Efficacy and Safety of Ultra-Low-Dose Immunotherapy in Relapsed Refractory Solid Tumors: Phase III Superiority Randomized Trial (DELII)

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ABSTRACT

PURPOSE Immune checkpoint inhibitors (ICIs) achieve sufficient receptor occupancy at much lower than standard approved doses. We hypothesized that ultra-low-dose nivolumab would retain clinical efficacy.

PATIENTS AND METHODS In this phase III randomized superiority trial, patients with advanced solid tumors (Eastern Cooperative Oncology Group 0-1) and progression on ≥1 prior line of systemic therapy were randomly assigned 1:1 to ultra-low-dose nivolumab (20 mg intravenously once every 2 weeks) or standard chemotherapy (docetaxel or paclitaxel, as per tumor type). Treatment continued until progression or intolerable toxicity. The primary end point was overall survival (OS).

RESULTS From June 2020 to February 2024, we enrolled 500 patients: 250 per arm; 52% had head and neck and 36% lung cancers. The median number of prior lines of therapy was 1 (range, 1-8); 29% had received ≥2 prior lines. Median OS was significantly longer with ultra-low-dose nivolumab: 5.88 months (95% CI, 4.99 to 7.13) versus 4.70 months (95% CI, 3.91 to 5.65; hazard ratio [HR], 0.80 [95% CI, 0.66 to 0.97]; $P = .022$). One-year OS was 27.3% versus 16.9%. Median progression-free survival was similar: 2.04 months (95% CI, 2.00 to 2.10) with ultra-low-dose nivolumab and 2.09 months (95% CI, 2.04 to 2.17) with chemotherapy (HR, 1.03 [95% CI, 0.86 to 1.23]; $P = .77$). Grade ≥3 treatment-related adverse events were less frequent with ultra-low-dose nivolumab (42.5% *v* 60.8%; $P < .001$). Quality of life (QoL) was significantly better with ultra-low-dose nivolumab.

CONCLUSION Ultra-low-dose nivolumab significantly improves OS versus chemotherapy in pretreated solid tumors, with fewer severe toxicities and better QoL. These findings support re-evaluation of ICI dosing strategies and may enhance global access.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have transformed cancer care since their approval in 2011.[1] In select patients, like those with mismatch repair-deficient tumors, ICIs may obviate surgery, offering the possibility of a single-modality cure.[2]

Unlike chemotherapy, where efficacy is based on maximum tolerated dose (MTD), ICIs activate the immune system. The MTD paradigm may not apply to immunotherapies, as higher doses may not improve efficacy, and dose-limiting toxicities may not manifest even at excessive doses.[3] Regulatory experts have advocated for a pharmacokinetics- and pharmacodynamics-based dose determination approach for biologics, including ICIs.[3]

The approved dose of nivolumab is 3 mg/kg or 240 mg intravenously (IV) once every 2 weeks.[4] PD-1, the target of nivolumab, is expressed on 20%-40% of peripheral T cells; 70%-75% receptor occupancy is necessary for immune activation. In phase I studies, even doses of 0.1 mg/kg achieved median receptor occupancy of 64%-70%, with

CONTEXT

Key Objective
Would an immune checkpoint inhibitor administered at a fraction of the approved dose be efficacious in patients with cancer?

Knowledge Generated
Nivolumab 20 mg intravenously once every 2 weeks significantly prolonged survival as compared with standard chemotherapy in patients with relapsed refractory solid tumors. Ultra-low-dose nivolumab resulted in significantly fewer grade ≥3 toxicities and better quality of life as compared with standard chemotherapy.

Relevance *(G. McArthur)*
The study addressed an important question for cancer care in resourced restrained environments. Ultra low dose anti-PD-1 improved survival after prior systemic therapy with acceptable toxicity promoting further evaluation of this approach.*

*Relevance section written by *JCO* Associate Editor Grant McArthur, MBBS, PhD.

minimal additional benefit at higher doses.[5] Notably, the serum concentration required for efficacy is only 1.2 μg/mL, while approved dosing achieves levels of approximately 33.7 μg/mL.[6] We previously demonstrated that ultra-low-dose nivolumab (20 mg IV once every 2 weeks) significantly improved survival in advanced head and neck carcinoma (HNC).[7]

ICIs are prohibitively expensive and inaccessible to many patients worldwide. At our hospital, only 2.8% of eligible patients could receive ICIs.[8] Even in high-income countries, disparities persist: non-Hispanic Black patients are 15% less likely to receive ICIs than non-Hispanic White patients.[9] Thus, advances in immunotherapy remain out of reach for many.

We, therefore, tested whether ultra-low-dose immunotherapy could be effective monotherapy in relapsed refractory solid tumors.

PATIENTS AND METHODS

General Study Overview

Development of Low-Dose Immunotherapy in India (DELII) was an open-label, phase III superiority trial conducted at the Department of Medical Oncology, Tata Memorial Hospital (Mumbai, India) between 2020 and 2024. The Institutional Ethics Committee (IEC) approved the study; monitoring was by the Data Safety Monitoring Subcommittee. Registration was with Clinical Trials Registry-India (CTRI/2020/02/023441). All patients provided written informed consent. The study adhered to standard ethical principles. Funding was by R G Manudhane Foundation for Excellence, Trilokchand Papriwal Trust, and an institutional grant.

Patients

Adults with relapsed solid tumors after ≥1 line of palliative systemic therapy or recurrence within 6 months of curative treatment were enrolled. Eligible cancers included non–small cell lung cancer (NSCLC), HNC, esophageal, bladder, and any solid tumor with microsatellite-instability-high (MSI-H) or deficient mismatch repair. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 and adequate organ and marrow function. Exclusion criteria included active autoimmune disease, immunosuppressive therapy, active infections including hepatitis B/C, and organ transplant (Protocol).

Aims/Objectives

The primary objective was to compare overall survival (OS) between ultra-low-dose immunotherapy versus physician's choice standard chemotherapy. Secondary end points included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), toxicity, and quality of life (QoL).

Study Methodology

Patients were divided into NSCLC and non-NSCLC cohorts, on the basis of the primary tumor. Patients with NSCLC were stratified by age, ECOG PS, brain metastasis, driver mutation, histology, and immunotherapy biomarkers (PD-L1 high/MSI-H). Stratification in nonlung cohort was by age, tumor, and biomarker. An independent statistician randomly assigned patients (1:1) to ultra-low-dose nivolumab or chemotherapy. Nivolumab dosing was 20 mg IV over 1 hour once every 2 weeks. Standard chemotherapy regimens for NSCLC and HNC: docetaxel 75 mg/m² IV or paclitaxel

175 mg/m² IV once every 3 weeks, or paclitaxel 80 mg/m² IV weekly; for esophageal/urothelial cancer: paclitaxel 175 mg/m² IV every 3 weeks or paclitaxel 80 mg/m² IV once a week. Treatment continued until disease progression or intolerable toxicity. Toxicities were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.03. Radiologic assessment was at baseline and every 2 months, using RECIST, version 1.1. QoL was assessed at baseline and every 2 months with European Organization for Research and Treatment of Cancer forms: general (QLQ-C30) and site-specific (lung: QLQ-LC13, HNC: QLQ-H&N35, esophagus: QLQ-OES-18).

Sample Size

Originally designed in 2018, this study aimed to separately analyze lung (noninferiority analysis) and nonlung cohorts (superiority analysis). In relapsed NSCLC, docetaxel improved 1-year OS from 16% (best supportive care) to 40% ($P = .016$) but caused grade ≥3 side effects in >70% patients.[10] Immunotherapy led to grade ≥3 side effects in 7%-10% patients.[11,12] Lowering toxicity, without affecting survival was deemed worthwhile; hence, a noninferiority design was planned for the lung cohort. In other tumors like relapsed HNC, immunotherapy is superior to chemotherapy; hence, this cohort was planned as a superiority design.[13,14] Power calculations were done separately for the cohorts, with a total planned sample size of 884 (lung: 446; nonlung: 438). Following disease-management group review because of shifts in practice toward earlier use of immunotherapy, the protocol was amended (October 2023) to combine cohorts and evaluate a unified superiority end point. Assuming a median OS in chemotherapy arm of 6 months,[11,13,15,16] with $\alpha = .05$, 80% power, and hazard ratio (HR) = 0.75, the revised sample size was 445, adjusted to 500, accounting for 10% lost to follow-up.

Statistics

Analyses followed intention-to-treat principle. $P < .05$ was considered significant. ORR was the percentage of patients who attained either complete or partial remission as best response. DCR was the percentage of patients with complete or partial remission or stable disease as best response. Duration of response (DoR) was the time from first documented complete or partial response to progression or death, whichever occurred first. Patients without progression or death were censored on date of last follow-up. Nonresponders were excluded from DoR analysis. OS was the duration in months from the date of random assignment to death. In patients who were alive at last follow-up, this duration was calculated from the date of random assignment to the last follow-up. PFS was defined as the duration in months from the date of random assignment to progression or death, whichever was earlier. In patients without progression or death, PFS was calculated to the date the patient was last known to be alive and progression free. Survival estimation was by Kaplan-Meier method.[17,18] The log-rank test was used for comparison, and HRs were estimated using Cox proportional hazards model.[19,20] QoL changes were analyzed using linear mixed-effects model. Statistical details are provided in Supplementary File 2.

RESULTS

Baseline Characteristics

Between June 2020 and February 2024, we enrolled 500 patients: 250 to each arm (Fig 1). Baseline demographic and clinical characteristics were balanced (Table 1). Next-generation sequencing was performed in 87 (17.4%) patients: 40 (16%) on chemotherapy and 47 (18.8%) on ultra-low-dose immunotherapy. Actionable genomic alterations were noted in 14 of 182 (7.7%) participants with lung cancer: five (5.6%) on chemotherapy (*EGFR* [3], *ROS1* [1], *ERBB2* [1]) and nine (9.8%) on ultra-low-dose immunotherapy (*EGFR* [5], *RET* [1], *BRAF* [1], *ERBB2* [2]). Prior curative therapy was received by 42.6% of participants. Twenty-nine percent of participants (26.4% in chemotherapy arm, and 31.2% in ultra-low-dose immunotherapy arm) had received ≥2 prior lines of therapy. There were 14 patients with MSI-H tumors: six on chemotherapy and eight on ultra-low-dose immunotherapy. Prior platinum was received by 420 of 441 patients with NSCLC and HNC: 211 (95.2%) on chemotherapy and 209 (93.7%) on ultra-low-dose immunotherapy. Patients who received prior taxane (n = 156, 62.4%) roughly belonged to three categories: patients with HNC who received docetaxel-cisplatin-5-fluorouracil as induction chemotherapy, patients with advanced NSCLC who received first-line paclitaxel + platinum and were then planned for second-line docetaxel,[21,22] and patients with progression on multiple lines (including a taxane). In general, patients who received prior taxane and were randomly assigned to the standard arm received the alternative taxane, for example, patients who received docetaxel as induction chemotherapy then received paclitaxel in this study.

Oncologic Outcomes

Overall Survival

The median follow-up was 28.05 months (IQR, 26.09-30.02). At the end of the study, 47 (9.4%) patients were alive (17 and 30 in chemotherapy and ultra-low-dose immunotherapy arms, respectively), seven (1.4%) were lost-to-follow-up (three and four in chemotherapy and ultra-low-dose immunotherapy arms, respectively), and 446 (89.2%) had died: 230 (92%) and 216 (86.4%) in chemotherapy and ultra-low-dose immunotherapy, respectively. The proportional hazards assumption was tested using Schoenfeld residuals; the global test was not significant ($P = .44$), indicating no violation of the assumption. Ultra-low-dose immunotherapy was associated with a modest but statistically significant improvement in OS compared with chemotherapy. One-year OS was 16.88% (95% CI, 12.75 to 22.34) in chemotherapy and

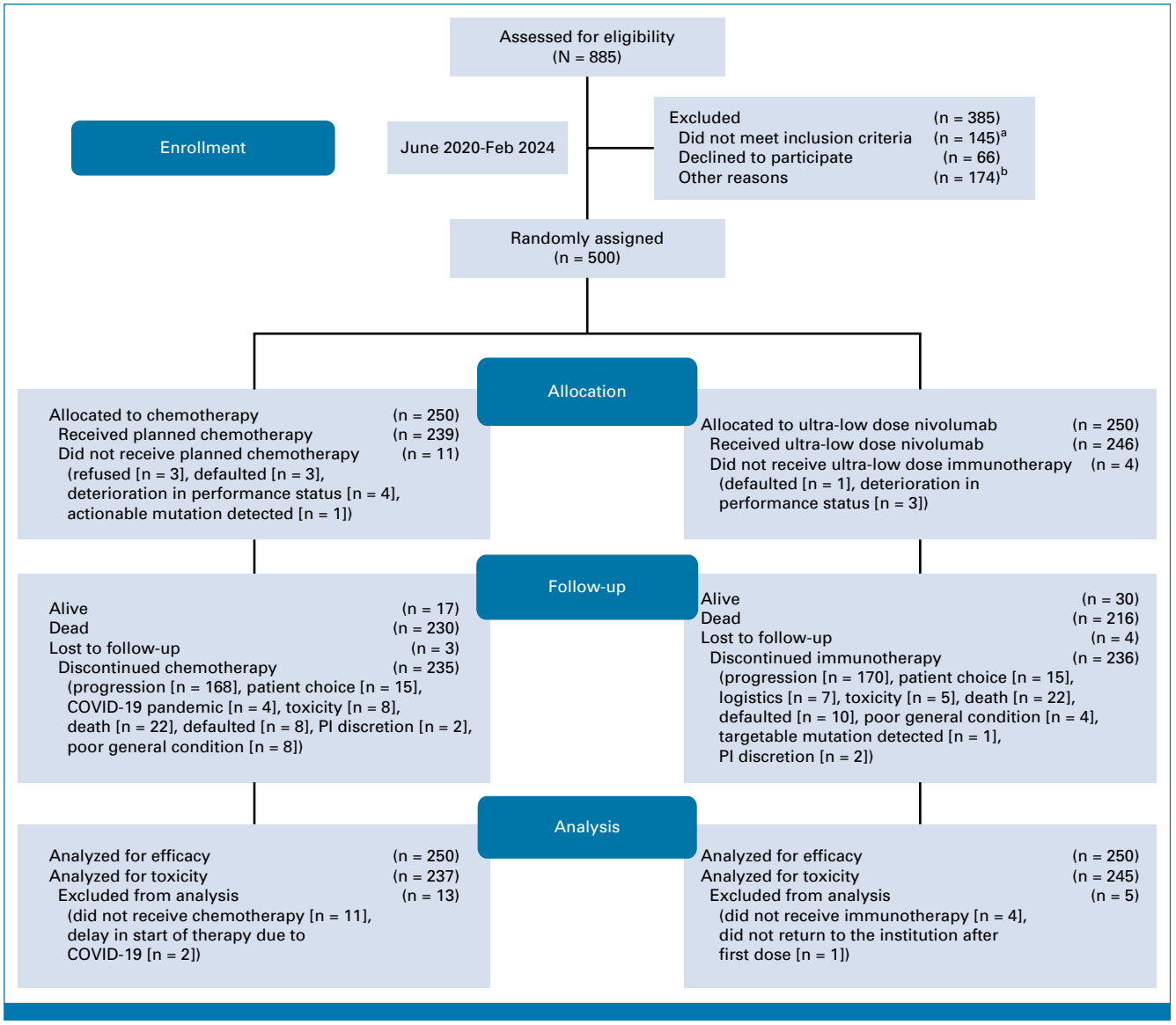


FIG 1. Patient disposition, as per the CONSORT. [a]Systemic therapy naïve (n = 7), deranged organ/marrow function (n = 7), active infection (n = 4), received prior immunotherapy (n = 6), hepatitis B/C (n = 5), poor performance status (n = 75), rare histopathology (n = 4), other primary cancer (n = 3), not progressed on first-line systemic therapy (n = 10), peripheral neuropathy > grade 2 (n = 1), curative systemic therapy received over 6 months prior (n = 12), hypersensitivity to docetaxel (n = 1), dyselectrolytemia (n = 6), psychiatric disorder (n = 1), comorbidities (n = 2), autoimmune disorder (n = 1); [b]noncompliance (n = 77), patient desired therapy at another facility (n = 60), already received physician's choice chemotherapy (n = 8), defaulted (n = 8), PD-L1 negative (n = 7), died (n = 3), refused chemotherapy (n = 2), enrolled on another trial (n = 1), hypothyroidism (n = 1), lung cancer with targetable mutation (n = 2), PD-L1 high (n = 1), imaging done beyond 21 days prior (n = 1), refractory malignant hypercalcemia (n = 1), on alternative medicines (n = 1), extensive disease (n = 1). PI, principal investigator.

27.28% (95% CI, 22.19 to 33.54) in ultra-low-dose immunotherapy; HR, 0.80 (95% CI, 0.66 to 0.97), $P = .022$. The median OS in chemotherapy and ultra-low-dose immunotherapy arms was 4.70 months (95% CI, 3.91 to 5.65) and 5.88 months (95% CI, 4.99 to 7.13), respectively (Fig 2A). The differential impact of chemotherapy versus ultra-low-dose immunotherapy in various subgroups of interest is shown in Figure 2B. All point estimates favored ultra-low-dose nivolumab, suggesting benefit in patients regardless of age, sex, smoking status, ECOG PS, malignancy, histology, PD-L1 level, brain metastases, and line of therapy.

Progression-Free Survival

At the data cut-off date, there were 484 events for PFS: 246 (98.4%) in chemotherapy arm and 238 (95.2%) in ultra-low-dose immunotherapy. Disease progression occurred in 464 (92.8%) patients: 231 (92.4%) in chemotherapy arm and 233 (93.2%) in ultra-low-dose immunotherapy arm. Deaths occurred in 15 (6%) patients in chemotherapy arm, and five (2%) in ultra-low-dose immunotherapy. The median PFS was similar (2.09 *v* 2.04 months; HR, 1.03, $P = .77$; Fig 3). We performed a post hoc analysis to assess whether receipt of

TABLE 1. Demographic and Clinical Characteristics of Patients With Relapsed Refractory Solid Tumors Randomly Assigned to Receive Standard Chemotherapy or Ultra-Low-Dose Immunotherapy

Factors	Chemotherapy, No. (%), n = 250	Ultra-Low-Dose Immunotherapy, No. (%), n = 250	Overall, No. (%), N = 500	*P*
Age, in years				
Median (IQR)	49.0 (41.0-58.0)	50.0 (42.0-58.0)	49.5 (42.0-58.0)	.827
<60	196 (78.4)	198 (79.2)	394 (78.4)	
≥60	54 (21.6)	52 (20.8)	106 (21.2)	
Sex				
Male	206 (82.4)	202 (80.8)	408 (81.6)	.644
Female	44 (17.6)	48 (19.2)	92 (18.4)	
Alcohol use				
No	196 (78.4)	206 (82.4)	402 (80.4)	.260
Yes	54 (21.6)	44 (17.6)	98 (19.6)	
Tobacco use				
None	49 (19.6)	59 (23.6)	108 (21.6)	.378
Smoker	96 (38.6)	83 (33.2)	179 (35.9)	
Smokeless tobacco	104 (41.8)	108 (43.2)	212 (42.5)	
Comorbidities				
None	166 (66.4)	165 (66.0)	331 (66.2)	.925
Diabetes mellitus	28 (11.2)	28 (11.2)	48 (9.6)	.225
Hypertension	43 (17.2)	39 (15.6)	82 (16.4)	.629
COPD/asthma	7 (2.8)	8 (3.2)	15 (3.0)	.793
Hypothyroidism	15 (6.0)	19 (7.6)	34 (6.8)	.477
Others[b]	26 (10.4)	28 (11.2)	54 (10.8)	.772
Monthly per capita family income, in ₹, median (IQR)	4,500 (2,000-8,000)	7,000 (0-7,000)	4,000 (1,500-7,000)	.287
Eastern Cooperative Oncology Group performance status score				
0	10 (4.0)	11 (4.4)	21 (4.2)	.590
1	240 (96.0)	239 (95.6)	479 (95.8)	
Cancer primary				
Head and neck	128 (51.2)	131 (52.4)	259 (51.8)	.959
Lung	90 (36.0)	92 (36.8)	182 (36.4)	
Esophagogastric	17 (6.8)	14 (5.6)	31 (6.2)	
Urothelial	8 (3.2)	6 (2.4)	14 (2.8)	
Colorectal	7 (2.8)	7 (2.8)	14 (2.8)	
Head and neck cancer subsite				
Buccal mucosa	71 (28.4)	74 (29.6)	145 (29.0)	.439
Oral tongue	34 (13.6)	34 (13.6)	68 (13.6)	
Oropharynx	14 (5.6)	9 (3.6)	23 (4.6)	
Hypopharynx	4 (1.6)	5 (2.0)	9 (1.8)	
Larynx	1 (0.4)	7 (2.8)	8 (1)	
Maxilla	2 (0.8)	2 (0.8)	4 (0.8)	
Histology				
Squamous	164 (65.6)	158 (63.2)	322 (64.4)	.806
Adenocarcinoma	72 (28.8)	81 (32.4)	153 (30.6)	
Urothelial	8 (3.2)	5 (2.0)	13 (2.6)	
Other	6 (2.4)	6 (2.4)	12 (2.4)	
PD-L1 status				
Not tested	33 (13.2)	36 (14.4)	69 (13.8)	.696
Negative (<1%)	53 (24.4)	47 (22.0)	100 (23.2)	
Positive (≥1%)	164 (75.6)	167 (78.0)	331 (76.8)	

(continued on following page)

TABLE 1. Demographic and Clinical Characteristics of Patients With Relapsed Refractory Solid Tumors Randomly Assigned to Receive Standard Chemotherapy or Ultra-Low-Dose Immunotherapy (continued)

Factors	Chemotherapy, No. (%), n = 250	Ultra-Low-Dose Immunotherapy, No. (%), n = 250	Overall, No. (%), N = 500	*P*
PD-L1 status category				
Low	139 (64.1)	140 (65.4)	279 (64.7)	.928
High[a]	78 (35.9)	74 (34.6)	152 (35.3)	
Prior curative therapy				
None	107 (42.8)	106 (42.4)	213 (42.6)	.928
Surgery	72 (28.8)	65 (26.0)	137 (27.4)	.483
Radiation	73 (29.2)	75 (30.0)	148 (29.6)	.841
Chemotherapy	117 (46.8)	127 (50.8)	244 (48.8)	.373
No. of prior lines of systemic therapy received				
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	.234
1	184 (73.6)	172 (68.8)	356 (71.2)	
2	48 (19.2)	61 (24.2)	109 (21.8)	
3	15 (6.0)	9 (3.6)	24 (4.8)	
4	2 (0.8)	5 (2.0)	7 (1.4)	
5	1 (0.4)	1 (0.4)	2 (0.4)	
6	0	1 (0.4)	1 (0.2)	
8	0	1 (0.4)	1 (0.2)	
Disease extent at random assignment				
Locally advanced	118 (47.2)	119 (47.6)	237 (47.4)	.704
Metastatic	132 (52.8)	131 (52.4)	263 (52.6)	
Metastatic sites				
Lung/pleura/pericardium	79 (31.6)	87 (34.8)	166 (33.2)	.447
Bone	56 (22.4)	45 (18.0)	101 (20.2)	.218
Nonregional lymph nodes	45 (18.0)	43 (17.2)	88 (17.6)	.818
Liver	27 (10.8)	26 (10.4)	53 (10.6)	.880
Adrenal	12 (4.8)	11 (4.4)	23 (4.6)	.833
Brain	9 (3.6)	15 (6.0)	24 (4.8)	.207
Other[c]	8 (3.2)	15 (6.0)	23 (4.6)	.136

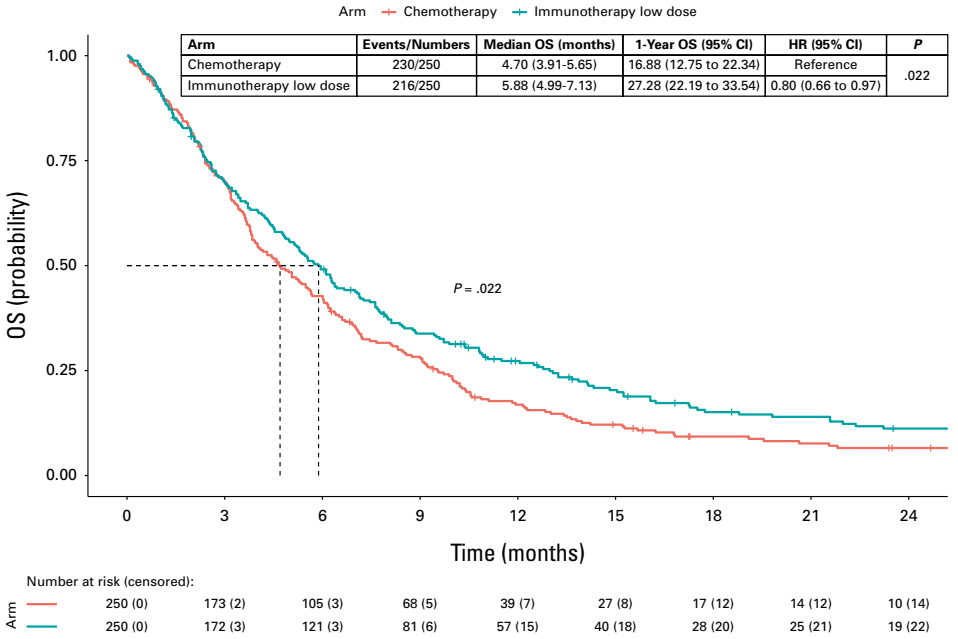
Abbreviations: COPD, chronic obstructive pulmonary disease; CPS, combined positive score; TPS, tumor proportion score.
[a]PD-L1 level was considered high in the following situations: for lung cancer, PD-L1 TPS ≥50%; for head and neck cancer, PD-L1 CPS ≥20 or PD-L1 TPS ≥50%, for esophagogastric and urothelial cancers, PD-L1 CPS ≥10 or PD-L1 TPS ≥50%.
[b]Other comorbidities: Chemotherapy arm: tuberculosis-10, ischemic heart disease-1, curatively treated cancer-6, Parkinson disease-1, cataract-2, bleeding hemorrhoids-1, hernioplasty-1, thalamic infarction-1, dilated cardiomyopathy-1, umbilical hernia-1, atrial fibrillation-1; ultra-low-dose immunotherapy arm: tuberculosis-10, rheumatoid arthritis-2, ischemic heart disease-5, curatively treated cancer-3, rheumatic heart disease-1, cataract-1, psoriasis-1, hydrocele-1, amenorrhea-1, cholelithiasis-1, HIV-1, cerebrovascular accident-1.
[c]Other sites of metastases: Chemotherapy arm: pancreas-1, spleen-1, peritoneum/omentum-3, parotid-1, kidney-1, thyroid-1; ultra-low-dose immunotherapy arm: spleen-1, peritoneum/omentum-11, esophagus/bowel-1, kidney-2.

prior taxane affected efficacy. ORR, median PFS, and median OS in patients in the standard arm who had or had not received prior taxane were 6.1% versus 11.3% (P = .472); 2.07 months (95% CI, 2.00 to 2.20) versus 2.10 months (95% CI, 2.07 to 3.06; HR, 1.28 [95% CI, 0.98 to 1.66], P = .062); and 4.44 months (95% CI, 3.78 to 5.55) versus 5.29 months (95% CI, 3.91 to 7.23; HR, 1.3 [95% CI, 0.99 to 1.70], P = .058). Paclitaxel was received as postprogression therapy in four (1.6%) patients in the standard arm and 50 (20%) patients in ultra-low-dose immunotherapy arm.

Objective Response Rate

ORR was low in both groups: 8.1% (n = 15) in chemotherapy and 7.1% (n = 13) in ultra-low-dose immunotherapy (P = .728). DCR was 39.3% and 37.7% in chemotherapy and ultra-low-dose immunotherapy, respectively; P = .761. The median DoR was 4.93 (95% CI, 2.00 to 17.1) months in the chemotherapy arm, and 8.28 (95% CI, 2.66 to not reached) months in ultra-low-dose immunotherapy; P = .191 (Appendix Fig A1, online only).

A



Arm	Events/Numbers	Median OS (months)	1-Year OS (95% CI)	HR (95% CI)	P
Chemotherapy	230/250	4.70 (3.91-5.65)	16.88 (12.75 to 22.34)	Reference	.022
Immunotherapy low dose	216/250	5.88 (4.99-7.13)	27.28 (22.19 to 33.54)	0.80 (0.66 to 0.97)	

B

Survival Outcomes: HR Comparing Chemotherapy and Low-Dose Immunotherapy

Variable	Chemotherapy	Immunotherapy	HR (95% CI)	P
Age	Event/Total	Event/Total		
<60	179/196	175/198	0.88 (0.71 to 1.08)	.21
≥60	51/54	41/52	0.59 (0.39 to 0.9)	.014
Sex				
Male	190/206	171/202	0.78 (0.63 to 0.96)	.019
Female	40/44	45/48	0.93 (0.61 to 1.43)	.753
Smoking				
Smoker	87/96	68/83	0.62 (0.45 to 0.86)	.004
Nonsmoker	142/153	148/167	0.94 (0.75 to 1.19)	.614
ECOG				
0	10/10	6/11	0.23 (0.07 to 0.76)	.016
1	220/240	209/238	0.84 (0.69 to 1.01)	.069
Primary site				
Head and neck	122/128	112/131	0.86 (0.67 to 1.11)	.247
Other	108/122	104/119	0.77 (0.59 to 1.01)	.06
Histopathology				
Squamous	157/166	136/160	0.78 (0.62 to 0.98)	.038
Nonsquamous	73/84	80/90	0.88 (0.64 to 1.20)	.417
PD-L1 high or MSI high				
No	206/224	198/227	0.81 (0.67 to 0.99)	.038
Yes	24/26	18/23	0.77 (0.41 to 1.44)	.412
Brain metastases				
Absent	221/241	206/235	0.85 (0.70 to 1.02)	.088
Present	9/9	10/15	0.35 (0.14 to 0.90)	.028
Beyond second line				
No	169/184	148/172	0.84 (0.67 to 1.05)	.124
Yes	61/66	68/78	0.7 (0.49 to 0.99)	.046

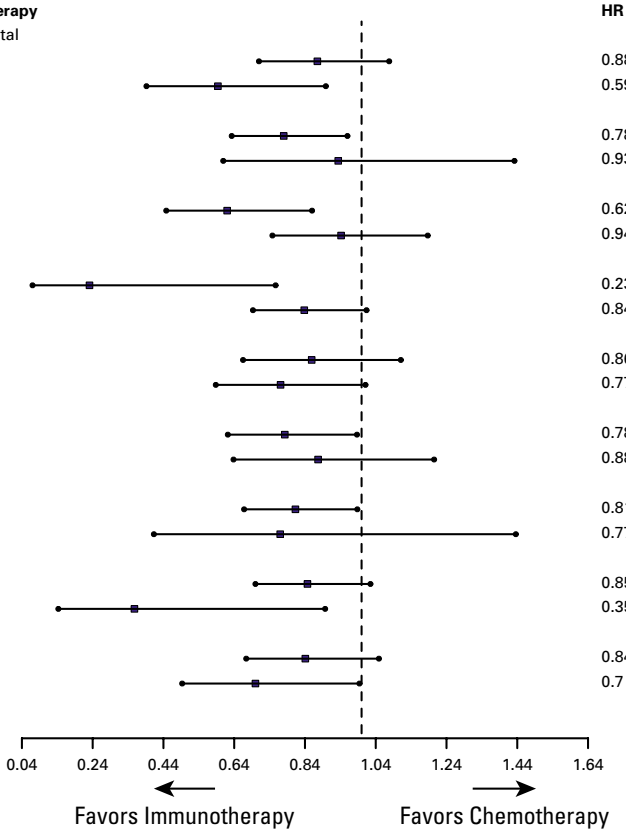


FIG 2. OS. (A) OS of patients with relapsed refractory solid tumors randomly assigned to chemotherapy or ultra-low-dose immunotherapy. The *P* value provided is from the log-rank test. (B) The differential impact of chemotherapy versus ultra-low-dose immunotherapy on OS in various subgroups of interest. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MSI, microsatellite instability; OS, overall survival.

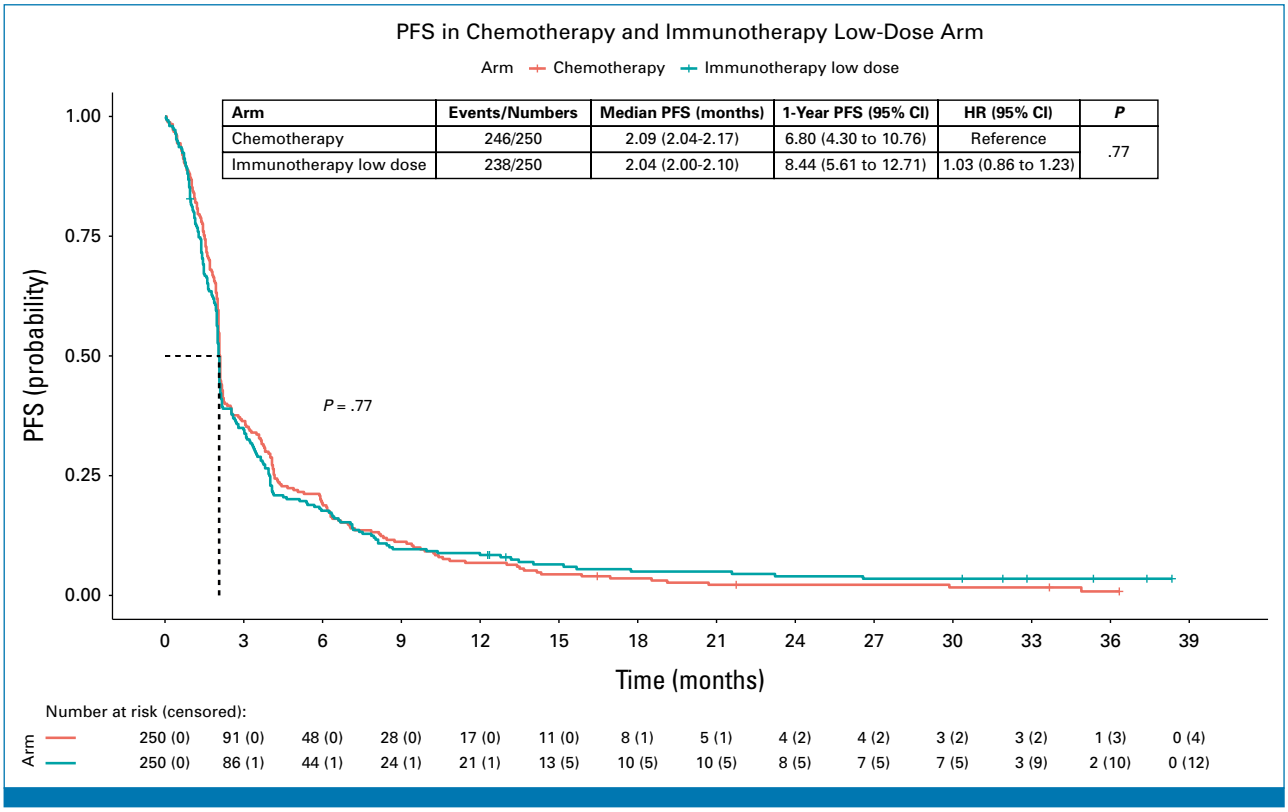


FIG 3. PFS of patients with relapsed refractory solid tumors randomly assigned to chemotherapy or ultra-low-dose immunotherapy. The *P* value provided is from the log-rank test. PFS, progression-free survival.

Adverse Events

Ultra-low-dose nivolumab was better tolerated than chemotherapy. Grade ≥3 adverse events were noted in 143 (60.3%) and 103 (42.0%) patients in chemotherapy and ultra-low-dose immunotherapy, respectively; $P < .001$ (Table 2). Significantly more patients developed grade ≥3 anemia, neutropenia, hyponatremia, diarrhea, and infection in the chemotherapy arm. Grade ≥3 pneumonitis occurred in four (1.7%) patients on chemotherapy and two (0.8%) patients on ultra-low-dose immunotherapy, $P = .388$. Hospitalization for toxicity was required in 50 (21.1%) and 21 (8.6%) patients on chemotherapy and ultra-low-dose immunotherapy, respectively, $P < .001$. There were 10 (2.1%) deaths attributable to therapy: eight in chemotherapy (sepsis-6, pneumonitis-2) and two in ultra-low-dose immunotherapy (sepsis-2), $P = .059$.

Drug Delivery and Compliance

There were 483 (96.6%) patients in the systemic therapy administration analysis set: 237 (94.8%) on chemotherapy and 246 (98.4%) on ultra-low-dose immunotherapy. In the chemotherapy arm, 13 patients were excluded from the therapy administration analysis set: 11 did not receive therapy and two developed COVID-19 after random assignment. In ultra-low-dose immunotherapy arm, four patients did not receive any therapy. Common chemotherapy regimens included once-in-3-weeks docetaxel (59.1%), once-in-3-weeks paclitaxel (28.3%), and once-a-week paclitaxel (9.7%; Appendix Table A1). The median number of cycles was 3 (IQR, 2-7; range, 1-36) and 4 (IQR, 2-7; range, 1-59) in chemotherapy and ultra-low-dose immunotherapy, respectively. In 47 (19.8%) patients (2 on chemotherapy and 45 on ultra-low-dose immunotherapy), the drug was continued beyond radiologic progression because of investigator's assessment of continued benefit. Dose was reduced in nine (3.8%) patients on chemotherapy and in none on ultra-low-dose immunotherapy. Dose delays occurred in 83 (35.0%) patients: 43 (18.1%) on chemotherapy and 40 (16.3%) on ultra-low-dose immunotherapy.

Quality of Life

At baseline (Appendix Table A2), there were no substantial differences in global health status, functional QoL, and symptom scales between patients receiving chemotherapy versus ultra-low-dose immunotherapy.

In the longitudinal analysis using linear mixed-effects models (Appendix Table A3), global health status significantly improved over time ($P < .001$) in both treatment arms, with an overall better trajectory in the immunotherapy group (arm effect $P = .014$). However, the nonsignificant

TABLE 2. Treatment-Related Grade 3 and Higher Adverse Events Noted in Patients Who Were Randomly Assigned to Receive Either Standard Chemotherapy or Ultra-Low-Dose Immunotherapy

Adverse Event	Chemotherapy Arm, No. (%) (n = 237)	Ultra-Low-Dose Immunotherapy Arm, No. (%) (n = 245)	Total, No. (%) (N = 482)	*P*
Any grade ≥3 TRAE	143 (60.3)	103 (42.0)	246 (51.0)	<.001
Anemia	51 (21.5)	19 (7.8)	70 (14.5)	<.001
Neutropenia	18 (7.6)	1 (0.4)	19 (3.9)	<.001
Thrombocytopenia	5 (2.1)	3 (1.2)	8 (1.7)	.498
Hepatic dysfunction	5 (2.1)	10 (4.1)	15 (3.1)	.213
Elevated creatinine	1 (0.4)	0	1 (0.2)	.492
Microscopic hematuria	0	2 (0.8)	2 (0.4)	.164
Proteinuria	1 (0.4)	5 (2.0)	6 (1.2)	.109
Hyponatremia	96 (40.5)	70 (28.6)	166 (34.4)	.006
Fatigue	26 (11.0)	15 (6.1)	41 (8.5)	.056
Anorexia	1 (0.4)	0	1 (0.2)	.492
Skin reaction	2 (0.8)	0	2 (0.4)	.241
Vomiting	9 (3.8)	10 (4.1)	19 (3.9)	.873
Mucositis	4 (1.7)	3 (1.2)	7 (1.5)	.720
Diarrhea	25 (10.5)	3 (1.2)	28 (5.8)	<.001
Hypersensitivity	1 (0.4)	0	1 (0.2)	.492
Infection	26 (11.0)	7 (2.9)	33 (6.9)	<.001
Peripheral neuropathy	5 (2.1)	2 (0.8)	7 (1.5)	.278
Pneumonitis	4 (1.7)	2 (0.8)	6 (1.2)	.388

Abbreviation: TRAE, treatment-related adverse events.

interaction effect (ArmVisit $P = .734$) suggested a similar pattern of improvement over time in both groups. Patients receiving ultra-low-dose immunotherapy experienced more favorable symptom trajectories over time compared with those receiving chemotherapy. Median time to deterioration in QoL was similar between the arms: 9 weeks (95% CI, 8 to 9) in chemotherapy and 9 weeks (95% CI, 8 to 9) in ultra-low-dose immunotherapy arm, $P = .11$ (Appendix Fig A2).

Follow-up of patients, particularly with relation to the QoL forms, is provided in Appendix Tables A4-7. Trendline plots showed that patients receiving ultra-low-dose immunotherapy generally experienced more stable or improving QoL trajectories, particularly in domains such as swallowing (OES18), dry mouth, and alopecia, whereas those on chemotherapy showed worsening or more variable trends (Fig 4).

DISCUSSION

In this randomized study, we found that in patients with relapsed refractory solid tumors, intravenous nivolumab at 20 mg once every 2 weeks significantly improved OS compared with standard chemotherapy, with fewer toxicities and improved QoL. Thus, ICIs may be efficacious at doses far lower than approved levels, which has implications for patients with cancer worldwide, particularly in low-income and lower- and middle-income countries (LMICs). Of the 20 million new cancer cases and 9.7 million cancer deaths annually, 55.1% of new cases and 63.9% of cancer deaths occur in Asia and Africa.[23] Health spending is limited in LMICs. The total health expenditure in 2022 was 3.3% and 2.7% of the Gross Domestic Product of India and Nigeria, respectively; that for the United States was 17.6%.[24-26] Approximately 70%-80% of patients in LMICs lack health insurance, and most cancer care is funded out of-pocket.[27,28] The cost of nivolumab 20 mg is approximately ₹18,700 or $211 (half the cost of nivolumab 40 mg vial, which costs ₹37,422 or $422). Nivolumab 240 mg costs ₹223,377 ($2,520). A month of standard dose nivolumab costs ₹446,754 (approximately $5,000), whereas the average Indian monthly income is ₹15,000-₹20,000 (approximately $175-$233). Thus, full-dose ICIs are unaffordable for almost all patients in LMICs. Reducing the dose would make ICIs more affordable and accessible, decreasing the wide disparities in cancer care that exist between high-income countries and LMICs. Rational drug dosing has implications for curbing health spending in high-income countries as well, as evidenced by the efforts of the US Food and Drug Administration's Project Optimus[29] and organizations like Friends of Cancer Research, ASCO, and American Association for Cancer Research.[30]

Although ultra-low-dose nivolumab did not significantly improve ORR or PFS, it significantly prolonged OS, consistent with previous trials including KEYNOTE 048 in advanced HNC,[31] KEYNOTE-010, and CheckMate 057 in relapsed NSCLC.[12,32] In approximately 20% patients, the drug was

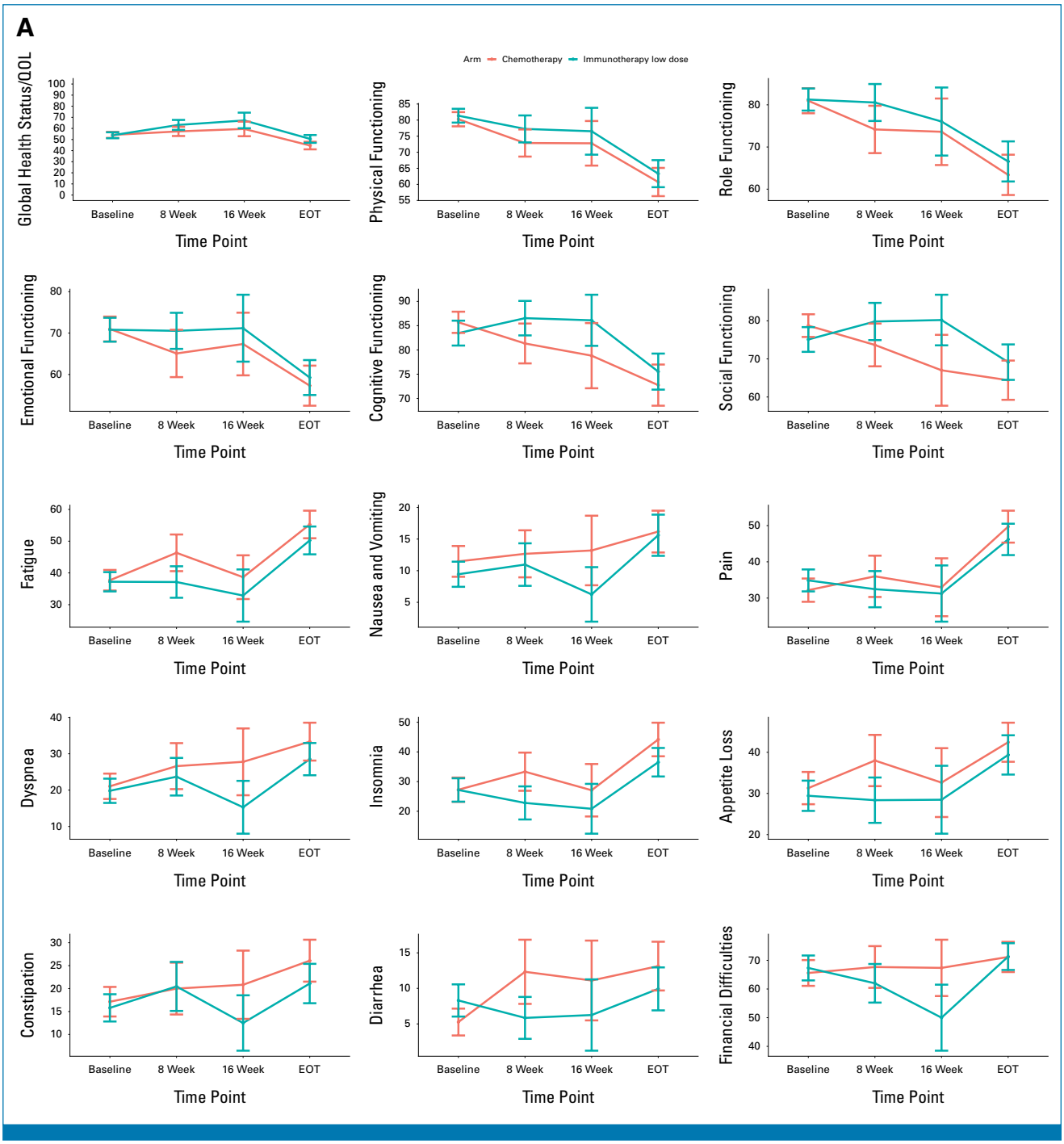


FIG 4. Trendline plots for QoL: (A) Global QoL, as measured by the EORTC QLQ-C30. (B) QoL of patients with head and neck cancer as measured by QLQ-HN35. (C) QoL of patients with lung cancer as measured by QLQ-LC13. (D) QoL of patients with esophageal cancer, as measured by QLQ-OES18. EORTC, European Organization for Research and Treatment of Cancer; QoL, quality of life. (continued on following page)

continued beyond radiologic progression, because of perceived ongoing clinical benefit. This practice of immunotherapy beyond progression is widely practiced with some evidence of improved oncologic outcomes, although prospective studies are lacking.[33-36] Multiple explanations have been postulated, including the fact that ICIs act via an entirely different mechanism than chemotherapy, and immune-mediated efficacy takes time to manifest.[37] This may also explain the fact that OS curves did not separate and rather crossed for the first 2-3 months. A systematic review of studies investigating ICI use in advanced/metastatic solid tumors reported that studies testing single-agent PD-(L)1 inhibitors against chemotherapy were most likely to be associated with early crossing of the survival curves, which occurred in 30% of cases for OS and 28.6% of cases for PFS. Studies that combined ICIs with chemotherapy were least

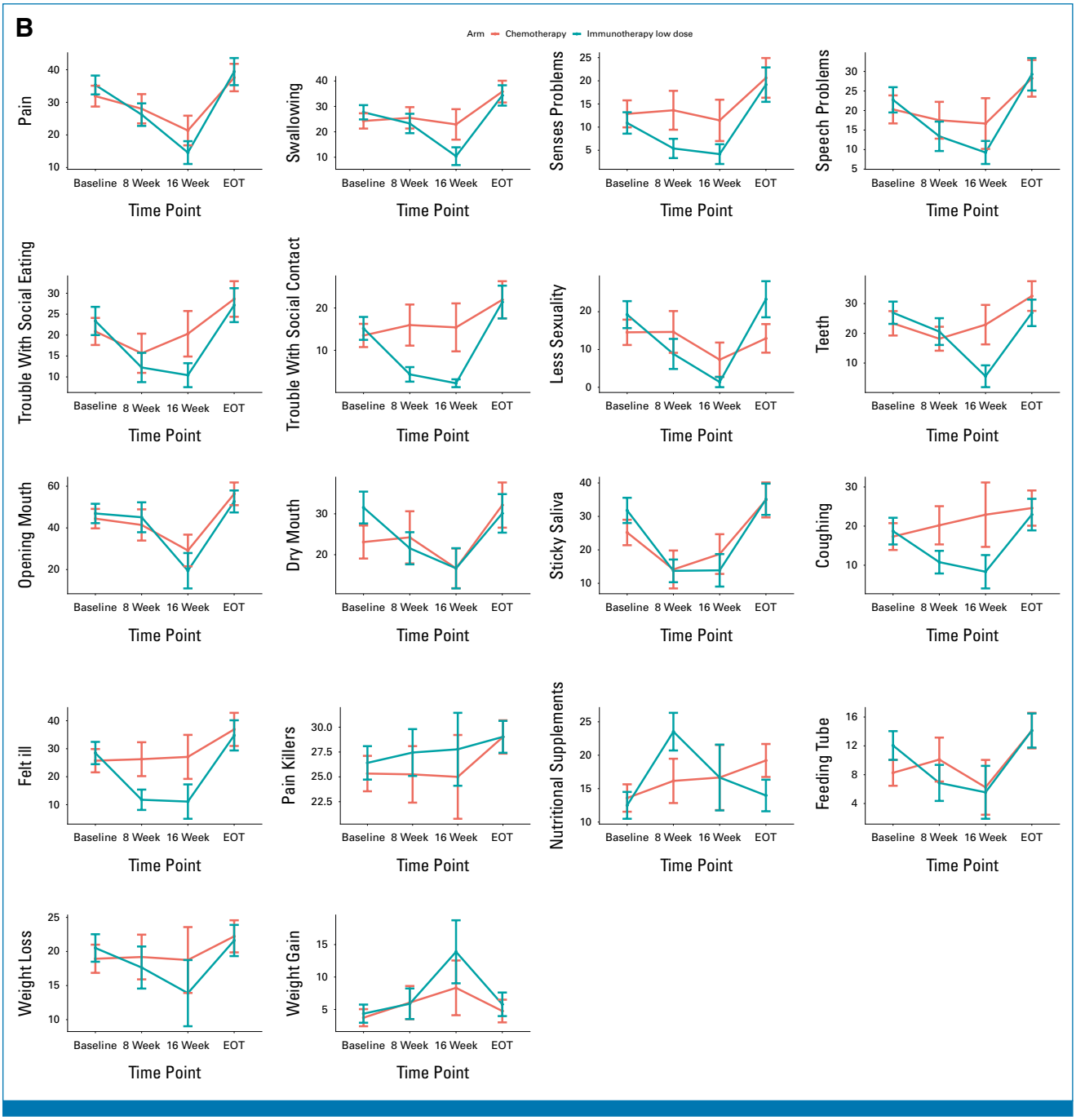


FIG 4. (Continued).

likely to have delayed separation of the curves.[38] Future studies could explore whether short-course chemotherapy at initiation may bridge the delayed onset of ICI activity.[25,39]

The median OS in the standard arm (4.7 months) was slightly lower than anticipated. This was likely due to the heavily pretreated nature of our cohort, in which one-third had received ≥2 prior lines of therapy and many had platinum-refractory or rapidly progressing disease. Similar OS figures have been reported in CheckMate 141 and real-world studies from Asia.[13,15,40] Thus, the standard arm in our study did not underperform, rather the significant OS benefit of ultra-low-dose immunotherapy was related to true efficacy of ICI.

Ultra-low-dose ICI therapy caused significantly fewer toxicities and improved the QoL. Patients with relapsed refractory tumors have a dismal prognosis with limited survival. For these patients, optimizing oncologic outcomes is important but avoiding excessive toxicity and maximizing QoL are equally important. Ultra-low-dose ICI is ideal for these patients. We did not observe any immune-related

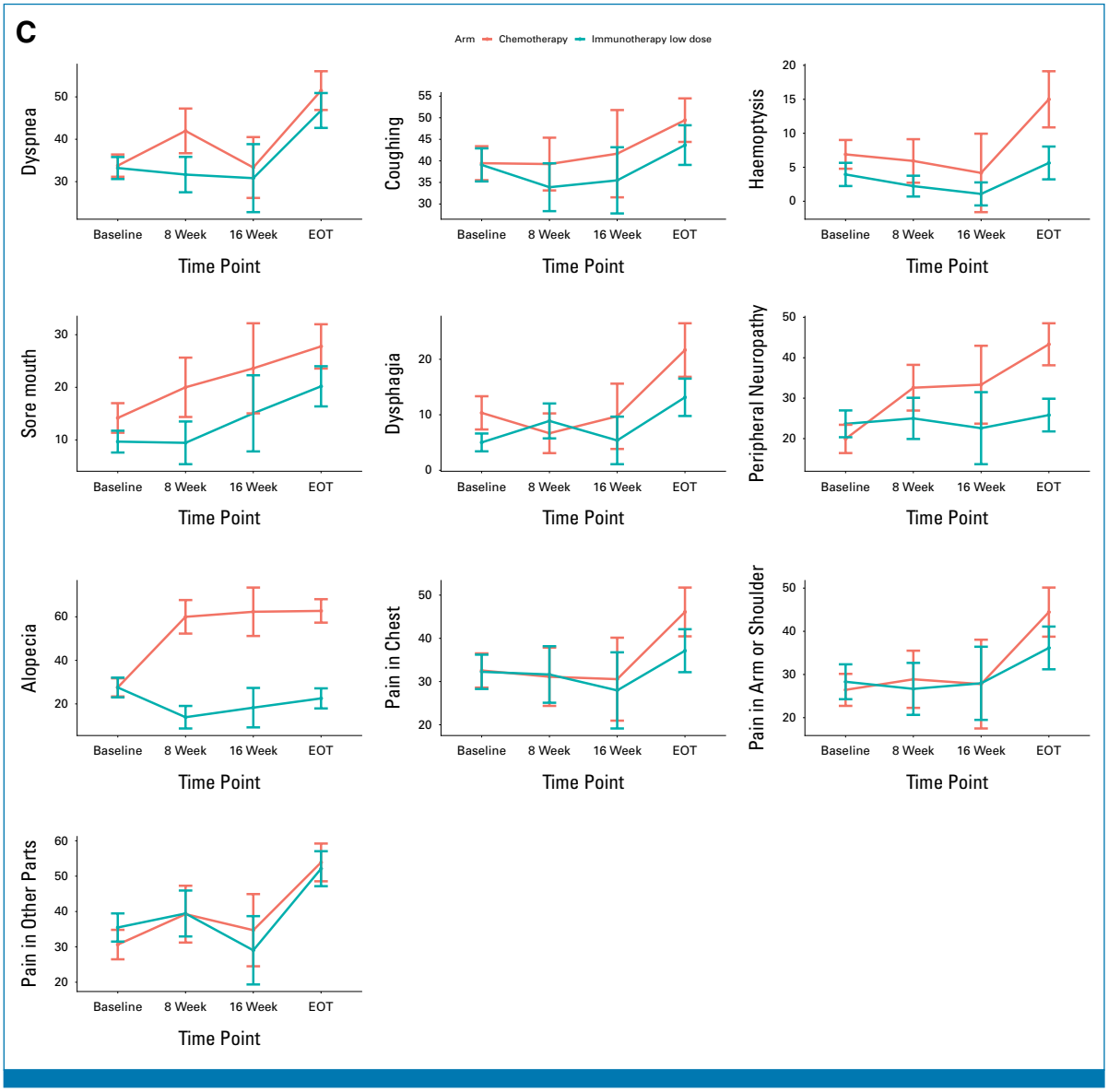


FIG 4. (Continued).

adverse events (irAEs), other than skin rash and pneumonitis, and both occurred to a similar extent in the two arms. Full-dose anti–PD-1 antibodies cause grade ≥3 irAEs in approximately 10% patients.[41] Ultra-low-dose nivolumab may cause fewer irAEs, which will need to be confirmed in future studies.

In our study, 42% of patients on ultra-low-dose nivolumab developed grade ≥3 toxicities, which was much higher than the 7%-13% level reported in landmark studies.[11-13] Grade ≥3 toxicities consisted predominantly of hyponatremia, which occurred in 28.6% of patients on ultra-low-dose immunotherapy and 40.5% on chemotherapy. Hyponatremia is an unusual side effect which has been reported in other Indian studies—in our phase III study that established the role of low-dose nivolumab in advanced HNC, 30.3% of patients on low-dose nivolumab and 27% patients on oral metronomic chemotherapy developed grade ≥3 hyponatremia.[7] In the study evaluating the addition of gefitinib to chemotherapy in advanced *EGFR*-mutant NSCLC, 24% of patients on gefitinib + chemotherapy developed grade ≥3 hyponatremia.[42] We earlier reported grade ≥3 hyponatremia in 35% of patients with advanced NSCLC treated with pemetrexed + carboplatin.[43] The reason behind the high rates of hyponatremia in Indian patients with cancer on cancer-directed therapy is unclear and may be related to ethnic/pharmacogenomic, dietary, or other undetermined factors.

Our study was conducted at a single center. We enrolled a diverse group of patients with various primary cancers. The study was not powered to evaluate the efficacy of ultra-low-dose nivolumab in individual tumors. However, the consistency of benefit across subgroups strengthens the overall conclusion. Additionally, patients in the chemotherapy

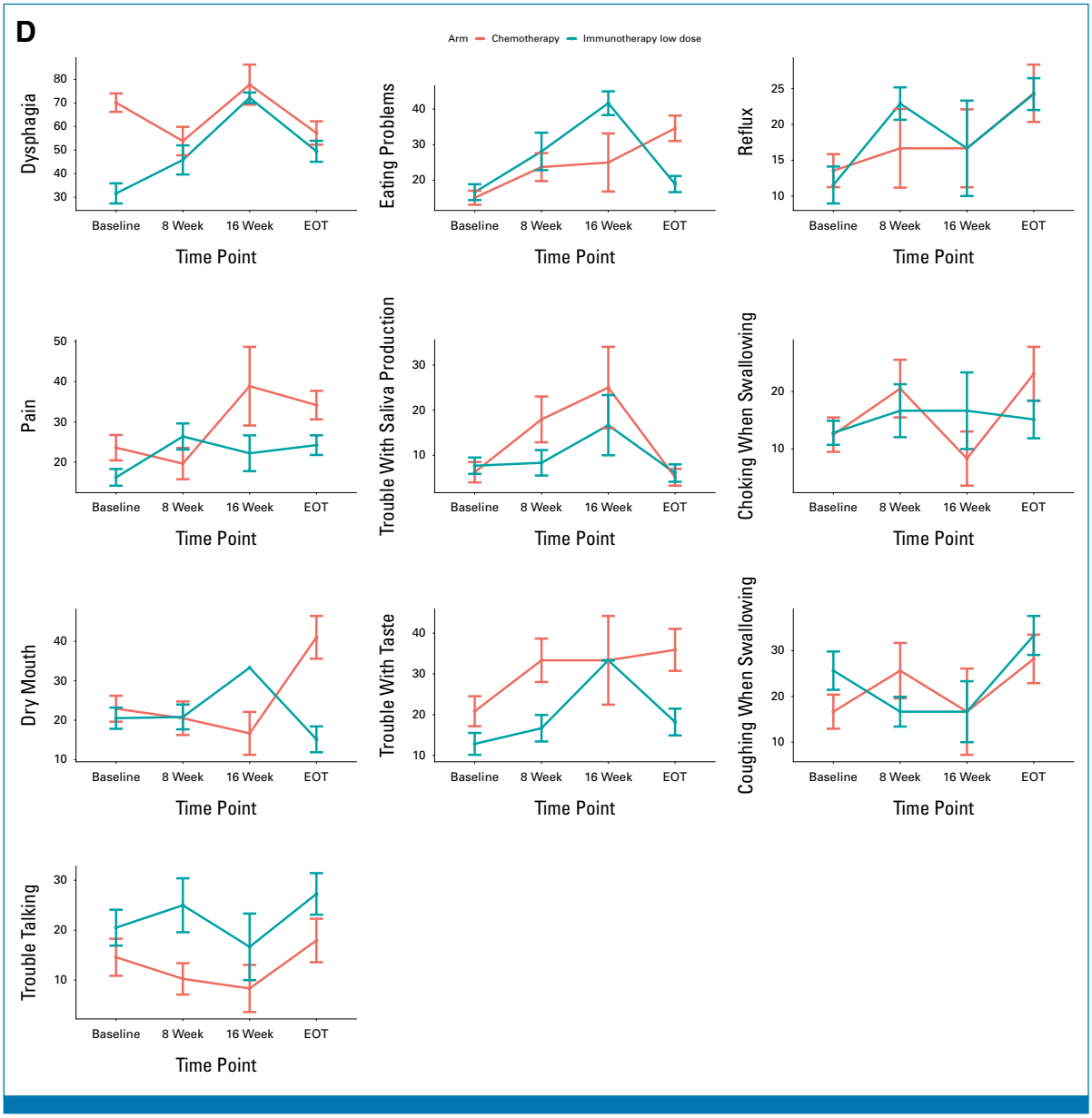


FIG 4. (Continued).

group could receive one of several chemotherapy regimen options, which may have introduced heterogeneity in follow-up and response assessment. A substantial proportion of patients in the standard arm received a prior taxane, which may have limited the efficacy of the control arm. However, a post hoc analysis did not reveal any statistically significant differences in oncologic outcomes based on receipt of prior taxanes. Only approximately 5% of patients had brain metastases, which was lower than expected. NSCLC accounted for about a third of the patients in the study. In non-NSCLC tumors, routine brain imaging was not considered the standard of care. Even in patients with NSCLC, brain imaging was not routinely performed at our institution, except in patients with neurologic symptoms/signs. We did not perform correlative pharmacokinetic/pharmacodynamic studies, drug levels, or biomarker studies. Our study was conducted during the COVID-19 pandemic, which may have affected the administration of cancer-directed therapy and follow-up imaging, although this would have affected both arms similarly. Finally, our study did not compare ultra-low-dose immunotherapy with standard-dose immunotherapy, and thus, the question of comparative efficacy of ultra-low-dose immunotherapy to standard full-dose immunotherapy remains unanswered.

In conclusion, ultra-low-dose nivolumab at one-twelfth the standard dose significantly improves survival compared with chemotherapy in relapsed refractory solid tumors, with fewer side effects and improved QoL. This offers an affordable treatment option for patients lacking access to

full-dose immunotherapy. Future studies should evaluate ultra-low-dose immunotherapy earlier in therapy and in curative-intent settings. Our findings support the need for more rational dose-finding strategies in immunotherapy, with the goal of improving global affordability and patient outcomes.

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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 email 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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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Ultra-Low-Dose Immunotherapy in Relapsed Refractory Solid Tumors: Phase III Superiority Randomized Trial (DELII)

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APPENDIX 1. STATISTICAL ANALYSIS

All analyses followed the intention-to-treat principle. *P* value <.05 was considered statistically significant for all tests. Statistical analysis was performed using the Statistical Program for the Social Sciences (version 25.0) and R Studio (version 4.4.1). Categorical variables were summarized as percentages and continuous variables with means or medians after testing for normality. For data that were skewed, nonparametric alternatives were used. The Chi-square test/Fisher exact test was used to compare categorical baseline characteristics between chemotherapy and ultra-low-dose immunotherapy arms. The Independent *t*-test or Mann-Whitney U test were applied to compare continuous baseline variables between the groups, depending on the normality of the data.

Objective response rate was calculated as the percentage of patients who attained either a complete or partial remission as the best response. Disease control rate was the percentage of patients having either a complete or partial remission or stable disease as the best response. Duration of response (DoR) was defined as the time from the first documented complete or partial response to progression or death, whichever occurred first. Patients without progression or death were censored on the date of last follow-up. Nonresponders were excluded from the DoR analysis. The median DoR and its 95% CI were estimated using the Kaplan-Meier method.[17,18] OS was defined as the duration in months from the date of random assignment to death. Patients who were alive at last follow-up were censored at that date of last follow-up. Death was considered an event for OS analysis. PFS was defined as the duration in months from the date of random assignment to progression or death, whichever was earlier. In patients without progression or death, PFS was calculated to the date the patient was last known to be alive and progression free. Events for PFS included progression as per RECIST version 1.1, clinical progression (if radiologic reassessment was not done), which was any increase in symptoms which did not have an alternative explanation or any increase in signs of disease, and death.

The survival analysis aimed to compare OS and PFS between the chemotherapy and ultra-low-dose immunotherapy arms. For OS, the median OS, along with 1-year and 2-year OS estimates and their respective 95% CIs were reported. HR for OS between the two treatment arms was reported, with chemotherapy as the reference group. A similar approach was applied to PFS, reporting the median PFS, 1-year and 2-year PFS with CIs, and the HR between the two arms. Survival estimation was by the Kaplan-Meier method.[17,18] The log-rank test was used to evaluate statistical significance. The HRs for OS and PFS were estimated using Cox proportional hazards model.[19,20] We compared survival outcomes between chemotherapy and ultra-low-dose immunotherapy across various subgroups of interest. PD-L1 level was considered high in the following situations: for NSCLC, PD-L1 tumor proportion score (TPS) ≥ 50%; for HNC, PD-L1 combined positive score (CPS) ≥ 20 or PD-L1 TPS ≥50%, and for esophagogastric and urothelial cancers, PD-L1 CPS ≥10 or PD-L1 TPS ≥50%. For each subgroup, HRs with 95% CI were calculated using Cox proportional hazards regression models. The forest plot was created by plotting the HRs and their 95% CIs for each subgroup.

For QoL analysis, we compared the baseline QoL and symptom scores between patients receiving chemotherapy and those receiving ultra-low-dose immunotherapy using the QLQ-C30, HN35, LC13, and OES18 scales. For each QoL and symptom scale, the mean scores and standard deviations for both chemotherapy and ultra-low-dose immunotherapy groups were reported. The difference in mean scores between the two groups was calculated. For functional scales, higher scores indicated better QoL. For symptom scales, higher scores indicated poorer QoL. Additionally, the effect size (Cohen's d) was calculated to assess the magnitude of the treatment effect, with larger effect sizes indicating more substantial differences between the groups. Linear mixed-effects model was used to analyze longitudinal changes in QoL domains, assessing the impact of treatment (arm) and time on QoL scores. No data imputation was performed, and list-wise deletion was not applied. Only the available data for each visit were considered, with visits for which data were missing being excluded from the analysis. Trendlines were plotted to highlight the direction and magnitude of changes over time for both treatment groups, allowing for visual comparison. Time to deterioration in QoL was calculated from the date of random assignment to date of deterioration in QoL by ≥ 10 points or death, whichever was earlier. In patients in whom either of the events did not occur, this duration was calculated to the date of last follow-up.

TABLE A1. Chemotherapy Regimens Administered in the Patients Randomly Assigned to the Standard Chemotherapy Arm

Chemotherapy Regimen	Head and Neck Cancer (n = 120)	Lung Cancer (n = 85)	Esophagogastric (n = 17)	Urothelial Cancer (n = 8)	Colorectal Cancer (n = 7)	Total (N = 237)
Docetaxel 75 mg/m^2 once in 3 weeks	77 (64.2)	62 (72.9)	0	1 (12.5)	0	140 (59.1)
Paclitaxel 175 mg/m^2 once in 3 weeks	43 (35.8)	16 (18.8)	6 (35.3)	2 (25.0)	0	67 (28.3)
Paclitaxel 80 mg/m^2 once a week	0	7 (8.2)	11 (64.7)	5 (62.5)	0	23 (9.7)
Irinotecan	0	0	0	0	3 (42.9)	3 (1.3)
FOLFOX	0	0	0	0	1 (14.3)	1 (0.4)
Regorafenib	0	0	0	0	1 (14.3)	1 (0.4)
Capecitabine + irinotecan	0	0	0	0	2 (28.6)	2 (0.8)

Abbreviation: FOLFOX, 5-fluorouracil + oxaliplatin + leucovorin

TABLE A2. Baseline Quality of Life and Symptom Scale in Patients Randomly Assigned to Receive Either Chemotherapy or Low-Dose Immunotherapy

	Chemotherapy	Immunotherapy		
QoL Scale	Mean Score (SD)	Mean Score (SD)	Difference in Mean Scores	Effect Size
Global health status (QoL)	54.16 (21.59)	53.84 (21.67)	0.3181	0.015
Functional scales				
PF	80.26 (17.75)	81.36 (17.31)	−1.0955	-0.062
RF	80.97 (23.80)	81.25 (21.14)	−0.2867	-0.013
EF	70.98 (24.07)	70.81 (23.27)	0.1683	0.007
CF	85.69 (17.52)	83.46 (20.68)	2.2276	0.116
SF	78.74 (23.88)	75.10 (26.18)	3.6447	0.145
Symptom scales				
FA	37.69 (25.98)	37.21 (24.50)	0.4816	0.019
NV	11.47 (19.50)	9.43 (16.02)	2.0332	0.114
PA	32.18 (25.76)	34.86 (24.38)	−2.687	−0.106
Dyspnea (DY)	21.05 (27.99)	19.81 (26.84)	1.2402	0.045
Insomnia (SL)	27.26 (32.84)	27.17 (31.78)	0.08514	0.002
Appetite loss (AP)	31.30 (31.44)	29.43 (29.66)	1.8657	0.061
CO	17.13 (25.82)	15.79 (23.95)	1.3459	0.053
DI	5.26 (15.15)	8.29 (18.27)	−3.0365	−0.18
Financial difficulties (FI)	65.58 (36.05)	67.33 (35.03)	−1.7514	−0.049
Symptom scales (H&N35)				
Pain (HNPA)	31.90 (25.68)	35.32 (23.33)	−3.4192	−0.139
Swallowing (HNSW)	24.27 (24.07)	27.69 (22.66)	−3.4134	−0.160
Senses problems (HNSE)	12.86 (23.39)	10.89 (18.64)	1.9632	0.093
Speech problems (HNSP)	20.28 (28.73)	22.73 (26.09)	−2.4528	−0.089
Trouble with social eating (HNSO)	20.86 (25.92)	23.37 (27.21)	−2.5096	−0.094
Trouble with social contact (HNSC)	13.50 (21.99)	15.18 (21.83)	−1.6745	−0.076
Less sexuality (HNSX)	14.54 (26.91)	19.23 (28.79)	−4.6807	−0.168
Teeth (HNTE)	23.35 (32.88)	26.92 (30.24)	−3.5636	−0.113
Opening mouth (HNOM)	44.44 (37.47)	46.92 (37.51)	−2.4787	−0.066
Dry mouth (HNDR)	23.09 (32.97)	31.53 (31.42)	−8.4415	−0.262
Sticky saliva (HNSS)	25.19 (30.49)	31.79 (30.46)	−6.5976	−0.216
Coughing (HNCO)	17.32 (27.49)	18.71 (27.53)	−1.3951	−0.050
Felt ill (HNFI)	25.72 (33.38)	28.46 (32.17)	−2.7394	−0.083
Pain killers (HNPK)	25.33 (14.29)	25.33 (14.29)	−1.0768	0.000
Nutritional supplements (HNNU)	13.59 (16.44)	12.49 (16.19)	1.0998	0.067
Feeding tube (HNFE)	8.26 (14.45)	12.21 (16.12)	−3.7842	−0.258
Weight loss (HNWL)	18.93 (16.57)	20.51 (16.27)	−1.5793	−0.096
Weight gain (HNWG)	3.73 (10.55)	4.35 (11.28)	−0.6255	−0.056
Symptom scales (LC13)				
Dyspnea (LCDY)	33.77 (21.06)	33.21 (20.94)	0.5664	0.027
Coughing (LCCO)	39.46 (31.55)	39.06 (30.93)	0.3953	0.013
Hemoptysis	6.89 (16.96)	3.94 (13.76)	2.9539	0.191
Sore mouth (LCSM)	14.17 (22.52)	9.67 (16.72)	4.4987	0.227
Dysphagia (LCDS)	10.34 (24.01)	5.01 (12.95)	5.3270	0.274
Peripheral neuropathy (LCPN)	19.92 (28.05)	23.65 (26.73)	−3.7320	−0.136
Alopecia (LCHR)	27.58 (33.41)	27.53 (36.51)	0.0497	0.001
Pain in chest (LCPC)	32.56 (31.73)	32.25 (32.02)	0.3083	0.010

(continued on following page)

TABLE A2. Baseline Quality of Life and Symptom Scale in Patients Randomly Assigned to Receive Either Chemotherapy or Low-Dose Immunotherapy (continued)

	Chemotherapy	Immunotherapy		
QoL Scale	Mean Score (SD)	Mean Score (SD)	Difference in Mean Scores	Effect Size
Pain in arm or shoulder (LCPA)	26.43 (29.70)	28.31 (32.58)	−1.8783	−0.060
Pain in other parts (LCPO)	30.65 (33.41)	35.48 (32.15)	−4.8325	−0.147
Symptom scales (OES18)				
Dysphagia (OESDYS)	70.13 (31.35)	31.36 (34.50)	38.5149	1.175
Eating (OESEAT)	15.10 (15.87)	16.66 (18.00)	−1.5625	−0.092
Reflux (OESRFX)	13.54 (18.47)	11.53 (20.84)	2.0032	0.102
Pain (OESPA)	23.61 (25.29)	16.23 (16.73)	7.3717	0.344
Swallowing (OESSV)	6.25 (18.13)	7.69 (14.61)	−1.4423	−0.087
Choking (OESCH)	12.50 (23.95)	12.82 (16.87)	−0.3205	−0.015
Dry mouth (OESDM)	22.91 (26.44)	20.51 (21.68)	2.4038	0.099
Taste (OESTA)	20.83 (29.50)	12.82 (21.68)	8.0128	0.310
Cough (OESCO)	16.66 (29.81)	25.64 (33.75)	−8.9743	−0.282
Speech (OESSP)	14.58 (29.73)	20.51 (28.99)	−5.9294	−0.202

NOTE. QoL was measured using EORTC QLQ C30 for all patients and HN35, LC13, and OES18 for patients with head and neck, lung, and esophageal cancers, respectively.

Abbreviations: CF, cognitive functioning; CO, constipation; DI, diarrhea; DY, dyspnea; EF, emotional functioning; EORTC, European Organization for Research and Treatment of Cancer; FA, fatigue; NV, nausea and vomiting; PA, pain; PF, physical functioning; QoL, quality of life; RF, role functioning; SD, standard deviation; SF, social functioning.

TABLE A3. Assessing Longitudinal Changes in QoL and Symptoms in Patients With Relapsed Cancers Who Received Either Chemotherapy or Low-Dose Immunotherapy, Using Linear Mixed-Effects Models

Groups	Arm (*P*)	Visit (*P*)	Arm × Visit
Global health status (QoL)	.014	<.001	.734
Functional scales			
PF	.641	<.001	.985
RF	.375	<.001	.963
EF	.222	<.001	.798
CF	.376	<.001	.556
SF	.223	<.001	.117
Symptom scales			
FA	.780	<.001	.786
NV	.919	.022	.986
PA	.490	<.001	.821
DY	.576	.003	.917
Insomnia (SL)	.139	<.001	.915
Appetite loss (AP)	.927	<.001	.958
CO	.734	.086	.939
DI	.866	.143	.402
Financial difficulties (FI)	.016	.162	.265
Symptom scales (H&N35)			
Pain (HNPA)	.546	<.001	.228
Swallowing (HNSW)	.241	<.001	.341
Senses problems (HNSE)	.660	.002	.848
Speech problems (HNSP)	.772	.005	.339
Trouble with social eating (HNSO)	.745	.003	.615
Trouble with social contact (HNSC)	.579	.007	.142
Less sexuality (HNSX)	.459	.217	.437
Teeth (HNTE)	.141	.198	.081
Opening mouth (HNOM)	.173	.002	.209
Dry mouth (HNDR)	.555	.181	.310
Sticky saliva (HNSS)	.543	<.001	.674
Coughing (HNCO)	.390	.231	.262
Felt ill (HNFI)	.770	.007	.270
Pain killers (HNPK)	.192	.396	.617
Nutritional supplements (HNNU)	.299	.008	.202
Feeding tube (HNFE)	.866	.014	.561
Weight loss (HNWL)	.986	.102	.553
Weight gain (HNWG)	.050	.125	.541
Symptom scales (LC13)			
Dyspnea (LCDY)	.757	<.001	.741
Coughing (LCCO)	.261	.205	.999
Hemoptysis (LCHA)	.309	.322	.848
Sore mouth (LCSM)	.960	.017	.741
Dysphagia (LCDS)	.453	.016	.607
Peripheral neuropathy (LCPN)	.831	.009	.229
Alopecia (LCHR)	<.001	.008	<.001
Pain in chest (LCPC)	.389	.035	.855
Pain in arm or shoulder (LCPA)	.880	.006	.778
Pain in other parts (LCPO)	.682	<.001	.984
Symptom scales (OES18)			
Dysphagia (OESDYS)	.548	.499	.242
Eating (OESEAT)	.515	.123	.240
Reflux (OESRFX)	.909	.459	.978
Pain (OESPA)	.007	.401	.083
Swallowing (OESSV)	.002	.001	.013
Choking (OESCH)	.013	.278	.034
Dry mouth (OESDM)	.332	.528	.274
Taste (OESTA)	.197	.665	.935
Cough (OESCO)	.588	.522	.756
Speech (OESSP)	.224	.849	.985

Abbreviations: CF, cognitive functioning; CO, constipation; DI, diarrhea; DY, dyspnea; EF, emotional functioning; FA, fatigue; NV, nausea and vomiting; PA, pain; PF, physical functioning; QoL, quality of life; RF, role functioning; SF, social functioning.

TABLE A4. Distribution of Patient Follow-Up Across Two Treatment Arms (all patients)

Time Point	Chemotherapy, (n = 250)	Immunotherapy, (n = 250)	Total (N = 500)
Baseline	247 (98.80)	250 (100.00)	497 (99.40)
8 weeks	100 (40.00)	115 (46.00)	215 (43.00)
16 weeks	48 (19.20)	48 (19.20)	96 (19.20)
24 weeks	25 (10.00)	32 (12.80)	57 (11.40)
32 weeks	13 (5.20)	20 (8.00)	33 (6.60)
40 weeks	9 (3.60)	14 (5.60)	23 (4.60)
48 weeks	5 (2.00)	10 (4.00)	15 (3.00)
56 weeks	5 (2.00)	7 (2.80)	12 (2.40)
64 weeks	5 (2.00)	2 (0.80)	7 (1.40)
72 weeks	3 (1.20)	3 (1.20)	6 (1.20)
80 weeks	2 (0.80)	3 (1.20)	5 (1.00)
88 weeks	1 (0.40)	4 (1.60)	5 (1.00)
96 weeks	1 (0.40)	2 (0.80)	3 (0.60)
104 weeks	0 (0.00)	1 (0.40)	1 (0.20)
112 weeks	1 (0.40)	1 (0.40)	2 (0.40)
128 weeks	1 (0.40)	1 (0.40)	2 (0.40)
144 weeks	0	1 (0.40)	1 (0.20)
End of treatment	173 (69.2)	188 (75.20)	361 (72.20)

TABLE A5. Distribution of Patient Follow-Up Across Two Treatment Arms in the Patients With Head and Neck Cancer

Time Point	Chemotherapy, (n = 128)	Immunotherapy (n = 130)	Total (N = 258)
Baseline	128 (100)	130 (100)	258 (100)
8 weeks	33 (25.78)	35 (26.92)	68 (26.36)
16 weeks	16 (12.5)	12 (9.23)	28 (10.85)
24 weeks	6 (4.68)	8 (6.15)	14 (5.43)
32 weeks	2 (1.56)	5 (3.85)	7 (2.71)
40 weeks	1 (0.78)	6 (4.62)	7 (2.71)
48 weeks	1 (0.78)	4 (3.08)	5 (1.94)
56 weeks	0	3 (2.31)	3 (1.16)
End of treatment	86 (67.18)	94 (72.31)	180 (69.77)

TABLE A6. Distribution of Patient Follow-Up Across Two Treatment Arms in the Patients With Lung Cancer

Time Point	Chemotherapy, (n = 87)	Immunotherapy, (n = 250)	Total, (N = 500)
Baseline	87 (100)	94 (100)	181 (100)
8 weeks	45 (51.72)	60 (63.83)	105 (58.01)
16 weeks	24 (27.59)	31 (32.98)	55 (30.39)
24 weeks	14 (16.09)	20 (21.28)	34 (18.78)
32 weeks	8 (9.20)	14 (14.89)	22 (12.15)
40 weeks	6 (6.90)	8 (8.51)	14 (7.73)
48 weeks	3 (3.45)	6 (6.38)	9 (4.97)
56 weeks	4 (4.60)	4 (4.26)	8 (4.42)
64 weeks	4 (4.60)	2 (2.13)	6 (3.31)
72 weeks	2 (2.30)	3 (3.19)	5 (2.76)
80 weeks	1 (1.15)	3 (3.19)	4 (2.21)
88 weeks	0	3 (3.19)	3 (1.66)
96 weeks	0	2 (2.13)	2 (1.10)
104 weeks	0	1 (1.06)	1 (0.55)
112 weeks	0	1 (1.06)	1 (0.55)
End of treatment	62 (71.26)	71 (75.53)	133 (73.48)

TABLE A7. Distribution of Patient Follow-Up Across Two Treatment Arms in the Patients With Esophageal Cancer

Time Point	Chemotherapy (n =16)	Immunotherapy (n = 13)	Total (N = 29)
Baseline	16 (100.00)	13 (100.00)	29 (100.00)
8 weeks	13 (81.25)	8 (61.54)	21 (72.41)
16 weeks	4 (25.00)	2 (15.38)	6 (20.69)
24 weeks	1 (6.25)	2 (15.38)	3 (10.34)
32 weeks	0 (0.00)	1 (7.69)	1 (3.45)
End of treatment	13 (81.25)	11 (84.62)	24 (82.76)

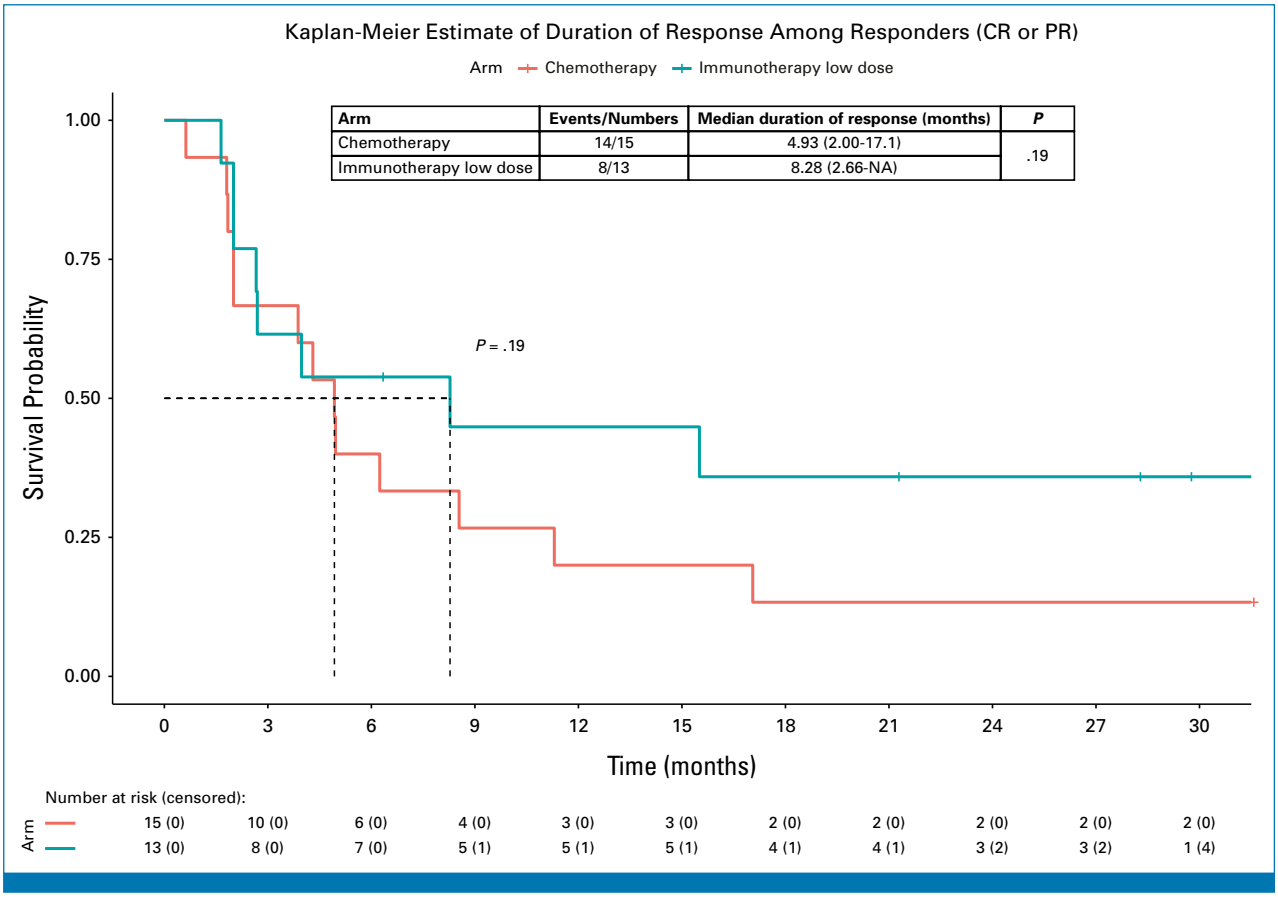

FIG A1. Duration of response in patients who received ultra-low-dose nivolumab compared with those who received chemotherapy. CR, complete response; NA, not available; PR, partial response.

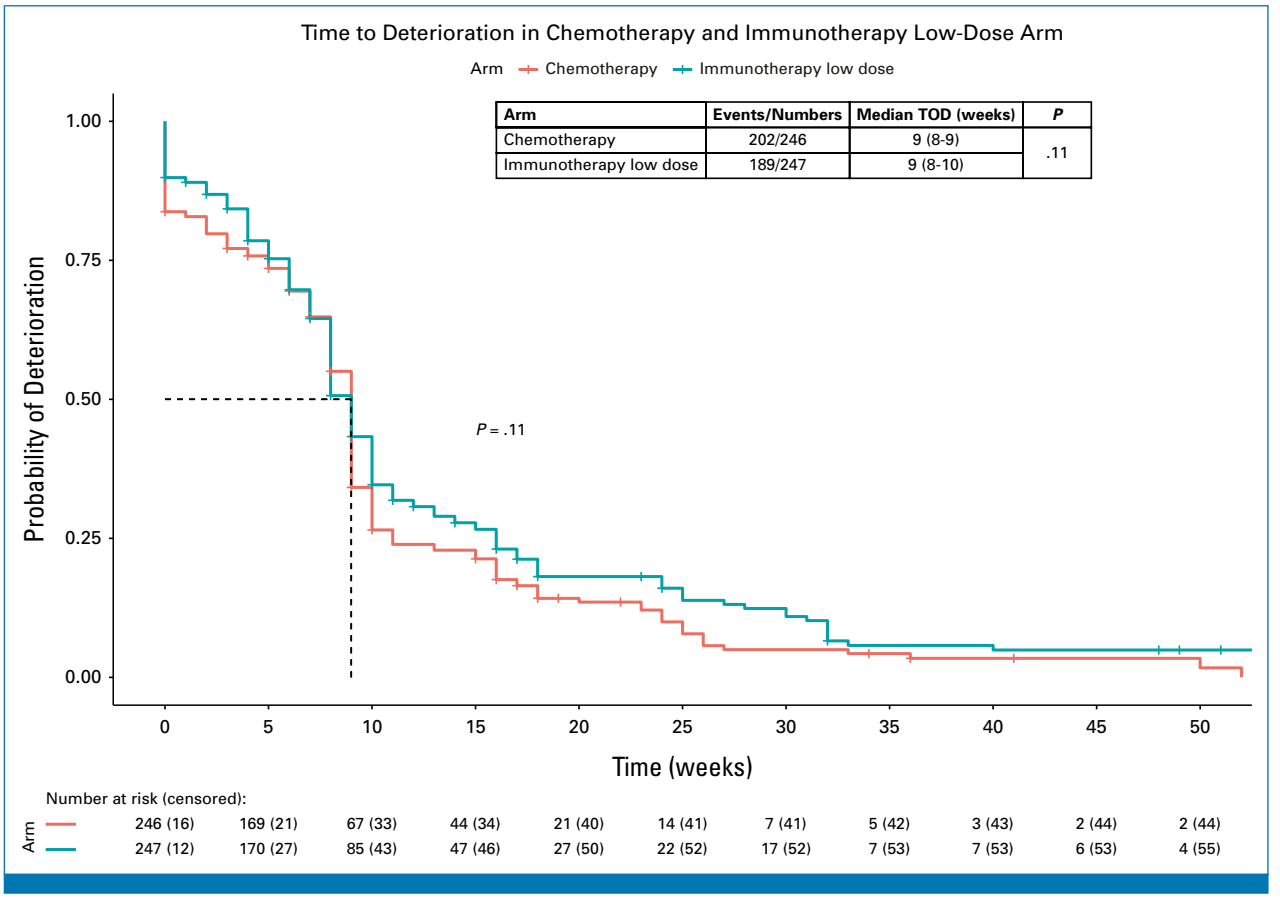

FIG A2. Time to deterioration in quality of life between patients randomly assigned to ultra-low-dose immunotherapy or to standard cytotoxic chemotherapy. TOD, time to deterioration.