original reports

Low-Dose Immunotherapy in Head and Neck Cancer: A Randomized Study

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abstract

PURPOSE The regimens approved for the treatment of advanced head and neck squamous cell carcinoma are accessible to only 1%-3% of patients in low- and middle-income countries because of their cost. In our previous study, metronomic chemotherapy improved survival in this setting. Retrospective data suggest that a low dose of nivolumab may be efficacious. Hence, we aimed to assess whether the addition of low-dose nivolumab to triple metronomic chemotherapy (TMC) improved overall survival (OS).

METHODS This was a randomized phase III superiority study. Adult patients with recurrent or newly diagnosed advanced head and neck squamous cell carcinoma being treated with palliative intent with an Eastern Cooperative Oncology Group performance status of 0-1 were eligible. Patients were randomly assigned 1:1 to TMC consisting of oral methotrexate 9 mg/m^2 once a week, celecoxib 200 mg twice daily, and erlotinib 150 mg once daily, or TMC with intravenous nivolumab (TMC-I) 20 mg flat dose once every 3 weeks. The primary end point was 1-year OS.

RESULTS One hundred fifty-one patients were randomly assigned, 75 in TMC and 76 in the TMC-I arm. The addition of low-dose nivolumab led to an improvement in the 1-year OS from 16.3% (95% CI, 8.0 to 27.4) to 43.4% (95% CI, 30.8 to 55.3; hazard ratio, 0.545; 95% CI, 0.362 to 0.820; $P = .0036$). The median OS in TMC and TMC-I arms was 6.7 months (95% CI, 5.8 to 8.1) and 10.1 months (95% CI, 7.4 to 12.6), respectively ($P = .0052$). The rate of grade 3 and above adverse events was 50% and 46.1% in TMC and TMC-I arms, respectively ($P = .744$).

CONCLUSION To our knowledge, this is the first-ever randomized study to demonstrate that the addition of low-dose nivolumab to metronomic chemotherapy improved OS and is an alternative standard of care for those who cannot access full-dose checkpoint inhibitors.

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BACKGROUND

Palliative systemic therapy has improved survival in head and neck squamous cell carcinoma (HNSCC); however, the results are still unsatisfactory.[1-3] The KEYNOTE 048 or the EXTREME regimen in the first-line setting[1,2] and the use of nivolumab or pembrolizumab in the platinum-refractory setting[4,5] are the recommended category 1 regimens by National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines.[6,7] However, the access to these regimens across the globe is limited to < 5 per cent.[8-10] Hence, we had developed a metronomic regimen of low-dose methotrexate and celecoxib. This regimen in a phase III randomized study had shown an improvement in overall survival (OS; unadjusted hazard ratio [HR] for death 0.773; 95% CI, 0.615 to 0·970; $P = .026$) over single-agent cisplatin.[3] It is a recommended regimen in multiple guidelines for patients who do not have access to the NCCN category 1 regimens.[11-13] In addition, the outcomes with the double metronomic regimen were further improved with the addition of erlotinib and optimization of the dose of methotrexate. This regimen in a platinum-refractory setting has a response rate of 42.9% (95% CI, 33.2 to 53.1) and improved outcomes over historical controls.[14] However, despite the impressive response rate, the duration of response is short-lived with metronomic regimens.

The immune checkpoint inhibitor nivolumab has a response rate of 13.3% (95% CI, 9.3 to 18.3) in platinum-refractory settings, but the duration of response is sustained, leading to a median progression-free survival (PFS) and OS of 2.0 (95% CI, 1.9 to 3.1) and 7.5 (95% CI, 5.5 to 9.1) months, respectively.[5] The nivolumab dose used in this study was 3 mg/kg once every 2 weeks, and its primary target was the T cell.[5] Around 20%-40% of peripheral blood T cells express programmed death 1 (PD-1) receptor, and

ASSOCIATED CONTENT

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Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Programmed death 1/programmed death-ligand 1 immune checkpoint inhibitors are accessible in low- and middle-income countries to only 1%-3% of patients with recurrent or metastatic head and neck squamous cell carcinoma. Retrospective data suggest that a low dose of nivolumab may be beneficial. Hence, a randomized clinical trial was performed to investigate whether the addition of low-dose nivolumab to palliative metronomic chemotherapy improves overall survival in this patient population.

Knowledge Generated

Relative to metronomic chemotherapy alone, the addition of low-dose nivolumab led to improvements in overall survival, progression-free survival, response rate, and certain domains of quality of life. This was achieved without an increase in the rate of adverse events.

Relevance

The combination of low-dose nivolumab and metronomic chemotherapy improves outcomes and is an alternative standard of care for those who cannot access full-dose programmed death 1/programmed death-ligand 1 checkpoint inhibitors.

70%-75% of these receptors are required to be occupied for its activation. Nivolumab is an anti–PD-1 monoclonal antibody, 70% of PD-1 receptor occupancy is achieved by nivolumab at a dose of 0.3 mg/kg (single dose), and hence, there is a theoretical possibility of benefit with this dose.[15-17] There are multiple retrospective analyses across different cancer sites, including ours, in HNSCC, suggesting that nivolumab might be effective in low doses.[18-21] The full dose of nivolumab is financially inaccessible to our population. We aimed to assess whether the addition of low-dose nivolumab to metronomic chemotherapy would improve the outcomes in a phase III randomized study. The primary objective of this study was to compare the OS between the two arms.

METHODS

Trial Design and Conduct

The study Protocol (online only) was approved by the institutional ethics committee. The study was prospectively registered with the Clinical Trials Registry of India (CTRI/2020/11/028953). All patients provided written informed consent before participating in the study. The study was conducted in accordance with the principles laid down by the declaration of Helsinki and the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines. The study was monitored by an institutional independent data monitoring and safety board.

Participants

Adults with HNSCC, with an Eastern Cooperative Oncology Group performance status of 0-1, who were planned for palliative systemic therapy, with normal organ function and at least one measurable lesion, were included in the study. Pregnant and lactating females, patients on any other investigational agent(s), with autoimmune disease, receiving immunosuppressants, and those with uncontrolled comorbidities were excluded. The detailed inclusion and exclusion criteria are provided in the Data Supplement (online only).

Interventions

A detailed history and clinical examination was performed on all patients. Blood investigations including a complete hemogram, renal function, liver function, and thyroid-stimulating hormone levels were performed at baseline. Axial imaging with either contrast-enhanced computed tomography or magnetic resonance imaging was performed.

Stratified random assignment with a block size of four was performed. The patient characteristics were communicated via e-mail, and 1:1 random assignment was performed. The following stratification factors were included: site (oral *v* nonoral), previous chemotherapy (yes *v* no), and time to treatment failure (0-6 months *v* 6-12 months *v* > 12 months or treatment-naive).

Patients allotted to the standard arm received triple metronomic chemotherapy (TMC arm). TMC consisted of capsule celecoxib 200 mg twice daily, weekly methotrexate 9 mg/m^2 once a week, and erlotinib 150 mg once daily, all administered orally. In the experimental arm, patients received TMC as above with the addition of intravenous nivolumab 20 mg (TMC-I arm) administered in 100 mL normal saline over 60 minutes once every 3 weeks. A 21-day period was considered a cycle. Patients continued on the respective arms until the development of intolerable side effects or progression, whichever was earlier. They underwent axial imaging every 2 months. Quality-of-life (QOL) assessments were performed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 version 3.0 and Head and Neck 35 at baseline and at two monthly intervals for the first 6 months. Adverse events were assessed at each visit in accordance with Common Terminology Criteria for Adverse Events version 4.03. The detailed dose modifications,

assessments, and criteria for discontinuation are provided in the study Protocol. Postprogression treatment was at the discretion of the treating physician.

End Points

The primary end point of the study was OS. OS was defined as the time from the date of random assignment until death. Patients who were alive were censored at the time that they were last known to be alive. The PFS was calculated from the date of random assignment to the date of progression or death, whichever was earlier. Time to deterioration (TTD) in QOL for each domain was defined as time duration in days from the date of random assignment to the first occurrence of deterioration in the respective QOL domain by 10 points or more or death, whichever occurred earlier. The response rate was calculated as a percentage of patients having a complete response and partial response as the best response, which was assessed in accordance with RECIST version 1.1 criteria. Duration of response was assessed post hoc, and it was defined as the duration in months from the first occurrence of response (complete response or partial response) until progression.

Sample Size

The sample size calculation was based on the Lachin and Foulkes method (fixed trial duration)[22] and the Kim and Tsiatis[23] method (fixed enrollment rates). It was calculated using RStudio 1.2.1335. The package used for the calculation of sample size was gsdesign version 3.0-1. Assuming a 1-year OS of 28.3% in the standard arm,[3] a superiority margin of 15%, which translated into a HR of 0.650, a type 1 error rate of 5% (one-sided), a power of 80%, an accrual duration of 3 years, a total study duration of 5 years, and 1:1 allocation using a group sequential design with one interim analysis, the calculated sample size was 184. The first analysis was to be performed after 75 events of death, and the nominal p value for stopping the study for efficacy was 0.006. The final analysis was to be

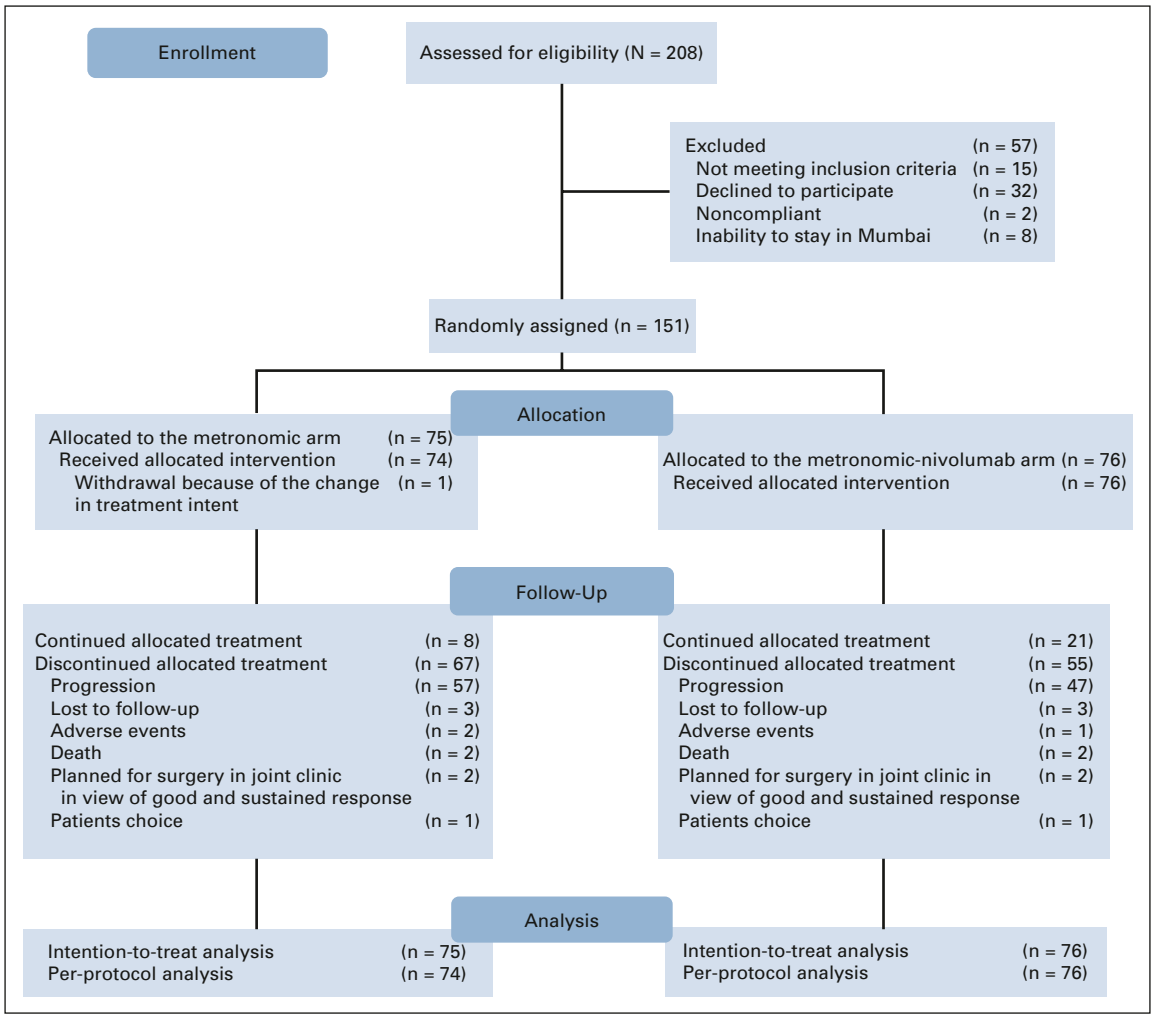

FIG 1. CONSORT diagram. All patients started allocated treatment except one patient in the TMC arm. The intent of therapy for this patient changed from palliative to curative, and the patient was withdrawn from the study and underwent surgery followed by chemoradiation. TMC, triple metronomic chemotherapy.

TABLE 1. Baseline Characteristics Between Both Arms

Variable	TMC Arm (n = 75)	TMC-I Arm (n = 76)	*P*
Age, years			.295
Median (range)	46 (28-74)	50 (28-77)	
Elderly,[a] No. (%)	11 (14.7)	17 (22.4)	
Sex, No. (%)			.009
Male	64 (85.3)	75 (97.4)	
Female	11 (14.7)	2 (2.6)	
ECOG PS, No. (%)			.327
0	6 (8.0)	3 (3.9)	
1	69 (92.0)	73 (96.1)	
Site of primary, No. (%)			.780
Nonoral	6 (8.0)	8 (10.5)	
Oral	69 (92.0)	68 (89.5)	
Tobacco use,[b] No. (%)			.970
None	6 (8.0)	6 (7.9)	
Oral	55 (73.3)	53 (69.7)	
Smoking	8 (10.7)	10 (13.2)	
Oral and smoking	6 (8.0)	7 (9.2)	
Previous treatment, No. (%)			.303
Yes	47 (62.7)	54 (71.1)	
No	28 (37.3)	22 (28.9)	
Previous local therapy, No. (%)			
Surgery	19 (25.3)	24 (31.6)	.472
Radiation	22 (29.3)	25 (32.9)	.726
Previous chemotherapy exposure, No. (%)			.769
No	35 (46.7)	30 (39.5)	
Platinum	6 (8.0)	7 (9.2)	
Taxane	—	1 (1.3)	
Taxane and platinum	34 (45.3)	38 (50)	
Time to failure, months, No. (%)			.509
< 6	44 (58.7)	50 (65.8)	
6-12	1 (1.3)	2 (2.6)	
> 12 or upfront	30 (40.0)	24 (31.6)	
Metastasis, No. (%)			.803
Yes	9 (12.0)	8 (10.5)	
No	66 (88.0)	68 (89.5)	
PD-L1 score, No. (%)			.307
Unknown	9 (12.0)	6 (7.9)	
Zero	12 (16.0)	8 (10.5)	
1-50	32 (42.7)	44 (57.9)	
> 50	22 (29.3)	18 (23.7)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1; TMC, triple metronomic chemotherapy; TMC-I, TMC with intravenous nivolumab.

[a]Elderly was defined as age 60 years or more.

[b]Two patients in each arm were continuing tobacco use.

performed after 150 deaths, and the nominal *P* value was .0481 for efficacy. Because of COVID-19–related logistic issues, the first interim analysis could only happen at 99 events of death. The corresponding nominal *P* value for stopping the study for efficacy was .0124. The study was stopped after the first analysis for efficacy.

Statistical Methods

Descriptive statistics were performed. The 95% CI was calculated according to the adjusted Wald method as suggested by Agresti-Coull. Ordinal and nominal variables were compared using Fisher's test. The reverse Kaplan-Meier method was used for the estimation of follow-up duration. The Kaplan-Meier method was used for the estimation of median values in both arms for OS, PFS, TTD, and duration of response. The Brookmeyer and Crowley method was used for the estimation of 95% CI of the median. The log-rank test was used for the comparison of OS, PFS, and TTD between both arms. The HR with its 95% CI was calculated using the COX regression analysis with Efron's method of tie handling, with the TMC arm being considered as a reference. The assumptions of the proportional hazard model were checked using Schoenfeld residuals and were met for OS and PFS analyses. Intention-to-treat analysis was performed for OS and PFS comparison, whereas the comparison of adverse events was on a per-protocol basis. Factors affecting OS and PFS were sought via a full COX regression model and a parsimonious model. The parsimonious model was developed using the fast backward step-down method proposed by Harrell.[24] The factors included in the parsimonious model were arms, time to treatment failure, site, and previous platinum exposure.

The data were censored for analysis on March 17, 2022.

RESULTS

Baseline Characteristics

Patients were recruited from January 2021 to September 2021, and the flow of the patients is shown in Figure 1. The baseline characteristics are shown in Table 1 and the Data Supplement. Forty (53.3%) patients in the TMC arm had previous chemotherapy exposure, with 33 (44.0%) having first-line exposure and seven (9.3%) having two lines of chemotherapy exposure. Forty-six (60.5%) patients in the TMC-I arm had previous chemotherapy exposure, with 36 (47.4%) having first-line exposure and 10 (13.2%) having two lines of chemotherapy exposure.

Outcomes

OS. The median follow-up was 10.9 months (95% CI, 10.6 to 12.2), and the interquartile range (IQR) was 9.1-12.7 months. There were 99 deaths, with 58 deaths in the TMC arm and 41 deaths in the TMC-I arm. The 1-year OS was 16.3% (95% CI, 8.0 to 27.4) and 43.4% (95% CI, 30.8 to 55.3) in the TMC and TMC-I arms, respectively (HR, 0.545; 95% CI, 0.362 to 0.820; $P = .0036$). The median OS in

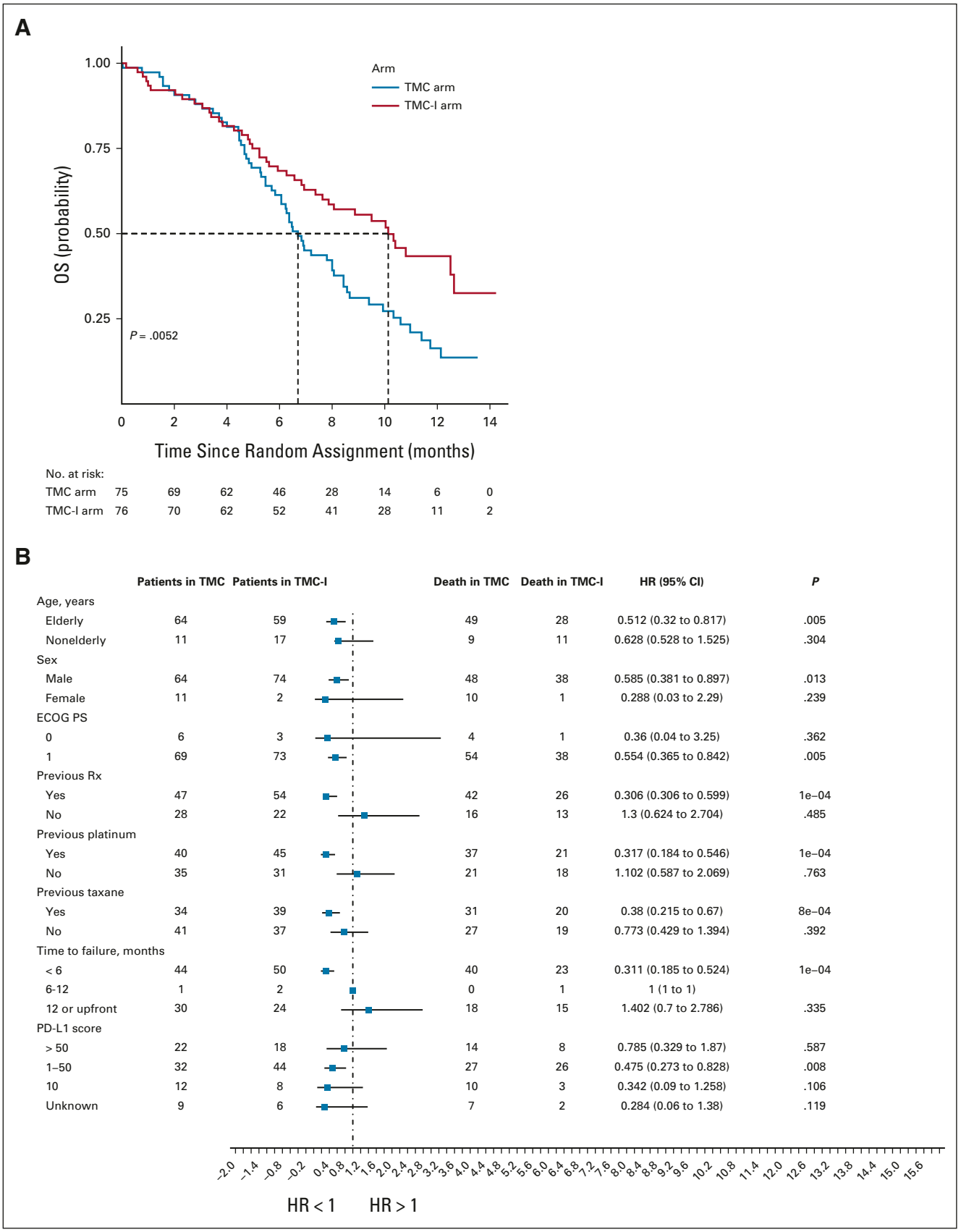

FIG 2. (A) OS graph. The *P* value shown is from the log-rank test. (B) Impact of addition of low-dose nivolumab across different groups. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1; Rx, treatment; TMC, triple metronomic chemotherapy; TMC-I, TMC with intravenous nivolumab.

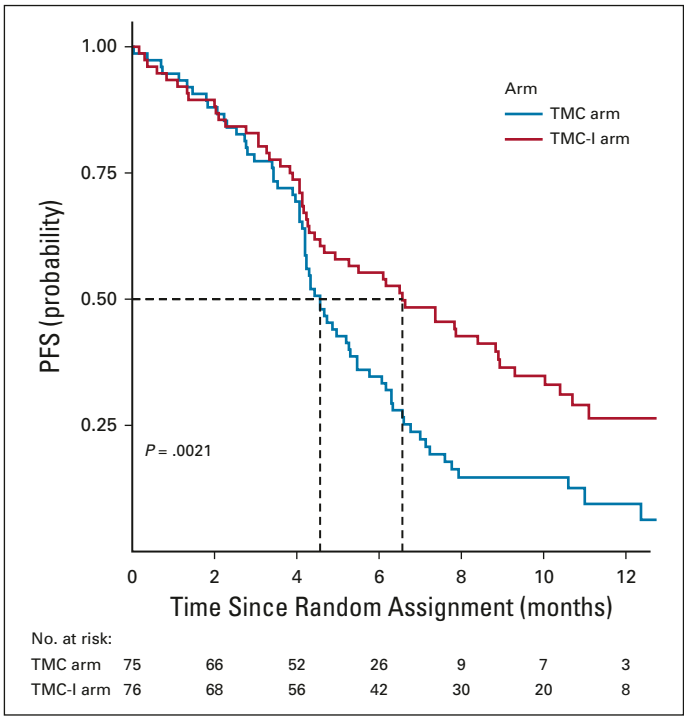

FIG 3. PFS graph. The *P* value shown is from the log-rank test. PFS, progression-free survival; TMC, triple metronomic chemotherapy; TMC-I, TMC with intravenous nivolumab.

TMC and TMC-I arms was 6.7 months (95% CI, 5.8 to 8.1) and 10.1 months (95% CI, 7.4 to 12.6), respectively ($P = .0052$; Fig 2). The causes of death between the two arms are given in the Data Supplement. The OS benefit of low-dose nivolumab across all subgroups of interest is shown in the Data Supplement. As a part of sensitivity analysis, the stratified log-rank test and Cox regression modeling were performed and the corresponding *P* values were .008 and .002, respectively. Multivariate analysis for OS is shown in the Data Supplement, and the adjusted HR in favor of the TMC-I arm was 0.486 (95% CI, 0.311 to 0.758; $P = .001$).

PFS. At the time of data censoring, there were 66 events in the TMC arm and 52 in the TMC-I arm for PFS. The median PFS in the TMC and the TMC-I arms was 4.6 months (95% CI, 4.2 to 5.3) and 6.6 months (95% CI, 4.4 to 8.9), respectively ($P = .002$; Fig 3). The addition of low-dose nivolumab to TMC decreased the hazard of progression to 0.564 (95% CI, 0.389 to 0.816; $P = .002$). As a part of sensitivity analysis, the stratified log-rank test and Cox regression modeling were performed and the corresponding *P* values were .003 and .002, respectively. Multivariate analysis for PFS is shown in the Data Supplement, and the adjusted HR in favor of the TMC-I arm was 0.486 (95% CI, 0.311 to 0.758; $P = .001$).

Progression as an event before death was seen in 61 patients (81.3%) in the TMC arm and in 46 patients (60.5%) in the TMC-I arm. The sites of the first progression in the TMC arm were locoregional, distant, or both in 50 (66.7%), three (4.0%), and eight (10.7%), respectively, whereas the corresponding figures in the TMC-I arm were locoregional, distant, or both in 39 (51.3%), three (3.9%), and four (5.3%), respectively. Treatment received post-progression is shown in the Data Supplement.

Any systemic therapy was received by 46 patients (61.3%) in the TMC arm and 28 (36.8%) in the TMC-I arm. Prior radiation therapy was received by four patients (5.3%) in the TMC arm and two patients (2.6%) in the TMC-I arm. Prior surgery was received by two patients (2.7%) in the TMC arm and one patient (1.3%) in the TMC-I arm.

Response. Response rates in TMC and TMC-I arms were 45.3% (95% CI, 34.6 to 56.6 [34, n = 75]) and 59.2% (95% CI, 48.0 to 69.5 [45, n = 76]), respectively ($P = .104$). The details of the response and the waterfall plot are given in the Data Supplement. The response in both arms according to PD-L1 expression is shown in the Data Supplement. The median time to attain the best response was 2.1 (IQR, 2.0-4.1) months and 2.4 (IQR, 2.1-5.6) months in TMC and TMC-I arms, respectively ($P = .015$; Data Supplement). The median duration of response was 3.3 (95% CI, 2.5 to 5.2) versus 8.7 (5.8 to NA) in TMC and TMC-I arms, respectively ($P = .003$, Data Supplement). Among patients in the TMC-I arm, the median duration of response was not reached (95% CI, 4.2 to NA) in patients with the PD-L1 score > 50% as opposed to it being 8.1 months (95% CI, 4.5 to 9.0) in patients with the PD-L1 score below 50% or unknown ($P = .045$; Data Supplement). The response in accordance with the previous treatment is shown in the Data Supplement.

Adverse Event

The adverse event analysis was performed per protocol, and the details are provided in Table 2. The rate of grade 3 and above adverse events was 50% (37, n = 74) and 46.1% (35, n = 76) in TMC and TMC-I arms, respectively. COVID-19 disease occurred in one patient (1.4%) in the TMC arm, and four patients (5.3%) in the TMC-I arm ($P = .367$). Two deaths were seen in the TMC-I arm during treatment. One patient developed aspiration pneumonia, whereas the other had a reactivation of Hepatitis B and developed the hepatorenal syndrome.

Compliance

Follow-up details of treatment in both arms are given in Figure 1. Dose reduction was required in six patients (8.0%) in the TMC arm and five patients (6.6%) in the TMC-I arm ($P = .765$). Erlotinib dose reduction was required in five patients (6.7%) in the TMC arm versus four patients (5.3%) in the TMC-I arm ($P = .745$), and methotrexate dose reduction was required in one patient each, in both arms ($P = 1$; Data Supplement). The median number of cycles in the TMC arm was seven (IQR, 4-10), whereas that in the TMC-I arm was eight (IQR, 5-13).

TABLE 2. Adverse Events in Both Arms as per per-Protocol Analysis

	TMC Arm (n = 74), No. (%)		TMC-I Arm (n = 76), No. (%)		*P*	
Variable	**Any Grade**	**Grade 3-5**	**Any Grade**	**Grade 3-5**	**Any Grade**	**Grade 3-5**
Any adverse events	74 (100)	37 (50.0)	76 (100)	35 (46.1)	1.000	0.744
Anemia	59 (79.7)	8 (10.8)	68 (89.5)	13 (17.1)	.116	0.348
Neutropenia	12 (16.2)	3 (4.1)	13 (17.1)	5 (6.6)	1.000	0.719
Thrombocytopenia	15 (20.3)	3 (4.1)	23 (30.3)	4 (5.3)	.190	1.000
SGOT rise	30 (40.5)	—	31 (40.8)	—	1.000	—
SGPT rise	37 (50.0)	3 (4.1)	40 (52.6)	2 (2.6)	.870	0.679
Bilirubin rise	37 (50.0)	—	32 (42.1)	3 (3.9)	.413	0.245
Creatinine rise	7 (9.5)	2 (2.7)	13 (17.1)	1 (1.3)	.230	0.617
Hyponatremia	62 (83.8)	20 (27.0)	71 (93.4)	23 (30.3)	.075	0.720
Hypernatremia	1 (1.4)	—	—	—	.493	—
Hypokalemia	9 (12.2)	2 (2.7)	3 (3.9)	—	.076	0.242
Hyperkalemia	10 (13.5)	—	18 (23.7)	2 (2.6)	.143	0.497
Hypothyroidism	4 (5.4)	—	5 (6.6)	—	1.000	—
Fatigue	74 (100)	5 (6.8)	75 (98.7)	7 (9.2)	1.000	0.765
Fever	2 (2.7)	—	1 (1.3)	—	.617	—
Diarrhea	50 (67.6)	1 (1.4)	49 (64.5)	1 (1.3)	.732	1.000
Rash	51 (68.9)	9 (12.2)	55 (72.4)	7 (9.2)	.721	0.605
Constipation	24 (32.4)	—	35 (46.1)	—	.097	—
Bleeding	13 (17.6)	—	19 (25.0)	1 (1.3)	.321	1.000
Mucositis	59 (79.7)	4 (5.4)	56 (73.7)	1 (1.3)	.442	.206
Anorexia	33 (44.6)	—	34 (44.7)	—	1.000	—
Nausea	34 (45.9)	—	35 (46.1)	—	1.000	—
Dyspnea	6 (8.1)	3 (4.1)	2 (2.6)	1 (1.3)	.164	.363
Dryness	26 (35.1)	—	24 (31.6)	—	.730	—
Odynophagia	28 (37.8)	—	26 (34.2)	2 (2.6)	.734	.497
Paronychia	7 (9.5)	1 (1.4)	3 (3.9)	—	.206	.493
Vomiting	20 (27.0)	—	18 (23.7)	—	.709	—
Pneumonia	2 (2.7)	2 (2.7)	2 (2.6)	2 (2.6)	1.000	1.000

NOTE. COVID-19 disease occurred in one patient (1.4%) in the TMC arm and in four patients (5.3%) in the TMC-I arm ($P = .367$). Two deaths were seen in the TMC-I arm during treatment. One patient developed aspiration pneumonia, whereas the other had a reactivation of Hepatitis B and developed hepatorenal syndrome.

Abbreviations: SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; TMC, triple metronomic chemotherapy; TMC-I, TMC with intravenous nivolumab.

Quality of Life

The details of median TTD in the quality-of-life scores are given in Table 3 and the Data Supplement. Per functional scales, patients in the TMC-I arm did relatively better compared with those in the TMC arm for physical functioning (HR, 0.687; 0.479 to 0.986) and role functioning (HR, 0.692; 0.484 to 0.990).

DISCUSSION

To the best of our knowledge, this is the first randomized study to show an improvement in outcomes with the addition of low-dose nivolumab in any cancer. In this study, the addition of low-dose nivolumab led to an absolute improvement in a 1-year survival of > 25%. This improvement in OS was a result of improvement in PFS and also an improvement in duration of response seen because of the addition of low-dose nivolumab. This intervention in accordance with the ESMO MCBS would be graded as A, which suggests a substantial benefit from this therapy.[25] The addition of low-dose nivolumab to metronomic chemotherapy did not lead to an increase in adverse events and also led to an increase in multiple domains of quality of life.

The results of this study have a social impact beyond its scientific implications. Checkpoint inhibitors have, over the

TABLE 3. Median Time to Deterioration in QOL Scores as per the Domain Between two Arms

QOL Domain	TMC	TMC-I	HR (95% CI)	P[a]
Global health status/QoL				
Global health status/QoL	74 (60 to 120)	60 (60 to 89)	1.224 (0.880 to 1.702)	.230
Functional scales				
Physical functioning	151 (126 to 180)	186 (157 to 240)	0.687 (0.479 to 0.986)	.042
Role functioning	127 (120 to 158)	180 (120 to 236)	0.692 (0.484 to 0.990)	.044
Emotional functioning	140 (120 to 180)	180 (128 to 180)	0.779 (0.552 to 1.100)	.156
Cognitive functioning	120 (120 to 164)	174 (120 to 183)	0.766 (0.540 to 1.088)	.136
Social functioning	171 (134 to 182)	161 (120 to 197)	1.035 (0.732 to 1.464)	.845
Symptom scales/item C30				
Fatigue	120 (108 to 120)	120 (120 to 129)	0.808 (0.5808 to 1.125)	.206
Nausea and vomiting	164 (140 to 187)	190 (127 to 242)	0.757 (0.528 to 1.086)	.130
Pain	121 (120 to 140)	134 (120 to 180)	0.733 (0.518 to 1.036)	.079
Dyspnea	148 (120 to 180)	157 (120 to 188)	0.758 (0.529 to 1.088)	.133
Insomnia	159 (120 to 180)	161 (120 to 180)	0.888 (0.626 to 1.260)	.506
Appetite loss	148 (120 to 180)	142 (120 to 180)	0.945 (0.667 to 1.339)	.749
Constipation	180 (140 to 194)	190 (129 to 246)	0.730 (0.506 to 1.054)	.093
Diarrhea	164 (136 to 191)	153 (120 to 208)	0.848 (0.590 to 1.218)	.372
Financial difficulties	159 (133 to 182)	179 (120 to 205)	0.930 (0.656 to 1.320)	.686
Symptom scales/item HN-35				
Pain	120 (108 to 148)	120 (100 to 120)	1.124 (0.798 to 1.583)	.686
Swallowing	127 (104 to 151)	144 (120 to 180)	0.902 (0.635 to 1.281)	.564
Senses problems	164 (136 to 188)	188 (168 to 266)	0.714 (0.489 to 1.042)	.081
Speech problems	140 (120 to 180)	229 (157 to 304)	0.643 (0.446 to 0.928)	.018
Trouble with social eating	140 (120 to 171)	149 (120 to 180)	0.812 (0.568 to 1.161)	.253
Trouble with social contact	127 (120 to 151)	165 (120 to 188)	0.834 (0.582 to 1.194)	.321
Less sexuality	NA	NA	NA	NA
Teeth	127 (120 to 145)	180 (122 to 191)	0.596 (0.421 to 0.8435)	.004
Opening mouth	151 (122 to 191)	128 (120 to 180)	0.891 (0.619 to 1.280)	.531
Dry mouth	180 (140 to 194)	180 (122 to 229)	0.844 (0.589 to 1.211)	.357
Sticky saliva	148 (133 to 182)	180 (128 to 240)	0.732 (0.509 to 1.052)	.092
Coughing	158 (120 to 188)	184 (144 to 240)	0.631 (0.439 to 0.906)	.013
Felt ill	158 (122 to 180)	168 (120 to 180)	0.906 (0.638 to 1.285)	.578
Pain killers	191 (164 to 216)	240 (180 to 310)	0.638 (0.433 to 0.939)	.023
Nutritional supplements	182 (136 to 207)	229 (165 to 285)	0.660 (0.453 to 0.960)	.030
Feeding tube	180 (145 to 201)	242 (178 to 310)	0.601 (0.408 to 0.885)	.010
Weight loss	164 (136 to 182)	180 (141 to 207)	0.870 (0.611 to 1.240)	.441
Weight gain	140 (120 to 180)	142 (100 to 180)	0.883 (0.623 to 1.252)	.485

NOTE. Sexuality domains were answered by very few patients, thus precluding any meaningful analysis.

Abbreviations: HR, hazard ratio; NA, not available; QOL, quality of life; TMC, triple metronomic chemotherapy; TMC-I, TMC with intravenous nivolumab.

[a]*P* values provided are obtained by COX regression analysis.

past decade, substantially improved outcomes in multiple cancers in the palliative, adjuvant, and neoadjuvant settings.[26] The ability of these agents to provide sustained long-term response has resulted in improvement in 3- to 5-year OS in multiple cancer sites even in palliative settings.[27] Unfortunately, these agents are inaccessible in low-income countries and low- and middle-income countries (LMICs).[9,28] Nearly five of the seven million deaths because of cancer globally occur in these regions.[29] Thus, the current study provides the proof of concept that low doses

of checkpoint inhibitors can improve outcomes. This will lead to further research in the development of accessible dosing of these agents in other cancers, which is the need of the hour in low-income countries and LMICs.

The dose used in the study was 20 mg once every 3 weeks, and the smallest vial strength of nivolumab was 40 mg. The vials were shared between the patients during the study. Now, with data suggesting the stability of the compound even after opening the vial for 1 month, drug vial optimization is possible in routine use.[30,31] The dose of 20 mg once every 3 weeks was selected as laboratory data, which suggested that 0.3 mg/kg once every 3 weeks might be effective,[15-17] the average weight of a patient with HNSCC in palliative settings in our country is usually below 60 kg, and even with 60 kg, the calculated dose was 18 mg once every 3 weeks. Hence, for logistic issues of division of vial, the dose of 20 mg once every 3 weeks was selected.

The annual cost of drugs at our center with the assumption of a body surface area of 1.5 kg per m^2 for the TMC-I regimen is $4,370.1 US dollars (USD; 331,472 Indian rupees [INR]), for the KEYNOTE 048 regimen, it is $81,711.93 USD (6,197,849.8 INR), for the EXTREME regimen, it is $46,661.17 USD (3,539,249.8 INR), for single-agent nivolumab, it is $63,741.99 USD (4,834,830 INR), and for single-agent pembrolizumab, it is $81,542.85 (6,185,025 INR). The use of the TMC-I regimen decreases the cost of therapy to 5%-9% of the cost of full-dose immunotherapy regimens. As the annual cost of the TMC-I regimen is below 500,000 INR, it can be provided in India by the Ayushman Bharat Pradhan Mantri Jan Arogya Yojana, which is a national public health insurance fund of the Government of India that aims to provide free health insurance coverage for low-income earners in the country. These costs are only for the drugs. The cost of administration, supportive medications, and adverse event management is not included. Considering that EXTREME and KEYNOTE 048 regimes led to 83%-85% grade 3 and above adverse events and require 120 hours of continuous infusion of fluorouracil, the cost would escalate further.[1] We have not performed a formal cost-effective analysis, and this is a limitation of the study.

This study has a few other limitations. It was a single-center study and was performed in an LMIC in patients who did not have access to full-dose immunotherapy. The efficacy of this low-dose regimen in comparison with full-dose regimens is unknown. So the results of this study are applicable to those patients who do not have access to full-dose immunotherapy. We had an overwhelmingly high number of oral cavity cancers, which reflects the pattern of head and neck cancer in India, where oral cavity malignancies predominate.[32] Hence, the applicability of this regimen in human papillomavirus–positive oropharyngeal cancers remains unknown.[32] The patients recruited in the study differ from those in the pivotal immunotherapy studies in terms of fewer patients with metastatic diseases. This is largely due to very locally advanced oral cancers seen in India, which are not amenable to local therapy and progress predominantly locoregionally, and is consistent with baseline characteristics of previous palliative chemotherapy studies reported from India.[3,14,33] The 1-year OS assumed in the current study was 28.3% and was on the basis of our previous phase III study, which enrolled predominantly platinum-sensitive patients. However, in the standard arm of this study, the 1-year OS was 16.3%, which is lower than our assumption. The reason for this was the differential proportion of platinum-refractory patients. In our phase III study, the 1-year OS of platinum-refractory patients was only 28.2%, whereas in the phase II study with a predominant platinum-refractory population ($>$ 95%), the 1-year OS was 10% with the TMC regimen. In the current study, $>$ 50% of patients in both arms had previous exposure to platinum and had failed within 6 months. Hence, the overall 1-year OS in the TMC arm was 16.3%. Notwithstanding these limitations, the study had a gold standard primary end point of OS, which is unaffected by a bias that might influence end points like response rates or PFS. The study enrolled patients with both platinum-refractory and platinum nonrefractory disease. At the time of conceptualization of the study, it was decided that the study needs to be pragmatic and include patients in whom worse outcomes are anticipated. The benefit of the addition of low-dose nivolumab was seen across all groups irrespective of PD-L1 status in the current study. Low-dose nivolumab had a relatively better impact on OS in a relatively poor prognostic subset of patients who had exposure to previous chemotherapy and had failed within 6 months. This might be due to increased expression of PD-L1 on tumor cells caused by previous exposure to chemotherapy.[34]

In conclusion, to our knowledge, in this first-ever randomized study in patients with head and neck cancer requiring palliative systemic therapy, the addition of low-dose nivolumab to metronomic chemotherapy led to improved OS and is an alternative standard of care for those who cannot access full-dose checkpoint inhibitors.

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DISCLAIMER

The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. V.M.P. and K.P. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Data analysis was conducted by V.M.P., A.B., and K.P.

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DATA SHARING STATEMENT

The deidentified data will be shared for future research for IEC-approved proposals. The data will be made available by the corresponding author and will be shared post an e-mail request to the corresponding author. The data will be shared in accordance with data sharing norms and rules and regulations of the Republic of India at the time of such requests.

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Low-Dose Immunotherapy in Head and Neck Cancer: A Randomized Study

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