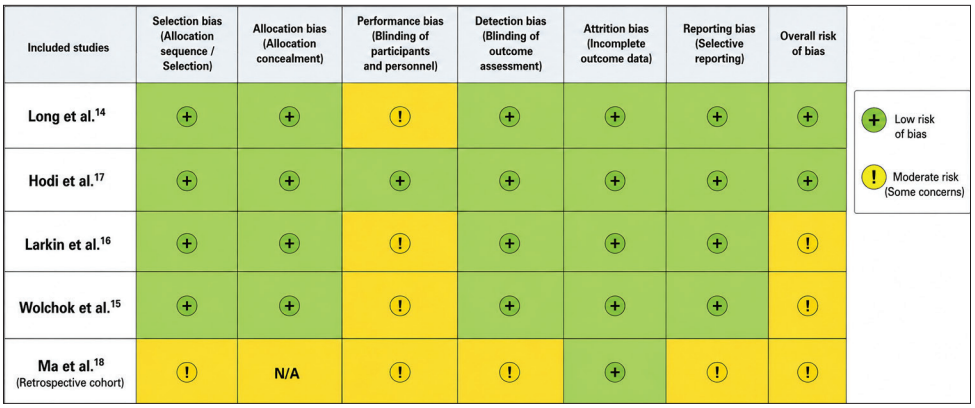

Figure 2: Individual risk of bias in included studies

combination showed a greater response, it lacked statistical significance, and the adverse effects were clearly associated with monotherapy. Chen *et al*. also found that the combination improved survival versus ipilimumab alone, whereas ipilimumab alone caused fewer severe adverse reactions.[20] Seidel *et al*. reported that anti-CTLA-4 plus anti-PD-1 was more effective than monotherapy but caused more adverse effects.[21] Menshawy *et al*. concluded that nivolumab, alone or in combination, outperformed ipilimumab alone for survival, with a better response in patients without a BRAF mutation.[22] Menshawy *et al*. concluded that nivolumab is safer than ipilimumab and chemotherapy.[22]

All studies in the review suggested that combination therapy could provide benefits in PFS and OS, although they also noted its limitations. Long *et al.* and Hodi *et al.* reported increased toxicity with combination therapies.[14,17] In contrast, Larkin *et al.* noted that the median survival in the combination therapy group was not reached after five years of follow-up, suggesting long-term benefits.[16] Wolchok et al. supported this by observing the continuation of the trend after 6.5 years of follow-up in the same clinical trial.[15] In contrast to other studies, Ma *et al*. found no statistically significant difference in PFS and OS between combination therapy and nivolumab alone, although they noted a trend toward improvement with the combination.[18] Ma *et al*. also observed that effectiveness was not influenced by BRAF mutation status.[18] Similarly, Hodi *et al.* suggested that combination therapy may be more effective for BRAF-mutant melanoma.[17]

The foundational trial lacked the statistical power to compare the clinical effectiveness of combination therapy with nivolumab monotherapy.[14-16] Furthermore, the cessation of double blinding during the third year resulted in a Jadad score of 3 out of 5 for the studies by Wolchok *et al*. and Larkin *et al.*[15,16] While combination therapy shows promise, further research is required to assess the benefit-risk ratio of reported toxicity to optimize patient selection.[16] The insufficient statistical power of these studies underscores the need for more robust research.[14-16]

This systematic review has implications for the management of advanced BRAF-mutant melanoma. The included studies showed that nivolumab plus ipilimumab improved PFS and OS compared with nivolumab alone, supporting dual immune checkpoint blockade in selected patients. Long-term follow-up has shown that combination therapy may produce antitumor immune responses and prolonged disease control.[23,24] In BRAF-mutated melanoma, treatment decisions often involve a balance between targeted therapy and immunotherapy.[25,26]

Evidence suggests that dual checkpoint inhibition offers long-term clinical benefits and should be considered a frontline option for patients with suitable performance status. However, efficacy must be weighed against the higher rates of immune-related adverse events. Patient selection, monitoring, and toxicity management are essential components of this approach. Patients with comorbidities, poor performance status, or limited tolerance to toxicity may still benefit from nivolumab monotherapy. Treatment should be individualized, and predictive biomarkers may identify patients likely to benefit from combination therapy and reduce unnecessary toxicity.

When interpreting the review results, the limitations must be considered. Only five studies met the eligibility criteria, limiting the conclusions and preventing meta-analysis and heterogeneity exploration. Three studies were follow-up analyses of the CheckMate-067 trial, creating a population overlap and magnifying the trial's influence on the results. Thus, the evidence may not represent the population with BRAF-mutated advanced melanoma. Heterogeneity in design, sample size, follow-up, characteristics, and outcomes reduced comparability and generalizability. One retrospective study was prone to confounding, selection bias, and incomplete adjustment for prognostic factors.

Moreover, several studies were not designed to compare nivolumab plus ipilimumab with nivolumab monotherapy in BRAF-mutated subgroups, which weakens the subgroup conclusions. Increased toxicity from combination immunotherapy may have affected discontinuation and outcomes, introducing performance and attrition bias. Changes in blinding during follow-up may have affected the

study quality. The search was limited to English-language studies in the three databases. Although comprehensive, studies in other languages or grey literature might have been overlooked, suggesting a publication bias.

CONCLUSION

This systematic review indicates that nivolumab plus ipilimumab improves PFS and OS compared to nivolumab alone in BRAF-mutated advanced melanoma. Consistent results across randomized trials suggest that dual immune checkpoint blockade provides substantial and durable benefits. However, survival gains are associated with more treatment-related adverse effects, underscoring the need for personalized decisions and effective toxicity management.

Although evidence supports combination immunotherapy, its benefits and risks must be assessed individually. Because comparative studies are limited and the evidence relies on a single trial program, prospective studies are needed to confirm these findings. Future research should identify predictive biomarkers, refine patient selection, and optimize treatment sequencing to maximize long-term survival while minimizing the toxicity of BRAF-mutated advanced melanoma.

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Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

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