Tepotinib treatment in patients with MET exon 14-skipping non-small cell lung cancer: long-term follow-up of the VISION phase 2 nonrandomized clinical trial

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Tepotinib Treatment in Patients With *MET* Exon 14–Skipping Non–Small Cell Lung Cancer

Long-term Follow-up of the VISION Phase 2 Nonrandomized Clinical Trial

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IMPORTANCE MET inhibitors have recently demonstrated clinical activity in patients with *MET* exon 14 (*MET*ex14)-skipping non–small cell lung cancer (NSCLC); however, data with longer follow-up and in larger populations are needed to further optimize therapeutic approaches.

OBJECTIVE To assess the long-term efficacy and safety of tepotinib, a potent and highly selective MET inhibitor, in patients with *MET*ex14-skipping NSCLC in the VISION study.

DESIGN, SETTING, AND PARTICIPANTS The VISION phase 2 nonrandomized clinical trial was a multicohort, open-label, multicenter study that enrolled patients with *MET*ex14-skipping advanced/metastatic NSCLC (cohorts A and C) from September 2016 to May 2021. Cohort C (>18 months' follow-up) was an independent cohort, designed to confirm findings from cohort A (>35 months' follow-up). Data cutoff was November 20, 2022.

INTERVENTION Patients received tepotinib, 500 mg (450 mg active moiety), once daily.

MAIN OUTCOMES AND MEASURES The primary end point was objective response by independent review committee (RECIST v1.1). Secondary end points included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

RESULTS Cohorts A and C included 313 patients (50.8% female, 33.9% Asian; median [range] age, 72 [41-94] years). The objective response rate (ORR) was 51.4% (95% CI, 45.8%-57.1%) with a median (m)DOR of 18.0 (95% CI, 12.4-46.4) months. In cohort C (n = 161), an ORR of 55.9% (95% CI, 47.9%-63.7%) with an mDOR of 20.8 (95% CI, 12.6-not estimable [NE]) months was reported across treatment lines, comparable to cohort A (n = 152). In treatment-naive patients (cohorts A and C; n = 164), ORR was 57.3% (95% CI, 49.4%-65.0%) and mDOR was 46.4 (95% CI, 13.8-NE) months. In previously treated patients (n = 149), ORR was 45.0% (95% CI, 36.8%-53.3%) and mDOR was 12.6 (95% CI, 9.5-18.5) months. Peripheral edema, the most common treatment-related adverse event, occurred in 210 patients (67.1%) (35 [11.2%] experienced grade ≥3 events).

CONCLUSIONS AND RELEVANCE The findings from cohort C in this nonrandomized clinical trial supported the results from original cohort A. Overall, the long-term outcomes of VISION demonstrated robust and durable clinical activity following treatment with tepotinib, particularly in the treatment-naive setting, in the largest known clinical trial of patients with *MET*ex14-skipping NSCLC, supporting the global approvals of tepotinib and enabling clinicians to implement this therapeutic approach for such patients.

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Supplemental content

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Cohort A from the phase 2 VISION nonrandomized clinical trial demonstrated robust and durable clinical activity with tepotinib in patients with *MET* exon 14 (*MET*ex14)-skipping NSCLC,[1-3] based on which, tepotinib was approved for use in several countries globally, including by the US Food and Drug Administration (FDA).

Herein, we report follow-up analysis of the independent similar findings from cohort C of the VISION trial along with the combined cohorts A and C outcomes after at least 18 months of follow-up.

Key Points

Question Does the long-term follow-up analysis of the VISION nonrandomized clinical trial demonstrate good clinical outcomes with tepotinib in patients with *MET* exon 14 (*MET*ex14)-skipping non–small cell lung cancer (NSCLC)?

Findings In the 18-month follow-up from cohort C (n = 161), objective response rate (ORR) was 55.9% and median duration of response (mDOR) was 20.8 months across treatment lines, supporting previous data from cohort A (n = 152). Across cohorts A and C, ORR was 57.3% with an mDOR of 46.4 months in treatment-naive patients (n = 164).

Meaning This large nonrandomized clinical trial of patients with *MET*ex14-skipping NSCLC supports global approvals of tepotinib, enabling clinicians to implement these therapeutic approaches.

Methods

The trial protocol and analysis plan are in Supplement 1. VISION (NCT02864992) was a phase 2, single-arm, open-label, multicenter nonrandomized clinical trial of tepotinib in patients with *MET*ex14-skipping advanced/metastatic NSCLC (cohorts A and C). Cohort C (enrollment: August 2019-May 2021) was an independent cohort, designed to confirm findings from cohort A (enrollment: September 2016-December 2019).

Patients with advanced *EGFR/ALK* wild-type and *MET*ex14-skipping NSCLC detected by tissue (TBx) and/or liquid biopsy (LBx) using next-generation sequencing, received tepotinib, 500 mg (450 mg active moiety), once daily. The primary end point was objective response by independent review committee (IRC) using RECIST v1.1. Secondary end points included duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. Predefined analysis sets for all end points included *MET*ex14-skipping detection by TBx (T positive), LBx (L positive), and T positive and/or L positive.[1]

An exploratory analysis using modified RANO-BM criteria assessed intracranial activity in patients with brain metastases (BM) and 1 or more evaluable postbaseline tumor assessments. Data cutoff for all analyses was November 20, 2022, except RANO-BM (data cutoff: February 20, 2022). For further details, see eMethods in Supplement 2.

Results

Patients and Efficacy

Cohorts A and C included 313 patients (median [range] age, 72 [41-94] years; 159 [50.8%] female, 106 [33.9%] Asian, 149 [47.6%] smoking history, 231 [73.8%] ECOG PS 1, 252 [80.5%] adenocarcinoma; eTable 1 and eFigure 1 in Supplement 2). Patients in cohort C (n = 161) had more than 18 months' follow-up, and patients in cohort A (n = 152) had more than 35 months' follow-up. Median (range) follow-up was 32.6 (0.3-71.9) months across cohorts A and C. Overall, the objective response rate (ORR) was 51.4% (95% CI, 45.8%-57.1%) with a median (m) DOR of 18.0 (95% CI, 12.4-46.4) months, mPFS of 11.2 (95% CI, 9.5-13.8) months, and mOS of 19.6 (95% CI, 16.2-22.9) months (**Table**).

Baseline characteristics were broadly consistent between cohorts, with higher proportions of Asian (68 [42.2%] vs 38 [25.0%]), treatment-naive (95 [59.0%] vs 69 [45.4%]), and patients with T-positive *MET*ex14-skipping detection (120 [74.5%] vs 88 [57.9%]) enrolled in cohort C vs A (eTable 2 in Supplement 2). With an ORR of 55.9% (95% CI, 47.9%-63.7%) and an mDOR of 20.8 (95% CI, 12.6-not estimable [NE]) months, these follow-up outcomes of longer than 18 months for cohort C are consistent with those from its primary analysis (>9 months' follow-up),[4] and were improved compared with primary analysis results for cohort A (>9 months' follow-up),[1] but mostly comparable to those reported herein with longer-term follow-up (>35 months' follow-up; eTable 3, eFigure 2 in Supplement 2).

In cohorts A and C, 164 patients were treatment-naive and 149 were pretreated. Baseline characteristics were broadly consistent; however, the treatment-naive subgroup had a higher proportion of White patients and patients with smoking history, as well as higher baseline tumor load (eTable 1 in Supplement 2).

In treatment-naive patients (n = 164), ORR was 57.3% (95% CI, 49.4%-65.0%) and mDOR was 46.4 (95% CI, 13.8-NE) months (Table, **Figure 1**). Most treatment-naive patients had T-positive *MET*ex14-skipping detection (n = 111), and time-dependent end points were longer in this subset. Treatment-naive T-positve ORR was 58.6% (95% CI, 48.8%-67.8%) with an mDOR of 46.4 (95% CI, 15.2-NE) months, mPFS of 15.9 (95% CI, 11.0-49.7) months, and mOS of 29.7 (95% CI, 18.8-NE) months (Table; eFigure 3 in Supplement 2). In cohort C, outcomes in treatment-naive patients with T-positive *MET*ex14-skipping detection (n = 69) were further improved, with an ORR of 65.2% (95% CI, 52.8%-76.3%), mPFS of 16.5 (95% CI, 11.0-NE) months, and mOS of 28.5 (95% CI, 14.1-NE) months; mDOR was not reached (95% CI, 10.4-NE).

In pretreated patients (n = 149), ORR was 45.0% (95% CI, 36.8%-53.3%) and mDOR was 12.6 (95% CI, 9.5-18.5) months. In second-line patients with 1 prior therapy (n = 92), ORR was 45.7% (95% CI, 35.2%-56.4%) and mDOR was 12.6 (95% CI, 8.3-18.5) months (eTable 4 in Supplement 2). Pretreated patients with T-positive *MET*ex14-skipping detection had slightly improved outcomes in the time-dependent end points. Patients with L-positive *MET*ex14-skipping detection had a similar ORR (treatment-naive patients, 58.9%; 95% CI, 48.4%-68.9%, and pretreated-patients, 43.4%; 95% CI, 32.5%-54.7%), but a trend

Table. Outcomes Following Tepotinib Treatment in Cohorts A and C According to Line of Therapy[a]

Outcome		Overall			Treatment naive			Previously treated		
		T positive and/or L positive (n = 313)	T positive (n = 208)	L positive (n = 178)	T positive and/or L positive (n = 164)	T positive (n = 111)	L positive (n = 95)	T positive and/or L positive (n = 149)	T positive (n = 97)	L positive (n = 83)
ORR[b], % (95% CI)		51.4 (45.8-57.1)	54.3 (47.3-61.2)	51.7 (44.1-59.2)	57.3 (49.4-65.0)	58.6 (48.8-67.8)	58.9 (48.4-68.9)	45.0 (36.8-53.3)	49.5 (39.2-59.8)	43.4 (32.5-54.7)
DCR, % (95% CI)		76.0 (70.9-80.7)	80.8 (74.7-85.9)	71.9 (64.7-78.4)	78.7 (71.6-84.7)	83.8 (75.6-90.1)	75.8 (65.9-84.0)	73.8 (66.0-80.7)	78.4 (68.8-86.1)	67.5 (56.3-77.4)
DOR	Median (95% CI), mo	18.0 (12.4-46.4)	18.0 (10.8-46.4)	15.2 (9.7-33.6)	46.4 (13.8-NE)	46.4 (15.2-NE)	19.4 (8.3-NE)	12.6 (9.5-18.5)	12.4 (8.3-18.0)	12.4 (8.4-33.6)
	Events, No. (%)	70 (43.5)	49 (43.4)	45 (48.9)	33 (35.1)	21 (32.3)	25 (44.6)	37 (55.2)	28 (58.3)	20 (55.6)
PFS	Median (95% CI), mo	11.2 (9.5-13.8)	13.7 (11.0-17.1)	8.9 (7.8-11.0)	12.6 (9.7-17.7)	15.9 (11.0-49.7)	10.3 (8.0-16.5)	11.0 (8.2-13.7)	11.5 (8.2-14.7)	8.2 (5.7-11.0)
	Events, No. (%)	165 (52.7)	101 (48.6)	107 (60.1)	81 (49.4)	50 (45.0)	53 (55.8)	84 (56.4)	51 (52.6)	54 (65.1)
OS	Median (95% CI), mo	19.6 (16.2-22.9)	22.9 (18.8-28.5)	17.6 (12.6-21.3)	21.3 (14.2-25.9)	29.7 (18.8-NE)	17.6 (10.4-23.7)	19.3 (15.6-22.3)	20.4 (17.0-25.5)	16.2 (12.0-21.0)
	Events, No. (%)	200 (63.9)	120 (57.7)	126 (70.8)	98 (59.8)	55 (49.5)	64 (67.4)	102 (68.5)	65 (67.0)	62 (74.7)
	12-mo rate, % (95% CI)	72 (59-81)	75 (59-86)	68 (52-80)	65 (57-72)	74 (64-81)	59 (49-68)	68 (59-75)	72 (62-80)	60 (48-70)
	24-mo rate, % (95% CI)	48 (35-59)	54 (37-68)	47 (31-61)	44 (36-52)	55 (44-64)	39 (29-49)	38 (30-46)	42 (32-52)	33 (23-43)

Abbreviations: DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; NE, not estimable.

[a] T positivity was determined by detection of *MET*ex14 skipping in tissue biopsy sample; L positivity by detection of *MET*ex14 skipping in liquid biopsy sample.

[b] One treatment-naive patient had a complete response; all other objective responses were partial responses.

toward shorter DOR, PFS, and OS (eFigure 4 in Supplement 2). Tumor shrinkage was observed in more than 90% of patients irrespective of treatment lines (**Figure 2**).

Of 57 patients in cohorts A and C with known baseline BM, systemic ORR per RECIST v1.1, accounting for intracranial and extracranial lesions, was 56.1% (95% CI, 42.4%-69.3%) (eTable 5 in Supplement 2). Among 15 patients with BM target lesions evaluable by RANO-BM (12 patients had received prior brain radiotherapy), intracranial ORR was 66.7% (95% CI, 38.4%-88.2%) (eTable 6 in Supplement 2). Five patients without baseline BM developed BM during treatment (per RECIST v1.1 by IRC).

Safety

In cohorts A and C, treatment-related AEs (TRAEs) occurred in 287 (91.7%) patients, and were grade 3 or higher in 109 (34.8%); 105 (33.5%) had dose reduction and 46 (14.7%) discontinued due to TRAEs (eTable 7 in Supplement 2). Peripheral edema was the most common TRAE (210 [67.1%]), with 35 (11.2%) experiencing grade 3 or higher peripheral edema. Other TRAEs occurring in more than 20% of patients included hypoalbuminemia (74 [23.6%]), nausea (73 [23.3%]), diarrhea (70 [22.4%]), and blood creatinine level increase (69 [22.0%]), and were mostly grades 1 to 2.

Discussion

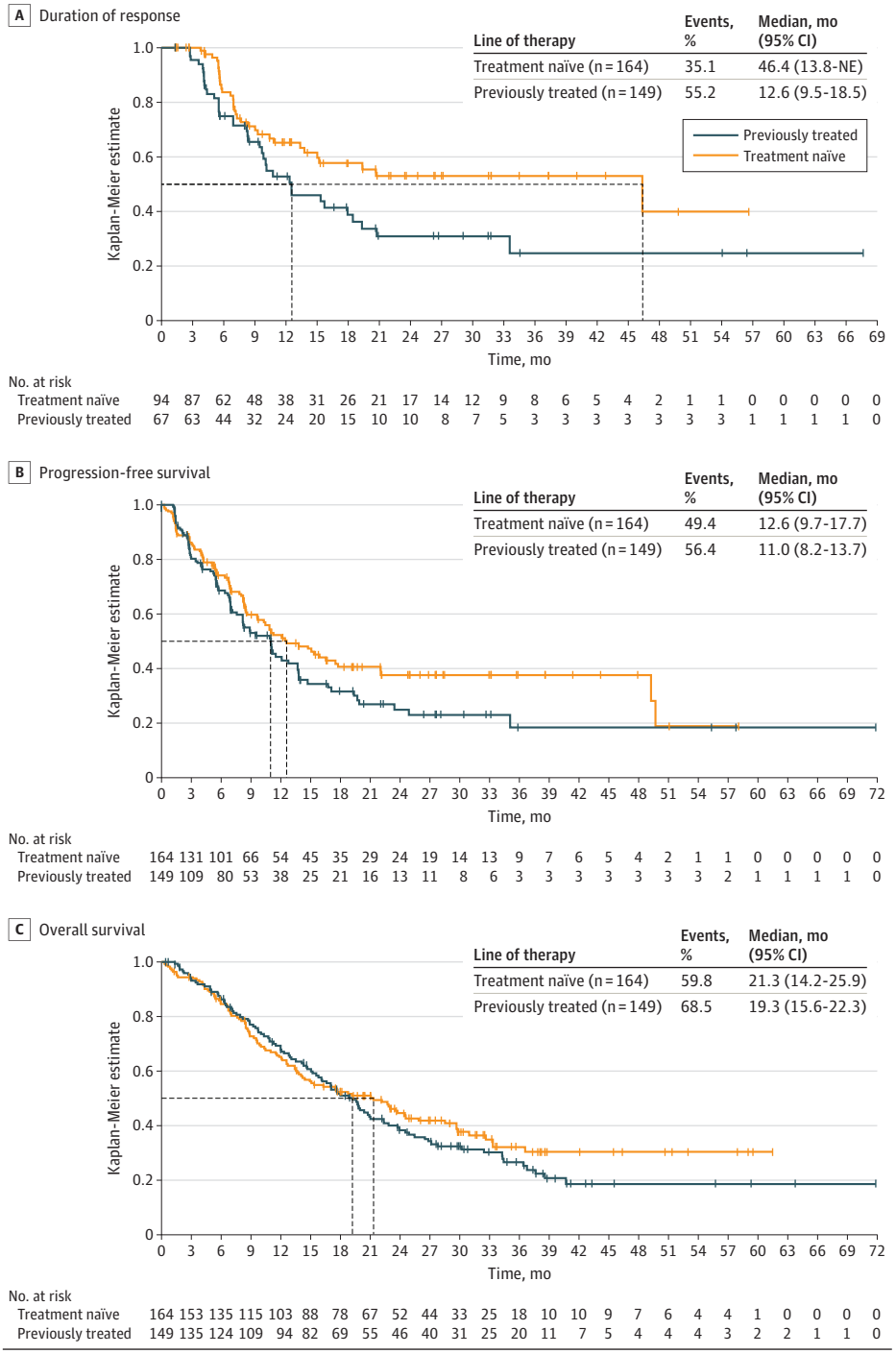
Outcomes from the independent cohort C of the VISION trial supported the positive outcomes of tepotinib first reported in cohort A,[1] which now has follow-up of more than 35 months. With updated results from a larger patient population, ORR increased, particularly in treatment-naive patients with T-positive *MET*ex14-skipping detection with an ORR of 58.6%, compared with the previously reported ORR of 46%.[1] Tepotinib demonstrated clinically meaningful outcomes both in treatment-naive and pretreated patients with *MET*ex14-skipping NSCLC, particularly when considering outcomes with nontargeted therapies.[5,6] Consistency in PFS between treatment-naive and pretreated patients has persisted with the larger population and increased follow-up duration. These data, and data from other studies,[6-8] support the use of MET inhibitors across therapy lines for patients with *MET*ex14-skipping NSCLC.

Importantly, the VISION trial allowed enrollment based on prospective testing by TBx (associated with higher sensitivity and considered the gold standard[9]) and/or LBx. Both patients with T-positive and L-positive *MET*ex14-skipping detection had clinically meaningful outcomes for patients treated with tepotinib. Using LBx, being less invasive than TBx,[9] enabled enrollment of a large population of patients who did not have TBx results. However, because LBx has limited sensitivity in low-ctDNA-shedding tumors and low tumor burden,[9] it may have selected patients with a worse prognosis due to higher tumor burden and/or ctDNA shedding.[9] This could explain the observations that patients with T-positive METex14-skipping detection had longer time-dependent end points, and cohort C treatment-naive patients (with more patients with T-positive *MET*ex14-skipping detection) had better outcomes than those in cohort A.

In patients with baseline BM, tepotinib demonstrated robust systemic and intracranial outcomes, which had comparable clinical benefit to patients without baseline BM. Aligned with guidelines,[10] this supports the use of brain-penetrating MET inhibitors, providing a systemic therapy alternative to radiation.

Tepotinib was generally well tolerated with a low proportion of TRAEs leading to discontinuation. The most common

Figure 1. Outcomes Following Tepotinib Treatment in Cohorts A and C



A, Duration of response.[a]
B, Progression-free survival.
C, Overall survival. NE indicates not estimable.

[a] Only patients with a response were included in Kaplan-Meier analyses.

TRAE, peripheral edema (a class effect of MET inhibitors[5-7]), was mostly mild to moderate.

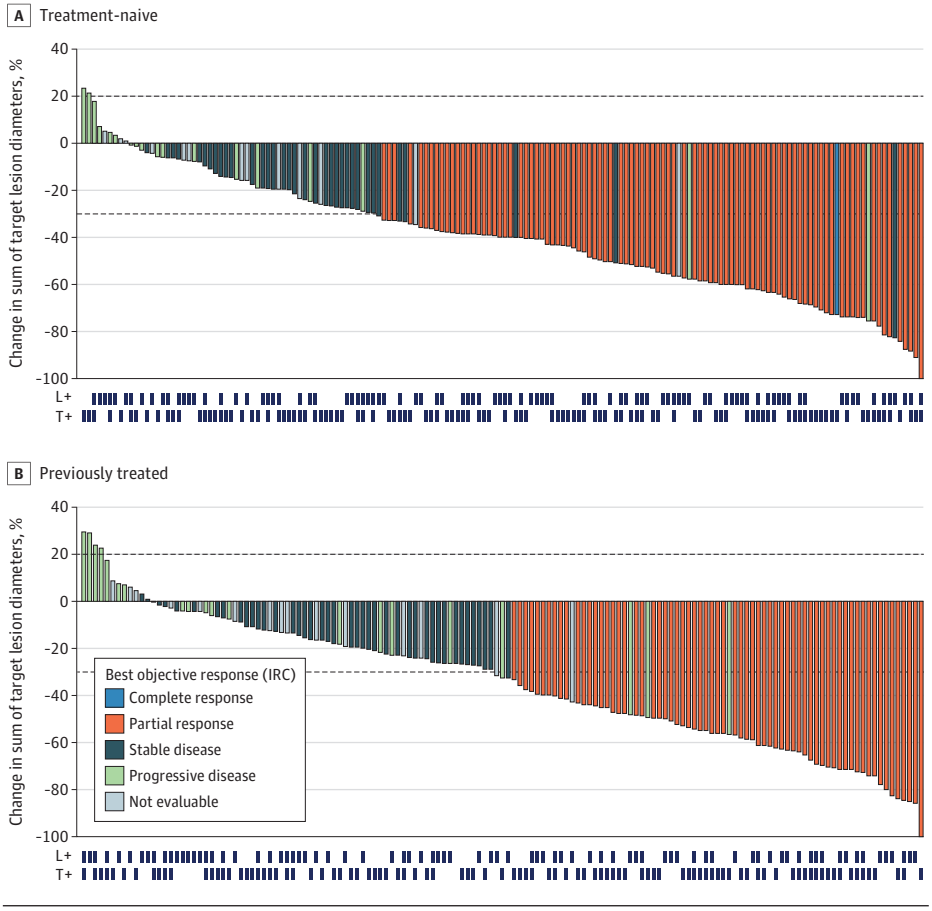
Limitations

The VISION study was a nonrandomized clinical trial. The confirmatory cohort C analysis was also limited by positive results in cohort A being reported while enrollment was ongoing, which may have encouraged recruitment of patients in a better clinical condition into cohort C.

Conclusion

In this long-term follow-up analysis of data from the VISION nonrandomized clinical trial, tepotinib demonstrated robust and durable clinical outcomes across therapy lines in the largest known clinical trial of patients with *MET*ex14-skipping NSCLC, enrolled based on TBx or LBx. Efficacy was clinically meaningful in patients with 1 or more prior therapies, and par-

Figure 2. Change in Sum of Longest Diameters Between Baseline and Best Postbaseline Assessment by IRC in Cohorts A and C



A, Treatment-naive patients. B, Previously treated patients. Four treatment-naive and 4 previously treated patients are not shown due to baseline/on-treatment measurement not being available. IRC indicates independent review committee; L^+, positive detection of *MET*ex14 skipping in liquid biopsy sample; T^+, positive detection of *MET*ex14 skipping in tissue biopsy sample.

ticularly in treatment-naive patients. This analysis of results from the VISION trial supports global approvals of tepotinib, enabling clinicians to implement this therapeutic approach for patients with *MET*ex14-skipping NSCLC.

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Correction: This article was corrected on July 20, 2023, to fix errors in the conflicts of interest section and to update some of the authors affiliations. In addition, there was 1 mark missing in the L-positive section of Figure 2, panel B.

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responsibility for the integrity of the data and the accuracy of the data analysis.
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