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Article

Quality-of-life outcomes and risk prediction for patients randomized to nivolumab plus ipilimumab vs nivolumab on LungMAP-S1400I

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Abstract

Background: An important issue for patients with cancer treated with novel therapeutics is how they weigh the effects of treatment on survival and quality of life (QOL). We compared QOL in patients enrolled to SWOG S1400I, a substudy of the LungMAP biomarker-driven master protocol.

Methods: SWOG S1400I was a randomized phase III trial comparing nivolumab plus ipilimumab vs nivolumab for treatment of immunotherapy-naïve disease in advanced squamous cell lung cancer. The primary endpoint was the MD Anderson Symptom Inventory–Lung Cancer severity score at week 7 and week 13 with a target difference of 1.0 points, assessed using multivariable linear regression. A composite risk model for progression-free and overall survival was derived using best-subset selection.

Results: Among 158 evaluable patients, median age was 67.6 years and most were male (66.5%). The adjusted MD Anderson Symptom Inventory–Lung Cancer severity score was 0.04 points (95% confidence interval [CI] = −0.44 to 0.51 points; $P = .89$) at week 7 and 0.12 points (95% CI = −0.41 to 0.65; $P = .66$) at week 13. A composite risk model showed that patients with high levels of appetite loss and shortness of breath had a threefold increased risk of progression or death (hazard ratio [HR] = 3.06, 95% CI = 1.88 to 4.98; $P < .001$) and that those with high levels of both appetite loss and work limitations had a fivefold increased risk of death (HR = 5.60, 95% CI = 3.27 to 9.57; $P < .001$)—compared with those with neither risk category.

Conclusions: We found no evidence of a benefit of ipilimumab added to nivolumab compared with nivolumab alone for QOL in S1400I. A risk model identified patients at high risk of poor survival, demonstrating the prognostic relevance of baseline patient-reported outcomes even in those with previously treated advanced cancer.

Advanced non-small cell lung cancer (NSCLC) is associated with a substantial symptom burden. Patients with NSCLC suffer from high severity levels of physical symptoms, especially cough, shortness of breath, and chest pain (1). These symptoms can have serious consequences on patient functionality and quality of life (QOL) (2). The ability to provide direct evidence reflecting

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the improvement, stabilization, or worsening of disease symptoms is invaluable to demonstrating clinical benefit, beyond survival, and informing decision making (3-6).

The Lung Master Protocol (Lung-MAP; S1400) was a large scale, biomarker-driven master protocol for patients with previously treated advanced stage squamous cell lung cancer (7,8). For patients not meeting the eligibility criteria to participate in a biomarker-driven substudy, the Lung-MAP infrastructure included nonmatch substudies evaluating therapies thought to have potentially broad activity. SWOG S1400I, one of the nonmatch substudies within Lung-MAP, was a randomized phase III trial that compared nivolumab plus ipilimumab (NI) with nivolumab alone for the treatment of immunotherapy-naïve disease. The primary efficacy findings for S1400I showed no evidence that NI improved survival outcomes compared with nivolumab alone, with no detectable differences between arms in overall survival (the primary clinical endpoint) or in progression-free survival or response (9). The incidence of severe toxicity did not differ between arms. More patients discontinued treatment on the NI arm (25.0%) compared with the nivolumab arm (15.4%).

To more fully reflect the complex symptom profile experienced by patients, this paper reports on health-related QOL outcomes pertaining to patient-reported symptom and functional status in S1400I. Additionally, given limited evidence of the prognostic value of PRO in previously treated lung cancer, we evaluated whether survival outcomes differed by QOL scores.

Methods

Patient population and study design

In SWOG S1400I, patients with previously treated stage IV or recurrent squamous cell lung cancer were randomly assigned to receive either NI or nivolumab alone. Patients received nivolumab by intravenous administration, receiving 3 mg/kg over 30 minutes on day 1 of 14-day cycles. Patients also received ipilimumab by intravenous administration, receiving 1 mg/kg over 60 minutes on day 1 of every third cycle beginning 30 minutes after the end of nivolumab infusion. Protocol treatment was discontinued at disease progression or if the patient experienced intolerable side effects.

Patients who participated in the clinical trial and who could complete patient-reported outcome (PRO) forms in English were required to participate in the QOL component of the trial. Although the trial was activated in December 2015, the QOL study was not added to the trial until September 1, 2016; thus, all patients enrolled prior to September 1, 2016, were not eligible for the QOL study.

To conduct this trial, each participating site required approval by the US National Cancer Institute central institutional review board or approval by its local institutional review board. This report follows recommendations described in the CONSORT PRO extension (10).

Patient race (Asian, Black, multiracial, Native American, Pacific Islander, White, or unknown) and ethnicity (Hispanic, not Hispanic, or unknown) were obtained by patient self-report.

QOL instruments

The MD Anderson Symptom Inventory–Lung Cancer (MDASI-LC) asks patients to rate the severity of 13 core symptoms, including fatigue, sleep disturbance, pain, drowsiness, poor appetite, nausea, vomiting, shortness of breath, numbness, difficulty remembering, dry mouth, distress, and sadness (11,12). Three additional lung-specific items are included in the MDASI-LC module (coughing, constipation, and sore throat); the sore throat item was excluded because S1400I did not include radiation therapy (13). Patients were asked to rate each symptom's presence and greatest severity in the previous 24 hours on a 0-10 scale, with 0 representing "not present" and 10 representing "as bad as you can imagine." The MDASI-LC questionnaire generates a mean core symptom score for the 13 general symptoms and a mean severity score for the core plus 2 lung cancer symptom items for a total of 15 items. The MDASI-LC interference score (6 items) was also included to address how symptoms interfere with the patient's general activity or functional status in the last 24 hours; these items also use a 0-10 scale. Therefore, 21 items were included.

The EQ-5D health utility measure addresses different health dimensions (mobility, self-care, usual activities, pain and/or discomfort, and anxiety and/or depression), each rated at 3 levels on a scale from no problems to some problems to extreme problems (14-17). We analyzed the EQ-5D index score, a derived value reflecting how patients value their health state, ranging from 0 (a state as bad as being dead) to 1 (full health). Additionally, the single item visual analogue scale was used to measure overall health status.

Assessment times

The MDASI-LC was administered in conjunction with clinical follow-up at baseline and weeks 3, 5, 7, 9, 11, 13, 25, and 37. The EQ-5D questionnaire was administered at baseline and weeks 5, 7, 9, 13, 25, and 37 and at years 1, 2, and 3. These assessments were specified to continue, as scheduled, regardless of progression or initiation of other treatments.

Minimally important difference

The primary endpoint was the MDASI-LC severity score. A target difference of 1.0 point was specified as clinically meaningful based on prior literature (11-13). We assumed a standard deviation of 2.0 points for both time points based on prior literature (13), corresponding to an minimally important difference (MID) of half a standard deviation (0.5), a medium effect size (18).

Statistical analysis

Two primary endpoints were assessed, an early assessment at week 7 when clinically meaningful differences by arm were determined to possibly first occur and a late assessment at week 13 to identify potentially long-term differences. Approximately 10% dropout because of death at week 7 was anticipated. We assumed, conservatively, another 10% would drop out because of worsening disease, and 10% would be nonadherent to their assigned treatment. In power calculations, the 10% nonadherence rate reduced the nominal effect size of a 1.0-point target difference to 0.9, and the total 20% dropout rate inflated the estimated sample size by 25%. The study anticipated enrolling 332 eligible patients. Using a 2-arm normal design and a 2-sided alpha-0.025 test (to account for multiple comparisons using Bonferroni), a difference of 1.0 points between arms at week 7 could be identified with 92% power. Power to detect a 1.0-point difference at week 13 was 81% assuming 35% dropout (20% because of death and 15% for other reasons) and 15% nonadherence.

At a planned interim analysis, the study was closed for futility, as ipilimumab added to nivolumab was determined not to have improved overall survival (9). Additionally, grade 3 or higher treatment-related adverse events and treatment discontinuation trended higher among those receiving NI compared with

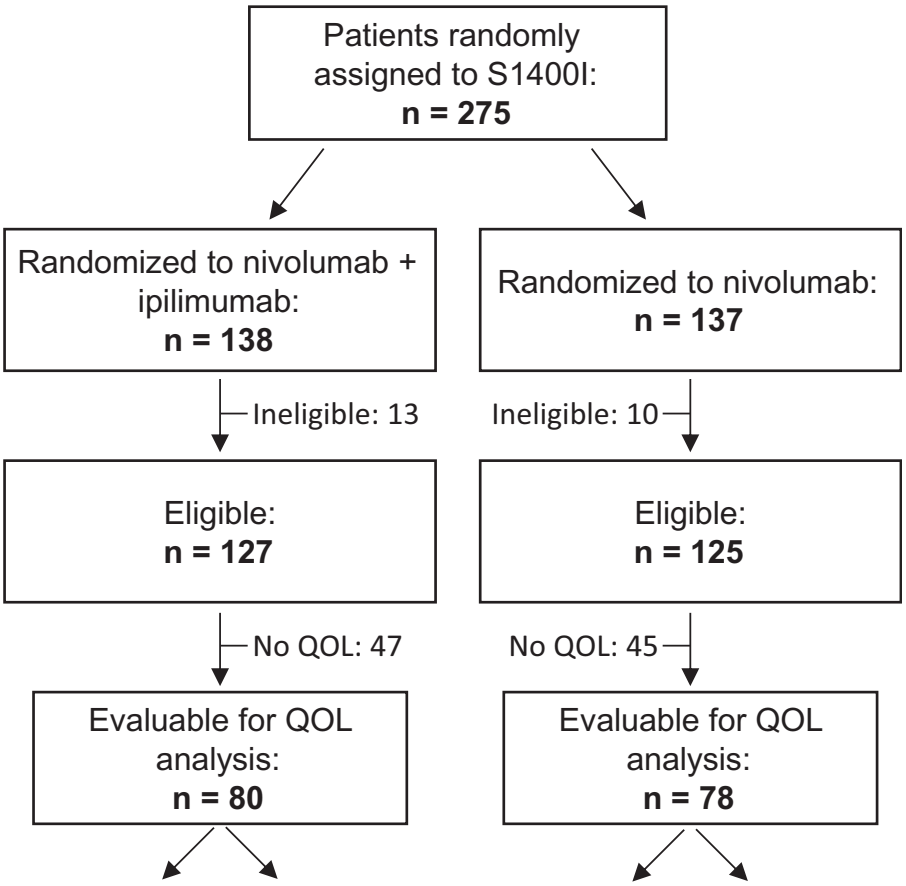
nivolumab alone. In post hoc power calculations, with 158 evaluable patients, actual power was 62% and 53% to detect the target difference of 1.0 points at weeks 7 and 13, respectively.

Differences between arms in week-7 and week-13 MDASI-LC severity scores were examined using multiple linear regression, adjusting for study stratification factors (sex, male vs female; number of prior therapies, 1 vs 2 or more) and the baseline severity score. Longitudinal analyses were conducted using linear mixed models, adjusting for intervention assignment, assessment time (as linear and quadratic functions), their interaction, and the baseline score, with individual patients considered random effects.

The MDASI-LC core, interference, and total scores and the EQ-5D health utility measure and overall health status measure were also examined by arm at each timepoint in multivariable linear regression. Each QOL domain was also examined in linear mixed models through week 37. Regression models included covariate adjustment for the stratification variables and the baseline score. Demographic information was self-reported.

Composite adverse risk model

Per protocol, we derived composite adverse risk models for progression-free and overall survival based on the individual MDASI-LC items. First, we examined whether each MDASI-LC



MDASI-LC	EQ-5D	Assessment	MDASI-LC	EQ-5D
80	80	Baseline	78	78
69	–	Week 3	68	–
70	68	Week 5	66	67
67	67	Week 7	66	67
62	62	Week 9	61	62
56	–	Week 11	54	–
55	53	Week 13	53	53
44	45	Week 24	43	43
34	35	Week 36	36	35
–	30	Year 1	–	28
–	18	Year 2	–	14
–	12	Year 3	–	8

Figure 1. Consort diagram. MDASI-LC = MD Anderson Symptom Inventory–Lung Cancer; QOL = quality of life.

Table 1. Characteristics of S1400I patients who participated in the PRO component[a]

Characteristic	Nivolumab + ipilimumab, No. (%) (n = 80)	Nivolumab, No. (%) (n = 78)	Total, No. (%) (n = 158)
Age, median (range), y	66.6 (41.8-81.2)	68.3 (50.2-84.4)	67.6 (41.8-84.4)
Younger than 65	36 (45.0)	32 (41.0)	68 (43.0)
65 or older	44 (55.0)	46 (59.0)	90 (57.0)
Sex			
Female	29 (36.3)	24 (30.8)	53 (33.5)
Male	51 (63.8)	54 (69.2)	105 (66.5)
Race			
Asian	—	2 (2.6)	2 (1.3)
Black	11 (13.8)	9 (11.5)	20 (12.7)
Multiracial	1 (1.3)	—	1 (0.6)
Native American	1 (1.3)	1 (1.3)	2 (1.3)
Pacific Islander	—	1 (1.3)	1 (0.6)
White	64 (80.0)	65 (83.3)	129 (81.6)
Unknown	3 (3.8)	—	3 (1.9)
Ethnicity			
Hispanic	2 (2.5)	—	2 (1.3)
Not Hispanic	76 (95.0)	78 (100.0)	154 (97.5)
Unknown	2 (2.5)	—	2 (1.3)
No. of prior systemic therapies for stage IV or recurrent disease			
1	65 (81.3)	63 (80.8)	128 (81.0)
2 or more	15 (18.8)	15 (19.2)	30 (19.0)
Zubrod performance status			
0	20 (25.0)	25 (32.1)	45 (28.5)
1	60 (75.0)	53 (67.9)	113 (71.5)
Weight loss in past 6 months			
<5%	56 (70.0)	56 (71.8)	112 (70.9)
5% to <10%	16 (20.0)	12 (15.4)	28 (17.7)
10% to <20%	7 (8.8)	9 (11.5)	16 (10.1)
≥20%	1 (1.3)	1 (1.3)	2 (1.3)
Smoking status			
Current	23 (28.8)	26 (33.3)	49 (31.0)
Former	55 (68.8)	49 (62.8)	104 (65.8)
Never	1 (1.3)	2 (2.6)	3 (1.9)
Not sure	1 (1.3)	1 (1.3)	2 (1.3)
Brain metastases at baseline			
No	74 (92.5)	68 (87.2)	142 (89.9)
Yes	6 (7.5)	10 (12.8)	16 (10.1)
Liver metastases at baseline			
No	68 (85.0)	65 (83.3)	133 (84.2)
Yes	12 (15.0)	13 (16.7)	25 (15.8)
Number of prior therapies			
1	65 (81.3)	63 (80.8)	128 (81.0)
2 or more	15 (18.8)	15 (19.2)	30 (19.0)

[a] Empty cells are indicated by an "—", indicating no patients with that specified characteristic were enrolled. PRO = patient-reported outcomes.

item was prognostic for time to progression or overall survival using Cox regression. Candidate variables were defined as those with a statistically significant association at the alpha less than .05 level. Using best subset selection, we identified the best 2 through 5 variable models for each outcome (19). For each q-variable model, we summed the number of adverse risk factors creating an adverse risk score, where each variable was split at its median value to define levels of high vs low risk of poorer survival. To enable a fair comparison across different domains, each q-variable adverse risk score was then split at the level that most closely approximated the median value, creating high (>median) and low (<median) risk groups. In a multivariable Cox regression, the best of the q-variable models was defined as the model that maximized the risk difference between groups based on the hazard ratio (HR). To examine whether potential threshold effects could further improve risk prediction, we used variable cut-point analysis to identify, for each of the q variables in the best model, the level that optimally differentiated survival outcomes between those with low (<cut point) vs high (≥cut point) values; only cut points that defined risk groups with at least 20% of the data were evaluated (20). The degree of risk separation between high- and low-risk groups was compared with the MDASI-LC severity, core, and total scores. Progression-free survival by investigator assessment was defined as time from random assignment to first occurrence of progression, symptomatic deterioration, or death due to any cause (21). Overall survival was defined as time from random assignment to death due to any cause. Patients alive without progression (death) were censored at the date of last disease assessment (date of last contact). All regression models adjusted for treatment and the baseline stratification variables.

Results

Baseline characteristics and study disposition

From December 2015 to April 2018, a total of 275 patients were randomly assigned of whom 252 patients (127 randomly assigned to NI and 125 to nivolumab alone) were eligible (Figure 1). QOL outcomes were evaluable for 80 patients on the NI arm and 78 on the nivolumab-alone arm. The predominant reason for

nonevaluability of QOL was enrollment prior to activation of the QOL substudy.

Median age was 67.6 (range = 41.8-84.4) years, and most patients were male (n = 105, 66.5%), with enrollment of 20 (12.7%) Black patients (Table 1). Most patients had a single prior platinum-based chemotherapy for stage IV or recurrent disease (n = 128, 81.0%) and performance status of 1 (n = 113, 71.5%) and were former (n = 104, 65.8%) or current (n = 49, 31.0%) smokers. There were no statistically significant differences by arm in any demographic, behavioral, or clinical characteristic.

MDASI-LC scores

At weeks 7 and 13 after random assignment, there were no statistically significant differences by arm in the submission of MDASI-LC forms (week 7: 83.8% for NI vs 84.6% for nivolumab, $P = 1.0$; week 13: 68.8% vs 67.9%, $P = 1.0$), indicating no evidence of informative missing data for the primary endpoint assessment. The mean (SD) baseline MDASI-LC severity score was 2.88 (2.12) in the NI group and 2.52 (1.52) in the nivolumab group (Supplementary Table 1, available online).

Primary outcome

Compared with baseline, the mean observed MDASI-LC severity score at week 7 was 0.22 points lower (indicating reduced symptom severity) in the NI group and 0.04 points lower in the nivolumab group, with differences in adjusted mean severity scores of 0.04 points (95% confidence interval [CI] = −0.44 to 0.51 points; $P = .89$) (Figure 2). Also compared with baseline, the mean observed MDASI-LC severity score at week 13 was 0.74 points lower in the NI group and 0.27 points lower in the nivolumab-alone group (adjusted difference = 0.12, 95% CI = −0.41 to 0.65; $P = .66$).

Secondary outcomes

In adjusted linear regression analyses, there were no statistically significant differences by arm in week-7 or week-13 MDASI-LC core scores, interference scores, or total scores, nor were there any differences in week-7 or week-13 EQ-5D utility index scores or global QOL (Figure 2). In linear mixed-model analysis, there was no statistically significant interaction between treatment arm and time (as either a linear or quadratic variable) with respect to either the MDASI-LC domain scores or the EQ-5D

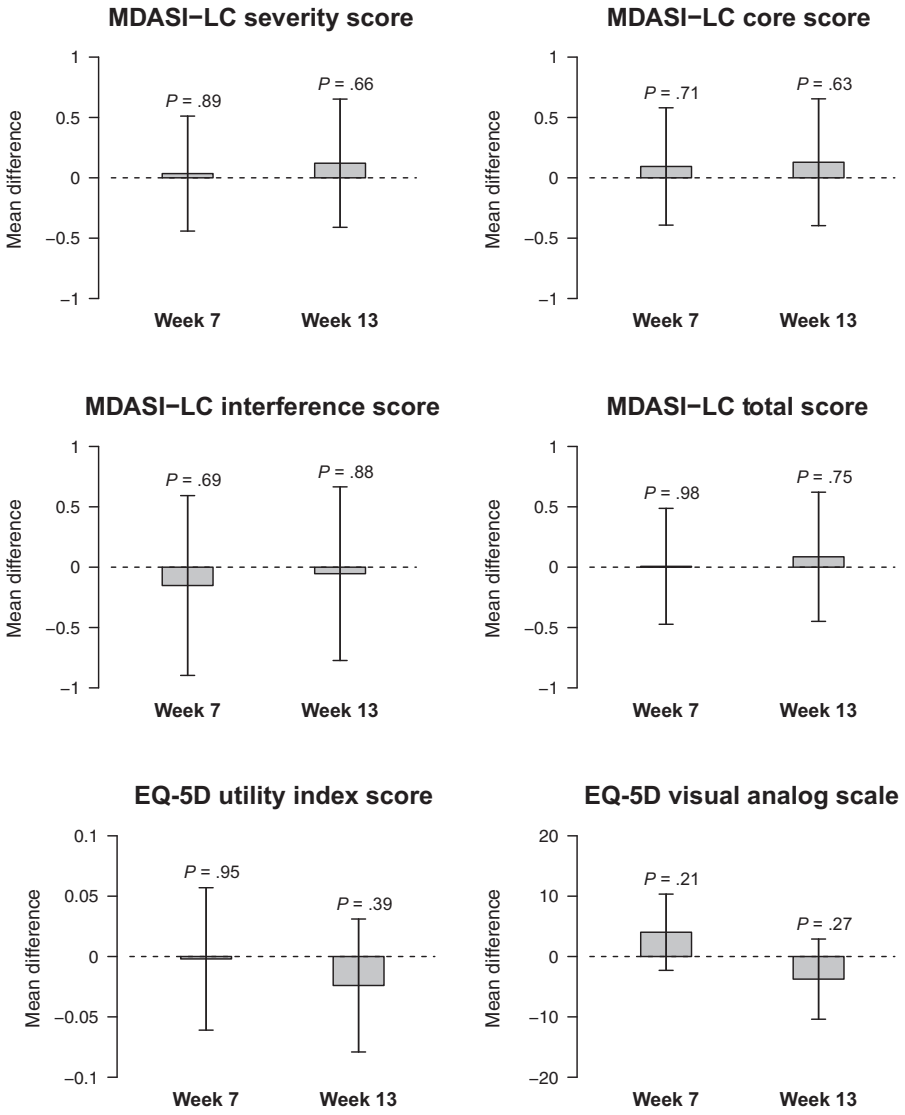


Figure 2. Bar plots of adjusted mean differences between nivolumab plus ipilimumab vs nivolumab alone. The **vertical lines** indicate the 95% confidence limits. MDASI-LC = MD Anderson Symptom Inventory–Lung Cancer.

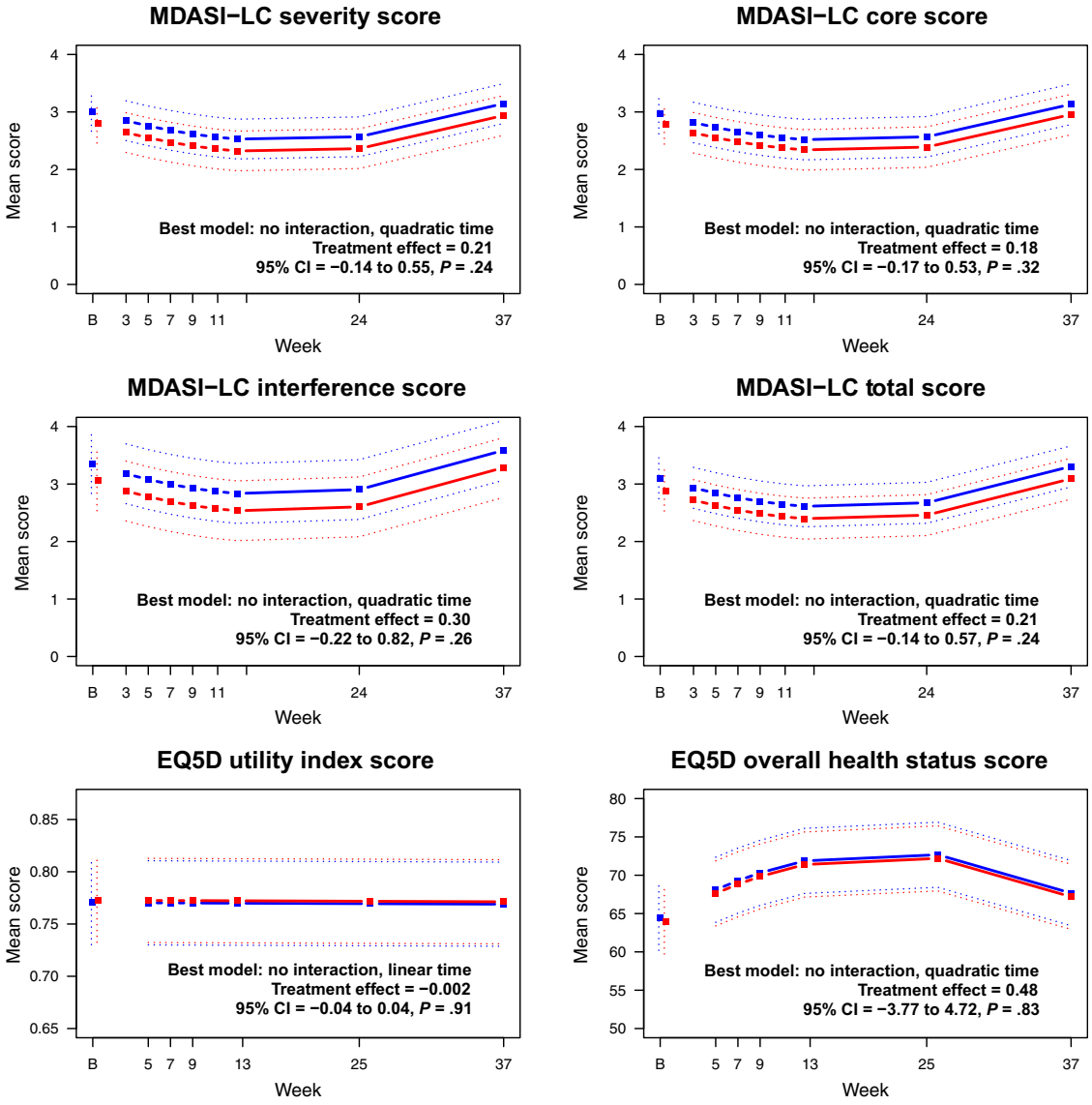


Figure 3. Linear mixed model regression results. **Blue** = nivolumab plus ipilimumab; **red** = nivolumab alone. The boxes indicate the model-derived point estimates, connected by **solid lines**. The **dashed lines** indicate the 95% confidence regions. CI = confidence interval; MDASI-LC = MD Anderson Symptom Inventory–Lung Cancer.

scores (Supplementary Table 2, available online). There was strong evidence of a quadratic relationship of follow-up scores over time for all MDASCI-LC domains and for the EQ-5D global QOL score, indicating reduced symptoms and improved QOL, respectively, through approximately week 24 that began to wane by week 37 (Figure 3).

PRO endpoints for clinical risk prediction

Bivariate analyses indicated that the MDASI-LC items pain, fatigue, shortness of breath, memory loss, appetite, dry mouth, sadness, activity limitations, work limitations, relations, walking, and enjoyment were each statistically significantly associated with progression-free or overall survival (Supplementary Table 3, available online). Using best subset selection, the best model for differentiating hazard risk of progression included appetite loss and shortness of breath (Supplementary Table 4, available online). One-third (32.9%) of patients had both appetite loss and shortness of breath above the median (≥1 and ≥4, respectively) at baseline. These patients had a 90% increased risk of progression (HR = 1.90, 95% CI = 1.32 to 2.72; $P < .001$), a larger increase in risk than any of the MDASI-LC scale scores, whether split at the median or (to better reflect the distribution of scores defined by the 2-variable risk scale) at the upper tertile (Figure 4). In variable cut-point analysis, the optimal cut point for appetite loss was 2 and for shortness of breath was 6. For this modified model, split into 3 levels (0 vs 1 vs 2 adverse risk variables), patients with both risk categories had more than 3 times the risk of progressive disease (HR = 3.06, 95% CI = 1.88 to 4.98; $P < .001$). Kaplan-Meier curves are shown in Figure 5.

The best model for differentiating risk of death included appetite loss and work limitations. One-third (34.8%) of patients had either appetite loss or work limitations above the median (≥1 and ≥4, respectively) at baseline; these patients had more than 2 times the risk of death (HR = 2.11, 95% CI = 1.48 to 2.99), a larger increase than for any of the MDASI-LC scale scores (Figure 4). In variable cut-point analysis, the optimal cut point for appetite loss was again 2 and for work limitations was 7. For this modified model, split into 3 levels, patients with both adverse risk

Model	High-risk level	Percent in high-risk group	Hazard ratio (95% confidence interval)	*P* Value
Progression–free survival				
MDASI–LC severity score	Above median	50.6%	1.31 (0.94 to 1.84)	.11
	Upper tertile	32.9%	1.56 (1.1 to 2.22)	.01
MDASI–LC core score	Above median	50.6%	1.39 (1 to 1.94)	.05
	Upper tertile	33.5%	1.7 (1.19 to 2.42)	.004
MDASI–LC total score	Above median	50.6%	1.38 (0.98 to 1.92)	.06
	Upper tertile	33.5%	1.44 (1.02 to 2.03)	.04
2–variable model (base)	Above median	32.9%	1.9 (1.32 to 2.72)	<.001
2–variable model (modified)	Low risk (reference)	43%	not applicable	
	Intermediate risk	37.3%	1.87 (1.28 to 2.73)	.001
	High risk	19.6%	3.06 (1.88 to 4.98)	<.001
Overall Survival				
MDASI–LC severity score	Above median	50.6	1.36 (0.95 to 1.94)	.09
	Upper tertile	32.9	1.38 (0.95 to 2.02)	.09
MDASI–LC core score	Above median	50.6	1.26 (0.89 to 1.79)	0.2
	Upper tertile	33.5	1.39 (0.96 to 2.02)	.08
MDASI–LC total score	Above median	50.6	1.34 (0.94 to 1.91)	.11
	Upper tertile	33.5	1.36 (0.94 to 1.98)	0.1
2–variable model (base)	Above median	34.8	2.62 (1.79 to 3.82)	<.001
2–variable model (modified)	Low risk (referent)	50	not applicable	
	Intermediate risk	36.1	1.76 (1.19 to 2.6)	.004
	High risk	13.9	5.6 (3.27 to 9.57)	<.001

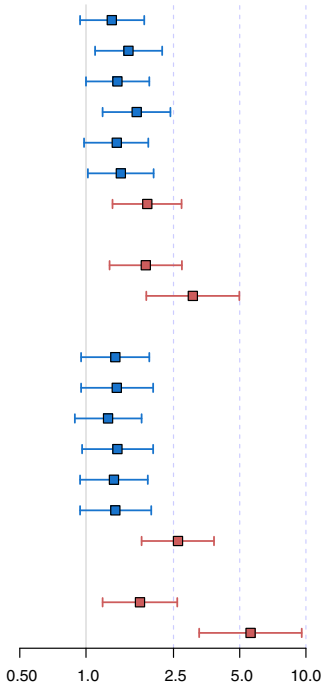


Figure 4. Forest plot of hazard ratio comparing risk of progression-free or overall survival by prognostic risk category. The **boxes** indicate the hazard ratios and the **horizontal lines** show the 95% confidence intervals. Results for the best 2-variable models are shown in **red**. MDASI-LC = MD Anderson Symptom Inventory–Lung Cancer.

categories had more than 5 times the risk of death compared with those with neither risk category (HR = 5.60, 95% CI = 3.27 to 9.57; $P < .001$; Figures 4 and 5).

Discussion

SWOG S1400I examined survival outcomes and QOL for patients with previously treated, advanced-stage squamous cell lung cancers randomly assigned to NI vs nivolumab alone. This phase III trial showed no benefit of the addition of ipilimumab with respect to survival outcomes (9). This current report showed no benefit of the addition of ipilimumab with respect to QOL measured using the MDASI-LC instrument at week 7 or week 13 after randomization. Further, longitudinal analyses showed little difference in QOL scores by treatment arm over time, nor did additional secondary analyses.

PROs in advanced NSCLC have been previously examined for both nivolumab and ipilimumab in trials, both alone and in combination with other immunotherapy agents. The Keynote-598 trial compared ipilimumab plus pembrolizumab vs pembrolizumab with placebo for patients with previously untreated metastatic NSCLC with a programmed death–ligand 1 tumor proportion score of at least 50% and without epidermal growth factor receptor or anaplastic lymphoma kinase genomic alterations. The study showed no benefit of ipilimumab added to pembrolizumab with respect to overall or progression-free survival and no improvement in global health status or time to deterioration (22,23). In the CheckMate 227 trial, the combination of NI was compared with chemotherapy as first-line treatment for advanced NSCLC with high mutational burden (24-27). First-line NI demonstrated improved overall survival compared with chemotherapy and improved PROs as reflected by the Lung Cancer Symptom Scale and the EQ-5D, including evidence of delayed deterioration and numerically improved symptoms and health-related QOL (25,26).

To our knowledge, this study is the first report of QOL outcomes for NI vs nivolumab alone in lung cancer. Combinations of these treatments have been compared in other cancers. In resected stage III melanoma, QOL analyses using the European Organization for the Research and Treatment of Cancer QOL Questionnaire–C30 to assess global health status showed no clinically meaningful differences between patients randomly assigned to ipilimumab treatment over nivolumab (28). In a randomized phase II trial for treatment-naïve advanced melanoma, patients treated with NI had similar mean European Organization for the Research and Treatment of Cancer QOL Questionnaire–C30 global health scores at week 7 and week 13 after registration compared with ipilimumab alone (29,30). The findings from our study are consistent with evidence indicating little difference in QOL outcomes in the literature to date when comparing combinations of nivolumab and ipilimumab.

We also showed that a simple baseline risk model that included patient-reported appetite loss and shortness of breath could identify patients with more than a threefold increased risk of progression; and a model that included appetite loss and work limitations could identify a group of patients with more than a fivefold increased risk of death. PROs can predict a wide variety of clinical and treatment outcomes. Serial symptom monitoring using electronic PROs demonstrated improved patient-provider communication and patient satisfaction (31,32). A randomized

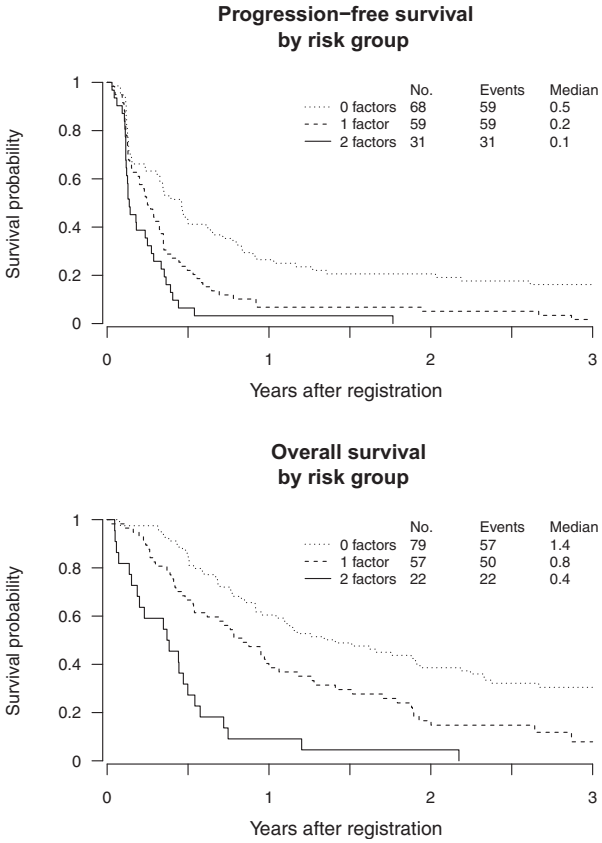


Figure 5. Progression-free and overall survival by risk score.

trial of electronic patient-reported symptom monitoring vs usual care in advanced cancer patients even showed a survival improvement in the PRO group (33). PRO risk factors were shown to predict nonadherence to aromatase inhibitors, greater levels of pain reduction in trials of interventions for aromatase inhibitor–associated musculoskeletal symptoms, and worse survival in advanced disease (34-37). Appetite loss in particular has previously been shown to be associated with worse outcomes in advanced lung and advanced breast cancer patients (38,39). No prior reports have demonstrated the prognostic relevance of QOL reports in previously treated lung cancer patients treated with novel therapeutics. Our findings add to the growing literature showing how patient self-report of health status and function can provide meaningful prognostic information, an important avenue of research that may help guide patients and physicians in decision making about treatment risks and benefits.

The QOL analyses were limited by the early closure of the parent trial because of futility, which reduced the anticipated sample size. However, the absence of an observed benefit in QOL outcomes is unlikely to be because of the lower than anticipated sample size, as the magnitude of the observed differences in MDASI severity scores (of 0.04 points at 7 weeks and 0.12 points at 13 weeks) was small and did not approximate the prespecified clinically meaningful difference of 1.0 points. Additionally, because the MDASI-LC does not specifically evaluate immunotherapy toxicities, but rather lung cancer–related symptoms, it may not have been sensitive to group differences in treatment toxicities. Further, although the validity of the risk model derivation was aided by its prospective, protocol-specified design, we were unable—given the limited sample size—to utilize a more commonly used strategy that incorporates initial development with independent validation. Also, patients with Hispanic ethnicity were poorly represented in the trial cohort.

In conclusion, we found no evidence that ipilimumab added to nivolumab improved QOL outcomes compared with nivolumab for patients with previously treated stage IV squamous cell lung cancer. These findings, along with the prior report that ipilimumab added to nivolumab did not improve clinical outcomes in these patients, support the conclusion that there is currently no role for combination immunotherapy with NI in patients with pretreated advanced NSCLC.

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Data availability

The data are available upon request from the SWOG Cancer Research Network. Please see provisions for data sharing at the following website: https://www.swog.org/sites/default/files/docs/2017-10/Policy43.pdf.

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