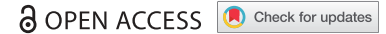


CLINICAL STUDY



## Comparing treatment outcomes of concurrent chemoradiotherapy with or without nimotuzumab in patients with locoregionally advanced nasopharyngeal carcinoma

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### ABSTRACT

**Purpose:** The benefits of additional use of nimotuzumab (NTZ) in the treatment of locoregionally advanced nasopharyngeal carcinoma (LA-NPC) is largely unclear. We aim to compare LA-NPC treatment outcomes in patients that received CCRT with nimotuzumab (NTZ) to patients that received CCRT only.

**Materials and Methods:** Between October 2009 and January 2012, 31 previously untreated and newly diagnosed LA-NPC patients were administered CCRT (3 cycles of 100 mg/m<sup>2</sup> cisplatin every third week with intensity-modulated radiotherapy) plus NTZ according to an IRB-approved institutional research protocol. A well-balanced cohort of 62 patients who received CCRT alone was created by matching each patient who received CCRT plus NTZ via propensity-matched analysis in a 2:1 ratio.

**Results:** Compared with CCRT only, CCRT plus NTZ was significantly associated with superior overall survival (5-year OS; 96.8% vs. 82.3%;  $P = 0.001$ ), superior distant metastasis-free survival (5-year DMFS; 90.3% vs. 80.6%,  $P = 0.012$ ) and superior progression-free survival (5-year PFS; 83.9% vs. 71.0%,  $P = 0.006$ ). In multivariate analysis, the inclusion of NTZ to CCRT was confirmed to be a favorable factor for OS (HR, 0.31; 95% CI, 0.02–0.71;  $P = 0.027$ ), DMFS (HR, 0.45; 95% CI, 0.13–0.77;  $P = 0.034$ ), and PFS (HR, 0.38; 95% CI, 0.11–0.89;  $P = 0.041$ ). In addition, no significant differences in hematology parameters, dermatitis, nausea, vomiting, xerostomia, nephrotoxicity or neurotoxicity were found between the two arms (all  $P > 0.05$ ).

**Conclusion:** The inclusion of NTZ to CCRT is more effective for long-term survival among LA-NPC patients than CCRT only.

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### Introduction

Nasopharyngeal carcinoma (NPC) is a relatively rare head and neck tumor in North America and Europe,<sup>1</sup> however, endemic in southern China.<sup>2</sup> Prior studies reported that<sup>3</sup> up to 70% of NPC patients are diagnosed with locoregionally advanced (Stage III-IVB) NPC at presentation. Based on guidelines set by the National Comprehensive Cancer Network (NCCN), treatment standards for locoregionally advanced NPC (LA-NPC) is concurrent chemoradiotherapy (CCRT).<sup>4</sup> However, for approximately thirty percent of NPC patients, this therapy can be ineffective, as majority of these failures in treatment are because of distant metastasis.<sup>5,6</sup> Thus, novel treatment strategies are needed for further improvement in outcomes of patients with LA-NPC.

In most human epithelial carcinomas, epidermal growth factor receptor (EGFR) is greatly expressed, and has shown to correlate with poor prognosis.<sup>7,8</sup> Moreover, previous studies have reported that EGFR is overexpressed in 80% of

NPC patients,<sup>9</sup> and has potential promise for new therapeutic target in NPC patients. Ideally, addition of EGFR-targeting antibody to the standard CCRT regimen could improve the outcomes of patients with NPC. However, the RTOG 0522 study<sup>10</sup> showed the combination of cetuximab (the first EGFR-targeting antibody to be approved by United States Food and Drug Administration) with CCRT cannot be recommended for head and neck carcinoma (not included NPC), as this regimen increased acute toxicities without improving survival outcomes. Nimotuzumab (NTZ) is another EGFR-targeting antibody that does not exert intrinsic stimulating activity.<sup>11</sup> A phase II trial found the addition of NTZ to CCRT was associated with encouraging survival outcomes in LA-NPC, though only 23 patients were enrolled to be administered CCRT and NTZ, with a follow-up median of 24.1 months.<sup>12</sup> Considering the absence of randomized controlled trial to determine the efficacy of CCRT plus NTZ vs. CCRT alone in patients with LA-NPC, it remains under

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debate if patients with LA-NPC benefit from the addition of NTZ for the recommended standard treatment of CCRT.

To address this knowledge gap, we reviewed data on 93 patients with LA-NPC who received the standard CCRT regimen with or without NTZ to provide additional information on the benefit of NTZ in the treatment of LA-NPC.

## Materials and methods

### Patients

Between October 2009 and January 2012, patients with histologically-confirmed NPC treated at Sun Yat-sen University Cancer Center were retrospectively reviewed. All included patients had to meet the following inclusion criteria: (1) disease classified as stage III-IVB in accordance to the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system (7th edition, 2009); (2) histologically confirmed NPC; (3) patient received the standard CCRT regimen with or without NTZ; (4) radiation delivery technique was intensity-modulated radiotherapy (IMRT); (5) molecularly-targeted drug was NTZ.

### Treatment

IMRT treatment details have been previously reported.<sup>13</sup> Target volumes were delineated according to a previously described treatment protocol by our institution,<sup>12</sup> in agreement with International Commission on Radiation Units (ICRU) and Measurements reports 62<sup>14</sup> and 83.<sup>15</sup> The prescribed radiation dose was defined as follows: a total dose of 68–70 Gy at 2.12–2.27 Gy/fraction to the planning target volume (PTV) of the GTV-P (primary gross tumor volume), 60 Gy to the PTV of CTV-1 (high-risk regions) and 54 Gy to the PTV of CTV-2 (low-risk regions). All patients were treated with one fraction daily, five days per week. Concomitant chemotherapy consisted of cisplatin (100 mg/m<sup>2</sup>) every three weeks, or cisplatin (40 mg/m<sup>2</sup>) weekly. Reasons for non-compliance included refusal by individual patients, age, or organ dysfunction suggestive of intolerance. NTZ was administered concomitantly with IMRT at a dose of 200 mg weekly, commencing on the first day of radiotherapy. NTZ was diluted in 250 mL saline and intravenously infused over 1 h.

### Ethical statement

This study was approved by our institutional review board (IRB-approved number, YB2017-040). As this was a retrospective analysis of routine clinical data, a waiver of the requirement for individual informed consent was granted by the institutional ethics committee.

### Follow-up

During treatment, evaluation of patients occurred at least one time a week. After treatment, patients were evaluated every third month during the first three years, every six months the

following two years, and every year afterward. During this period, for each follow-up visit, patients underwent a sequence of conventional examinations to detect potential relapse or distant metastasis. Biopsy, MRI (magnetic resonance imaging), or both was used to confirm local relapse. Clinical examination and MRI of the neck was used to diagnosis regional relapse, and in doubtful cases, by fine needle aspiration of lymph nodes. To diagnosis distant metastasis, physical examinations, clinical symptoms, and imaging methods with bone scan, chest radiography, abdominal sonography, and MRI was used. Further investigations were arranged if indicated.

### Statistical analysis

We used propensity score matching method to select patients treated with CCRT plus NTZ to match with CCRT treatment only.<sup>16</sup> According to presumed covariates, including age, Karnofsky score, pathology, total radiation dose, sex, chemotherapy, T category, N category and clinical stage, logistic regression was computed for each patient for propensity scores. At a 1:2 ratio, we matched patients without replacement using these scores, instead of by individual covariates.

Using  $\chi^2$  test, the balance of covariates between both study arms were examined. Kaplan-Meier method was used to estimate overall survival (OS), distant metastasis-free survival (DMFS), progression-free survival (PFS), locoregional relapse-free survival (LRRFS).<sup>17</sup> Cox regression analysis was used to calculate both crude and adjusted hazard ratios with 95% confidence intervals (for CCRT plus NTZ, using CCRT as the reference).<sup>18</sup> All test were two-tailed and P values < 0.05 were deemed statistically significant. We performed all analyses using R 3.1.2 software (Vienna, Austria; <https://mirrors.tuna.singhua.edu.cn/CRAN/>).

## Results

### Patient characteristics

31 patients treated with CCRT plus NTZ and 62 patients treated with CCRT only remained in the current analysis after propensity score matching. The follow-up median was 59.2 months (49.5–72.4 months) for the CCRT plus NTZ arm and 57.4 months (6.5–69.4 months) for the CCRT only arm. In the CCRT plus NTZ arm, 3 (9.7%) patients suffered distant metastasis, and 4 patients (12.9%) developed locoregional recurrence. In the CCRT only arm, 13 (21.0%) patients suffered distant metastasis, and 7 patients (11.3%) developed locoregional recurrence. Interestingly, only 33% (2/6) patients suffered disease progression within 3 years after radical RT in the CCRT plus NTZ arm. In contrast, up to 90% (16/18) patients suffered disease progression within 3 years after radical RT the CCRT only arm. **Table 1** presents the characteristics at baseline for the two study arms. We did not observe a significant difference in respect to age, pathology, sex, Karnofsky score, total radiation dose, radiotherapy treatment time, chemotherapy, T category, N category and overall stage. Subsequent analyses reported derived from propensity-matched cohort.

**Table 1.** Patient and tumor characteristics.

Characteristics	CCRT+ nimotuzumab (N = 31)		CCRT alone (N = 62)		P-value*
	No.	%	No.	%	
Age					NS
Median	43		43		
SD	9.67		10.12		
Sex					NS
Male	24	77.4	49	79.0	
Female	7	22.6	13	21.0	
WHO pathology					NS
II	1	3.2	3	4.8	
III	30	96.8	59	95.2	
T-stage <sup>§</sup>					NS
T1	2	6.5	4	6.5	
T2	1	3.2	2	3.2	
T3	21	67.7	42	67.7	
T4	7	22.6	14	22.6	
N-stage <sup>§</sup>					NS
N0	1	3.2	2	3.2	
N1	19	61.3	38	61.3	
N2	6	19.4	12	19.4	
N3	5	16.1	10	16.1	
Clinical stage <sup>§</sup>					NS
III	19	61.3	38	61.3	
IVA	7	22.6	14	22.6	
IVB	5	16.1	10	16.1	
Total radiation dose (Gy)					NS
Median	70	-	70	-	
SD	1.76	-	2.24	-	
RTT (days)					NS
Median	43	-	43	-	
Range	39–52	-	36–66	-	
Karnofsky scale					NS
≥ 90	24	77.4	46	74.2	
70–80	7	22.6	16	25.8	
Regimen for CRT					NS
Qw	10	32.3	20	32.3	
Q3w	21	67.7	42	67.7	

**Abbreviations:** WHO, World Health Organization; CCRT, Concurrent chemoradiotherapy; CRT, Concurrent chemotherapy; NS, not significant. RTT, Radiotherapy treatment time.

\* CCRT plus nimotuzumab vs. CCRT; chi-square or Fisher's exact tests.

<sup>§</sup> The 7th American Joint Commission on Cancer staging system.

### Treatment and compliance

All patients completed the full course of radiotherapy. In the CCRT plus NTZ arm, 2/31 patients (6.5%) completed four cycles of NTZ, 5 (16.1%) completed five cycles, 21 (67.7%) completed six cycles, and 3 (9.7%) completed seven cycles. 21 of the 31 patients (67.7%) received two or three cycles of 100 mg/m<sup>2</sup> cisplatin each third week, and 10 (32.3%) received 40 mg/m<sup>2</sup> cisplatin weekly for 5–7 planned cycles. Median administered total dose of cisplatin during radiotherapy was 240 mg/m<sup>2</sup> (IQR 200–280 mg/m<sup>2</sup>) in the CCRT plus NTZ arm. As shown in Table 1, propensity score matching ensured the chemotherapy regimens and cycles of the CCRT only arm were well-matched with those of the CCRT plus NTZ arm.

### Survival outcomes and multivariate analysis

The differences in efficacy between these two arms are presented in Figure 1. The 5-year OS was significantly higher for CCRT plus NTZ than those treated with CCRT only (96.8% vs. 82.3%;  $P = 0.001$ ; Figure 1A). The 5-year DMFS was significantly superior in CCRT plus NTZ treated patients than those treated with CCRT only (90.3% vs.

80.6%;  $P = 0.012$ ; Figure 1B). Similarly, the 5-year PFS was significantly higher in CCRT plus NTZ treated patients than those treated with CCRT only (83.9% vs. 71.0%;  $P = 0.006$ ; Figure 1C). There were trends towards improved LRRFS for the addition of NTZ over CRRT only, though no associated difference in LRRFS was observed between both arms (90.3% vs. 88.7%;  $P = 0.234$ ; Figure 1D). Consistent with univariate analysis, multivariate analysis showed that adding NTZ to CCRT was a favorable prognostic factor for OS ([hazard ratio (HR), 0.31; 95% confidence interval (CI), 0.02–0.71;  $P = 0.027$ ), DMFS (HR, 0.45; 95% CI, 0.13–0.77;  $P = 0.034$ ), and PFS (HR, 0.38; 95% CI, 0.11–0.89;  $P = 0.041$ ) (Table 2).

### Acute toxicities

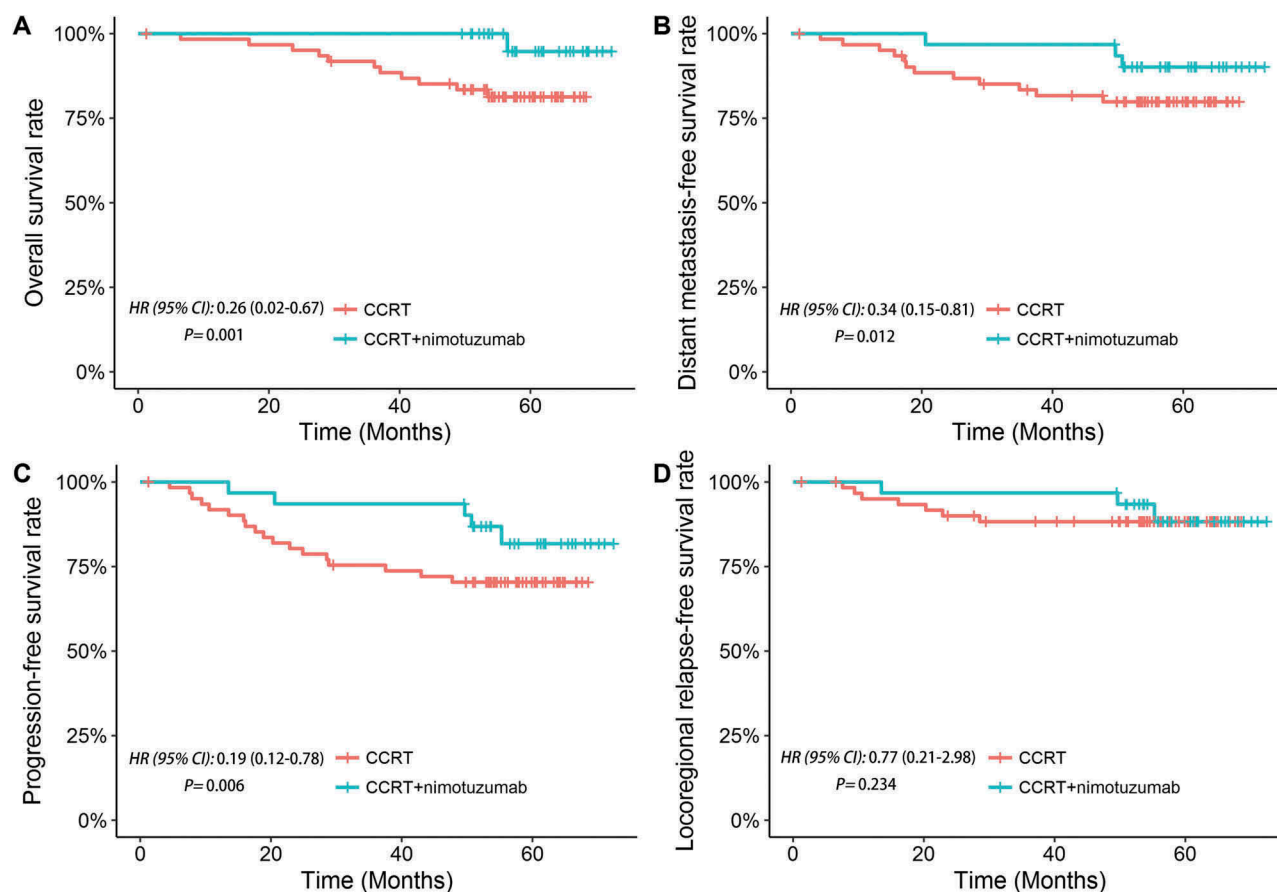
Table 3 displays the treatment toxicities of each arm. The most frequently observed toxicity was oral mucositis. The rates of grade 3–4 mucositis was 25.8% in CCRT plus NTZ group, and 19.4% in CCRT only group ( $P = 0.59$ ). No significant differences in hematology parameters, dermatitis, nausea, vomiting, xerostomia, nephrotoxicity or neurotoxicity were found between the two arms (all  $P > 0.05$ ). Overall, treatment toxicities during radiotherapy were well-tolerated, and no treatment-related deaths occurred in either arm.

### Discussion

This is the first assessment of the clinical outcomes of LA-NPC treated patients with standard CCRT regimen plus NTZ in comparison to CCRT treated patients only. To balance the baseline characteristics of the two arms, a propensity score-matched method was applied. In comparison to CCRT treated patients only, CCRT plus NTZ was statistically associated with superior OS, DMFS, and PFS. Strikingly, NTZ addition to the standard CCRT regimen did not increase acute toxicities.

EGFR has a major part in tumorigenesis and survival of cancer cells. Several studies<sup>9,19,20</sup> have demonstrated high EGFR expression is associated with an increased treatment resistance, elevated aggressive phenotype, and poorer prognosis in NPC. EGFR-blocking monoclonal antibodies may potentially exert encouraging effects in LA-NPC. Liu et al.<sup>21</sup> examined 42 cases of LA-NPC treated with NTZ plus CCRT. The follow-up median was twenty-five months (ranging 7–44 months), where only two patients had died by last follow-up. Recently, a preliminary clinical trial<sup>11</sup> of 23 patients with LA-NPC treated with CCRT plus NTZ reported an estimated 2-year OS rate of up to 95.0%. Consistent with these studies, we also found adding NTZ to CCRT resulted in encouraging survival outcomes in LA-NPC. Moreover, compared to CCRT only, including NTZ to CCRT was significantly associated with improved survival. This information suggest that combined NTZ with CCRT could maximize survival in LA-NPC patients compared to patients taking CCRT only.

Previous literature reported 90% control rates for NPC when using IMRT in combination with systematic



**Figure 1.** Kaplan-Meier curves of (A) overall survival, (B) distant metastasis-free survival, (C) progression-free survival and (D) locoregional relapse-free survival curves for the CCRT plus nimotuzumab arm versus CCRT arm.

Abbreviation: CCRT, concurrent chemoradiotherapy; HR, hazard ratio; CI, confidence interval.

chemotherapy even in patients presenting with LA-NPC.<sup>22,23</sup> As a result of recent advances in IMRT, there was no observed significant difference in 5-year LRRFS (90.3% vs. 88.7%,  $P = 0.704$ ) between the two arms. This seems reasonable, as IMRT provides excellent locoregional control,<sup>24,25</sup> and concurrent chemotherapy has been confirmed to improve locoregional control.<sup>26,27</sup> Collectively, these effects would limit the actual benefit of NTZ on LRRFS.

In the current study, the rate of grade 3–4 mucositis was comparable between patients receiving CCRT plus NTZ (25.8%) and patients receiving CCRT only (19.4%). A recent retrospective analysis by Liu and colleagues<sup>21</sup> also concluded NTZ could be safely combined with CCRT for treatment of LA-NPC. However, Huang et al.<sup>12</sup> reported 34.8% of patients receiving CCRT plus NTZ experienced grade 3 to 4 mucositis. These inconsistencies could be due to obvious differences between chemotherapy regimens, where only patients receiving concurrent chemotherapy consisting of cisplatin (100 mg/m<sup>2</sup>) every three weeks or cisplatin (40 mg/m<sup>2</sup>) weekly were eligible for the current study. However, the study by Huang et al.<sup>12</sup> included patients who received more intensive concurrent chemotherapy regimens (75 mg/m<sup>2</sup> docetaxel and 80 mg/m<sup>2</sup> nedaplatin), which may have increased the incidence of mucositis during radiotherapy.

Nonetheless, we must note inherent limitations in the present study. First, this was a single-center observational study, and the number of patients who received CCRT plus NTZ was relatively low. We expect promising results will soon be available from the phase III clinical trial of NTZ in combination with chemoradiation for LA-NPC, even though this study is ongoing but not recruiting participants (ClinicalTrials.gov: NCT01074021). Second, we failed to incorporate data on plasma Epstein–Barr Virus (EBV) DNA, where prior studies demonstrated strong prediction for NPC survival.<sup>28,29</sup> Further studies are urgently required to identify the individual patients who may benefit most from CCRT plus NTZ based on other biomarkers such as plasma EBV DNA, EGFR status or *K-ras* (kirsten rat sarcoma) gene levels before treatment, especially as NTZ is more expensive than conventional treatment.

In summary, including NTZ in addition to standard CCRT regimen is more effective for extending survival in LA-NPC patients in comparison to CCRT only. Additionally, CCRT plus NTZ was well-tolerated and did not increase acute toxicities. However, a prospective randomized clinical trial is required to validate the superiority of CCRT plus NTZ compared to CCRT only in LA-NPC.

**Table 2.** Multivariate analysis of treatment regimen status and other prognostic factors for treatment outcomes.

Endpoint	HR	95% CI	P-value
<b>Overall survival</b>			
Treatment regimen	Reference		
CCRT alone	Reference		
CCRT plus NTZ	0.31	0.02–0.71	0.027
N stage			
N0-1	Reference		
N2-3	1.74	1.12–8.92	0.041
Disease stage			
III	Reference		
IVA-B	1.21	0.89–9.32	0.063
<b>Distant metastasis-free survival</b>			
Treatment regimen	Reference		
CCRT alone	Reference		
CCRT plus NTZ	0.45	0.13–0.77	0.034
N stage			
N0-1	Reference		
N2-3	3.03	1.67–10.4	0.001
Disease stage			
III	Reference		
IVA-B	1.43	0.67–8.21	0.113
<b>Progression-free survival</b>			
Treatment regimen	Reference		
CCRT alone	Reference		
CCRT plus NTZ	0.38	0.11–0.89	0.041
N stage			
N0-1	Reference		
N2-3	2.12	0.91–6.97	0.083
Disease stage			
III	Reference		
IVA-B	2.28	1.35–7.54	0.012
<b>Locoregional relapse-free survival</b>			
Treatment regimen	Reference		
CCRT alone	NS	NS	NS
CCRT plus NTZ	NS	NS	NS

**Abbreviations:** OS, overall survival; DMFS, distant metastasis-free survival; PFS, progression-free survival; LRRFS, locoregional relapse-free survival; NS, not significant.

**Table 3.** Grade 3–4 adverse events during radiotherapy.

Characteristics	CCRT plus nimotuzumab	CCRT alone	P-value*
Number treated with CCRT	31	62	
<b>Haematological</b>			
Anaemia	0 (0%)	1 (1.6%)	NS
Thrombocytopenia	2 (6.4%)	3 (4.7%)	NS
Neutropenia	3 (9.7%)	7 (11.3%)	0.71
Leucopenia	4 (12.9%)	11 (17.7%)	0.77
<b>Non-haematological</b>			
Dermatitis	4 (12.9%)	7 (11.3%)	NS
Stomatitis (mucositis)	8 (25.8%)	12 (19.4%)	0.59
Nausea	4 (12.9%)	10 (16.1%)	0.77
Vomiting	3 (9.7%)	7 (11.3%)	NS
Xerostomia	1 (3.1%)	4 (6.5%)	0.66
Nephrotoxicity	0 (0%)	0 (0%)	NS
Neurotoxicity	0 (0%)	1 (1.6%)	NS

\*p values were calculated with the  $\chi^2$  test.

## Abbreviations

Nasopharyngeal carcinoma  
National Comprehensive Cancer Network  
locoregionally advanced NPC  
concurrent chemoradiotherapy  
epidermal growth factor receptor  
nimotuzumab  
American Joint Committee on Cancer  
progression-free survival  
locoregional relapse-free survival  
overall survival  
distant metastasis-free survival

NPC  
NCCN  
LA-NPC  
CCRT  
EGFR  
NTZ  
AJCC  
PFS  
LRRFS  
OS  
DMFS.

## Conflict of Interest

Conflict of interest relevant to this article was not reported.

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