Patient-Reported Outcomes with PD-1/PD-L1 Inhibitors for Advanced Cancer: A Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Health-related quality of life • PD-1/PD-L1 inhibitor • Meta-analysis • Patient-reported outcomes • Symptoms

ABSTRACT

Background. The aim of this meta-analysis was to compare patient-reported outcomes (PROs) between programmed death receptor-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors and standard-of-care therapy in patients with advanced cancer.

Methods. We searched randomized controlled trials (RCTs) comparing single-agent PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) with standard-of-care therapy in patients with advanced cancer reporting PROs with generic measures: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (QLQ-C30) and the Euro-Qol Five Dimensions Questionnaire. The summary outcomes were changes in PROs from baseline to follow-up within and between treatment groups and time to deterioration (TTD) in PROs based on clinically meaningful change.

Results. A total of 6,334 patients from 13 RCTs were included: six nivolumab, five pembrolizumab, and two

atezolizumab trials. For the QLQ-C30 global health status/quality of life, the pooled difference in mean change between treatment groups was 5.1 (95% confidence interval [CI], 3.3–6.9; $p < .001$) favoring PD-1/PD-L1 inhibitors. The pooled mean change from baseline in PD-1/PD-L1 inhibitors and controls was 0.1 (95% CI, –2.2, 2.5) and –6.1 (95% CI, –8.4, –3.8), respectively. The TTD was significantly longer with PD-1/PD-L1 inhibitors, with a hazard ratio of 0.72 (95% CI, 0.55–0.93; $p = .011$). Similarly, significantly better outcomes were noted with PD-1/PD-L1 inhibitors on most of the other PRO measures.

Conclusion. PD1/PD-L1 inhibitors maintained health-related quality of life to a greater degree and had less worsening in symptoms than standard-of-care therapy even though patients on these immune modulators were on treatment longer. The better PRO profile further supports the clinical benefit of this treatment strategy for advanced cancer. *The Oncologist* 2019;24:e565–e573

Implications for Practice: We conducted a systematic review and meta-analysis to compare patient-reported outcomes (PROs) of programmed death receptor-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors and standard-of-care therapy in patients with advanced cancer. PD-1/PD-L1 inhibitors were associated with consistently smaller PRO score deterioration from baseline to follow-up for different health-related quality-of-life and symptoms scales. In addition, the time to deterioration in multiple PRO domains was significantly longer with PD-1/PD-L1 inhibitors. Taken together, these findings indicate that the patients treated with PD-1/PD-L1 inhibitors maintained health-related quality of life to a greater degree and had less symptom burden compared with those treated with standard-of-care therapy.

INTRODUCTION

Immune checkpoint inhibitors have dramatically changed the treatment paradigm for a variety of cancer types. In particular, inhibitors of the programmed death receptor-1/programmed death-ligand 1 (PD-1/PD-L1) pathway have

produced durable responses and significantly improved survival outcomes compared with standard care in different advanced solid tumors [1]. Based on their superior efficacy, the U.S. Food and Drug Administration (FDA) has approved

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the PD-1 inhibitors nivolumab and pembrolizumab and the PD-L1 inhibitors atezolizumab, avelumab, and durvalumab for the treatment of advanced cancers [2–6].

The safety profiles of PD-1/PD-L1 inhibitors have been compared with chemotherapy in this population [7]. PD-1/PD-L1 inhibitors, irrespective of type, are associated with a lower risk of fatigue, anorexia, nausea, diarrhea, constipation, and sensory neuropathy but a higher risk of rash, pruritus, colitis, hypothyroidism, and pneumonitis, termed immune-related adverse events, based on the Common Terminology Criteria for Adverse Events (CTCAE) [8]. As clinicians' assessment of patients' symptoms may not accurately capture patients' perceptions of toxicity, patient-reported outcomes (PROs), including symptoms and health-related quality of life (HRQoL), are valuable for better understanding of the patients' experience of treatment [9]. PROs are particularly relevant to shared decision making regarding treatment choice between patients and their oncologists. The importance of incorporating PROs into cancer research has been emphasized, and recent clinical trials of PD-1/PD-L1 inhibitors have reported results of PROs [10, 11]. However, there has been no systematic attempt to synthesize the PRO data in order to more comprehensively evaluate benefits and harms of PD-1/PD-L1 inhibitors. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to compare PROs between PD-1/PD-L1 inhibitors and standard-of-care therapy in patients with advanced cancer.

MATERIALS AND METHODS

Search Strategy

We performed this analysis in accordance with the preferred reporting items for systematic reviews and meta-analyses statement [12]. Two authors (T.F.N. and S.S.S.) conducted an independent review of PubMed from January 2010 to April 2018. The following search string was used: (atezolizumab OR avelumab OR durvalumab OR nivolumab OR pembrolizumab) AND (patient reported outcomes OR quality of life). We also searched abstracts and meeting presentations on the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) websites using the same search terms. An independent search of the Web of Science, Embase, and Cochrane electronic databases was also performed to ensure that there were no additional studies. The references from relevant reports were also reviewed manually, and the most updated package inserts were retrieved and reviewed [2–6]. In instances of duplicate publications, only the most complete, recent, and up-to-date report of the study was included.

Study Selection

Studies that met the following criteria were included: (a) phase II and III trials in patients with advanced cancer; (b) random assignment of participants to treatment with a single-agent PD-1/PD-L1 inhibitor (nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab) or standard-of-care therapy that did not contain a PD-1/PD-L1 inhibitor; and (c) adequate reporting of PROs. Reviewers (T.F.N. and

S.S.S.) independently screened reports by their titles and abstracts for relevance, and the full texts of relevant articles were retrieved to assess eligibility.

Data Extraction

Data extraction was conducted independently by two investigators (T.F.N. and S.S.S.), and any discrepancies between reviewers were resolved by consensus. The following information was recorded for each study: study's name, first author's name, year of publication, trial phase, masking, cancer type, treatment arms, number of patients available for analysis, age, Eastern Cooperative Oncology Group performance status (ECOG PS), PRO measures used, and PRO results. When the PRO results were available only in graphical form, the WebPlotDigitizer tool was used to extract data (version 4.1, Ankit Rohatgi, Austin, TX). The quality of PRO reporting was assessed using the five-item CONSORT PRO checklist [13]. These items are (a) identification of the PROs in the abstract as an outcome, (b) description of the PRO hypothesis and relevant domains, (c) evidence of the PRO instrument validity and reliability, (d) statistical approaches for dealing with missing data, and (e) the PRO-specific limitations and implications for generalizability and clinical practice.

Outcome Measures

PROs were evaluated with generic and/or cancer site-specific measures in the eligible studies. To perform a meta-analysis with clinical trials of different cancer types, we considered only PROs assessed with the generic standardized and validated measures. We did not perform a meta-analysis of PROs assessed with cancer site-specific instruments. Two generic PRO instruments were used in the included trials: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 items (QLQ-C30) and the EuroQol Five Dimensions Questionnaire 3 L (EQ-5D-3 L) [14, 15]. The EORTC QLQ-C30 is a self-reported, 30-item cancer-specific questionnaire and assesses global health status/quality of life (QoL), five functional dimensions (physical, role, emotional, cognitive, and social), eight symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), and financial impact of the disease. Scores range from 0 to 100, and higher scores represent better outcomes on the global health status/QoL and functional scales and worse outcomes on the symptoms and financial impact. In general, the significance of changes in scores is interpreted as "trivial" (0–5 points), "small" (5–10 points), "moderate" (10–20 points), or "large" (>20 points), and a change in score of ≥ 10 is commonly used as the threshold for clinically meaningful change [16]. The EQ-5D-3 L is a self-reported, non-cancer-specific measure of health status composed of the EQ-5D utility index and EQ visual analog scale (VAS). The EQ-5D utility index consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels (no, some, or extreme problems). A summary score of 1 represents best possible health, and 0 represents death. The EQ VAS records the patient's self-rated health on a vertical, visual analog scale in which 0 represents the

worst imaginable health state and 100 represents the best imaginable health state. A clinically meaningful change is typically ≥ 0.08 points for the EQ-5D utility index and ≥ 7 points for the EQ-5D VAS [17]. The outcomes of interest were (a) changes in PROs from baseline to follow-up within and between treatment groups and (b) time from baseline to first deterioration in PROs (defined based on clinically meaningful change).

Statistical Analysis

The aim of this study was to compare PROs between PD-1/PD-L1 inhibitors (intervention) and standard-of-care therapy (control). We performed meta-analyses with the measure of effect size as the difference in mean change in PROs between treatment groups. For studies in which differences in mean change with 95% confidence interval (95% CI) were not reported, it was estimated where possible from the mean change and standard deviation of the intervention and control groups. We also conducted pooled analyses of mean change in PROs within treatment groups. For time to deterioration (TTD) in PROs, summary estimates of hazard ratios (HRs) were calculated. When HRs were not reported in studies, they were estimated using the abstracted survival probabilities in the Kaplan-Meier curve at specific time points according to the methods proposed by Parmar et al. [18]. We calculated all pooled estimates using the random-effects model according to the DerSimonian and Laird method, which considers both within-study and between-study variations [19]. Statistical heterogeneity in results between studies was examined using Cochrane's Q statistic and I^2 statistic, with an I^2 value of 25% representing low, 50% representing moderate, and 75% representing high heterogeneity [20]. The Q statistic indicated significant heterogeneity for p values less than .10. Exploratory subgroup analyses were conducted according to type of control arm therapy, type of tumor, and follow-up duration. We evaluated publication bias using funnel plots and the Egger test [21]. We assessed the quality of evidence for outcomes using the GRADE approach, which specifies four levels of quality (high, moderate, low, or very low). This approach involves consideration of within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias [22]. A two-sided p value of less than .05 was considered statistically significant. Statistical analyses were performed using the comprehensive meta-analysis program (version 2, Biostat, Englewood, NJ).

RESULTS

Search Results and Study Characteristics

Our search strategy yielded 251 potentially relevant records; 238 publications were excluded after screening and eligibility assessment. Our selection process and reasons for study exclusion are shown in Figure 1. A total of 11 phase III, one phase II/III, and one phase II randomized clinical trials were considered eligible for the meta-analysis. Three trials had two arms for pembrolizumab at different doses or frequency of drug administration. For these trials,

we included the arm that was closer to the FDA-approved dosing schedule: 200 mg once every 3 weeks (Table 1) [25, 26, 30]. A total of 6,334 patients (PD-1/PD-L1 inhibitors, 3,314; standard-of-care therapy, 3,020) were included in the analysis from six nivolumab trials, five pembrolizumab trials, and two atezolizumab trials. We categorized the standard-of-care therapy by class as chemotherapy (10 trials), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor (2 trials), and mammalian target of rapamycin inhibitor (1 trial). Five trials were performed in non-small cell lung cancer (NSCLC), four in patients with melanoma, two in urothelial cancer, and one each in head and neck cancer and renal cell carcinoma. There were differences in the follow-up duration for analysis of changes in PROs from baseline among the included studies. The follow-up period ranged from 12 to 104 weeks with a median of 15 weeks. The study characteristics are summarized in Table 1.

Changes in PROs from Baseline to Follow-Up

Changes in PROs from baseline to follow-up were reported with the EORTC QLQ-C30 in nine trials and the EQ-5D-3 L in nine trials. A total of nine trials were included in the analysis of the EORTC QLQ-C30 global health status/QoL. The pooled difference in mean change between treatment groups was 5.1 (95% CI, 3.3–6.9; $p < .001$; Fig. 2) favoring PD-1/PD-L1 inhibitors. The test for heterogeneity was not significant ($Q = 11.83$; $p = .159$; $I^2 = 32.36$). Eight trials were available for the within-group analysis, as one trial reported only difference in mean change between groups without mean change within each group [33]. The pooled mean change from baseline in PD-1/PD-L1 inhibitors and controls was 0.1 (95% CI, –2.2, 2.5) and –6.1 (95% CI, –8.4, –3.8), respectively (Table 2). For most of the other EORTC QLQ-C30 scales and items, differences in mean change between groups were significant in favor of PD-1/PD-L1 inhibitors (Table 2). Similarly, significant mean-change differences favoring PD-1/PD-L1 inhibitors were noted for the EQ-5D-3 L (Table 2).

Time from Baseline to First Deterioration in PROs

TTD in PROs was reported with the EORTC QLQ-C30 in five trials and the EQ-5D-3 L in four trials. TTD was defined as time from baseline to first clinically important deterioration in PROs. A clinically meaningful change used in the trials was 10 points for the EORTC QLQ-C30, 0.08 for the EQ-5D utility index, and 7 points for the EQ-5D VAS. A total of five trials were available for the TTD analysis of the EORTC QLQ-C30 global health status/QoL. The TTD was significantly longer with PD-1/PD-L1 inhibitors than with standard-of-care therapy, with an HR of 0.72 (95% CI, 0.55–0.93; $p = .011$; Fig. 3). There was significant heterogeneity among these trials ($Q = 15.60$; $p = .004$; $I^2 = 74.36$). In addition, PD-1/PD-L1 inhibitors significantly delayed the TTD compared with controls for five functional dimensions (physical, role, emotional, cognitive, and social) and six symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, and appetite loss) on the EORTC QLQ-C30 (Table 3). PD-1/PD-L1 inhibitors also showed significantly longer TTD for the EQ-5D utility index and the EQ-5D VAS (Table 3).

Figure 1. Flow diagram: selection process for the studies.

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PRO, patient-reported outcome.

Exploratory Subgroup Analysis

We conducted exploratory subgroup analyses by type of control arm therapy (chemotherapy vs. CTLA-4 inhibitor), type of tumor (melanoma vs. NSCLC), and follow-up duration for analysis of changes in PROs from baseline (≤ 15 weeks vs. > 15 weeks). Subgroup analyses were restricted to differences in the mean change in PROs because of the small group size for the TTD outcomes (less than two trials per group). Changes in PROs from baseline to follow-up were consistently in favor of PD-1/PD-L1 inhibitors across different subgroups (supplemental online Table 1).

Study Quality, Publication Bias, and Quality of Evidence

Ten trials were reported as published full-text articles, whereas three trials were presented only as meeting abstracts. Of ten articles, nine mainly reported the PRO results and one reported the PRO findings in the context of the other trial outcomes [34]. The five-item CONSORT PRO

score ranged from 1 to 5 with a mean of 3.5. We found no evidence of publication bias for the changes from baseline in the EORTC QLQ-C30 and the EQ-5D 3 L. Publication bias was not assessed for the TTD outcomes because of the inadequate numbers of included trials (two to five trials) to properly assess funnel plots or perform the Egger test.

Using the GRADE approach, we assessed the certainty of the evidence to be moderate and low for the changes in PRO and TTD outcomes, respectively. We included only RCTs in this study, and the level of the evidence started at high quality. However, 11 of 13 included trials used an open-label design, which led to a risk of bias for allocation concealment and blinding of participants, health care providers, and outcome assessors. Because of the within-study risk of bias, we downgraded the quality of the evidence by one level to moderate quality for changes in both PRO and TTD outcomes. For the TTD outcomes, the evidence level was downgraded one more level to low quality because of the statistical heterogeneity based on the I^2 statistic.

Table 1. Characteristics of the studies included in the meta-analysis

Trial name	First author, yr	Phase	Masking	Cancer type	Treatment arms	No. of patients ^a	Age, median (range), yr	ECOG PS	PRO measures	Follow-up duration, ^b wk
CheckMate 025 [23]	Cella D, 2016	III	Open-label	Renal cell carcinoma	Nivolumab 3 mg/kg Q2W	362	62 (23–88)	0–1	EQ-5D-3 L, FKS-DRS	104
					Everolimus 10 mg daily	344	62 (18–86)			
CheckMate 066 [24]	Long GV, 2016	III	Double-blind	Melanoma	Nivolumab 3 mg/kg Q2W + placebo	147	64 (18–86)	0–1	EORTC QLQ-C30, EQ-5D-3 L	61
					Dacarbazine 1,000 mg/m ² Q3W + placebo	135	66 (26–87)			
KEYNOTE-002 [25]	Schadendorf D, 2016	II	Open-label	Melanoma	Pembrolizumab 2 mg/kg Q3W ^c	169	62 (15–87)	0–1	EORTC QLQ-C30	12
					Pembrolizumab 10 mg/kg Q3W	170	60 (27–89)			
					Investigator-choice chemotherapy ^d	156	63 (27–87)			
KEYNOTE-010 [26]	Barlesi F, 2016	II/III	Open-label	NSCLC	Pembrolizumab 2 mg/kg Q3W ^c	318	63 (50–69)	0–1	EORTC QLQ-C30, EQ-5D-3 L, EORTC QLQ-LC13	12
					Pembrolizumab 10 mg/kg Q3W	311	63 (56–69)			
					Docetaxel 75 mg/m ² Q3W	273	62 (56–69)			
CheckMate 057 [27]	Reck M, 2016	III	Open-label	NSCLC	Nivolumab 3 mg/kg Q2W	240	61 (37–84)	0–1	EQ-5D-3 L, LCSS	NR
					Docetaxel 75 mg/m ² Q3W	222	64 (21–85)			
CheckMate 067 [28]	Schadendorf D, 2017	III	Double-blind	Melanoma	Nivolumab 3 mg/kg Q2W + placebo	270	59 (25–90)	0–1	EORTC QLQ-C30, EQ-5D-3 L	55
					Ipilimumab 3 mg/kg Q3W + placebo	259	61 (18–89)			
					Nivolumab 1 mg/kg Q3W + ipilimumab 3 mg/kg Q3W	274	59 (18–88)			
CheckMate 141 [29]	Harrington KJ, 2017	III	Open-label	Head and neck cancer	Nivolumab 3 mg/kg Q2W	191	59 (29–83)	0–1	EORTC QLQ-C30, EQ-5D-3 L, EORTC QLQ-H&N35	15
					Investigator-choice chemotherapy ^e	91	61 (28–78)			
KEYNOTE-006 [30]	Petrella TM, 2017	III	Open-label	Melanoma	Pembrolizumab 10 mg/kg Q3W ^c	263	63 (22–89)	0–1	EORTC QLQ-C30, EQ-5D-3 L	12
					Pembrolizumab 10 mg/kg Q2W ^b	267	61 (18–89)			
					Ipilimumab 3 mg/kg Q3W	237	62 (18–88)			
KEYNOTE-024 [31]	Brahmer JR, 2017	III	Open-label	NSCLC	Pembrolizumab 200 mg Q3W	151	65 (33–90)	0–1	EORTC QLQ-C30, EQ-5D-3 L, EORTC QLQ-LC13	15
					Investigator-choice chemotherapy ^f	148	66 (38–85)			
CheckMate 017 [32]	Reck M, 2017	III	Open-label	NSCLC	Nivolumab 3 mg/kg Q2W	110	62 (39–85)	0–1	EQ-5D-3 L, LCSS	60
					Docetaxel 75 mg/m ² Q3W	107	64 (42–84)			
OAK [33]	Bordoni R, 2017	III	Open-label	NSCLC	Atezolizumab 1,200 mg Q3W	425	63 (33–82)	0–1	EORTC QLQ-C30, EORTC QLQ-LC13	15
					Docetaxel 75 mg/m ² Q3W	425	64 (34–85)			
IMvigor211 [34]	Powles T, 2017	III	Open-label	Urothelial cancer	Atezolizumab 1,200 mg Q3W	408	67 (33–88)	0–1	EORTC QLQ-C30	NR
					Investigator-choice chemotherapy ^g	381	67 (31–84)			
KEYNOTE-045 [35]	Vaughn DJ, 2018	III	Open-label	Urothelial cancer	Pembrolizumab 200 mg Q3W	260	67 (29–88)	0–1	EORTC QLQ-C30, EQ-5D-3 L	15
					Investigator-choice chemotherapy ^g	242	65 (26–84)			

^aA number of patients who had at least one PRO assessment at baseline.

^bFollow-up duration for analysis of changes in PROs from baseline. CheckMate 057 and IMvigor211 did not report changes in PROs from baseline.

^cThis arm was included in analysis as it was closer to the Food and Drug Administration-approved dosing schedule: 200 mg once every 3 weeks.

^dPaclitaxel plus carboplatin, paclitaxel, carboplatin, dacarbazine, or oral temozolomide.

^eMethotrexate, docetaxel, or cetuximab.

^fCarboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine, or carboplatin plus paclitaxel.

^gPaclitaxel, docetaxel, or vinflunine.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-3 L, EuroQol Five Dimensions Questionnaire 3 L; FKS-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; LCSS, Lung Cancer Symptom Scale; NSCLC, non-small cell lung cancer; NR, not reported; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; QLQ-C30, Quality of Life Questionnaire Core 30 items; QLQ-H&N35, Quality of Life Questionnaire Head and Neck Cancer Module; QLQ-LC13, Quality of Life Questionnaire Lung Cancer 13 items.

DISCUSSION

This is, to our knowledge, the first meta-analysis of RCTs to compare the PROs of PD-1/PD-L1 inhibitors and standard-of-care therapy in patients with advanced cancer. We showed significant between-group differences in PRO

changes over time in favor of PD-1/PD-L1 inhibitors. PD-1/PD-L1 inhibitors were associated with consistently smaller PRO score deterioration from baseline to follow-up for different HRQoL and symptoms scales. Furthermore, the time to deterioration in the multiple PRO domains was significantly

Figure 2. Forest plot of difference in mean change from baseline to follow-up between treatment groups for the Quality of Life Questionnaire Core 30 items on global health status and quality of life by the European Organisation for the Research and Treatment of Cancer.

Abbreviations: CI, confidence interval; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Table 2. Changes in PROs from baseline to follow-up within and between treatment groups

PROs	Difference in mean change between groups			Mean change within group		
	No. of trials	Effect size (95% CI)	p value	No. of trials	PD-1/PD-L1 inhibitor (95% CI)	Control (95% CI)
EORTC QLQ-C30 Function scales						
Global health status/QoL	9	5.1 (3.3–6.9)	<.001	8	0.1 (–2.2, 2.5)	–6.1 (–8.4, –3.8)
Physical functioning	8	4.7 (2.6–6.8)	<.001	7	–3.5 (–5.1, –1.8)	–8.6 (–12.4, –4.9)
Role functioning	8	7.6 (4.2–11)	<.001	7	–2.2 (–4.9, 0.5)	–10.5 (–15.6, –5.4)
Emotional functioning	8	2.3 (1–3.6)	<.001	7	2.4 (–0.2, 5)	–0.3 (–4.1, 3.4)
Cognitive functioning	8	2.4 (0.7–4.1)	.006	7	–1.9 (–2.8, –1.1)	–5.3 (–8.4, –2.2)
Social functioning	8	5.0 (2.3–7.7)	<.001	7	–0.4 (–3.4, 2.7)	–6.9 (–10.5, –3.4)
EORTC QLQ-C30 Symptom scales/items						
Fatigue	8	–7.4 (–10.2, –4.5)	<.001	7	1.3 (–1.6, 4.2)	10.0 (5.8–14.2)
Nausea and vomiting	8	–2.1 (–3.2, –1.1)	<.001	7	0.1 (–1.2, 1.5)	3.3 (1.6–5)
Pain	8	–3.8 (–5.7, –1.9)	<.001	7	–1.7 (–4.8, 1.4)	3.7 (0.7–6.7)
Dyspnea	8	–6.5 (–9.5, –3.4)	<.001	7	–0.2 (–2.7, 2.2)	8.0 (3.1–12.9)
Insomnia	8	–5.0 (–8.6, –1.4)	.006	7	–4.1 (–5.8, –2.5)	3.8 (–2.1, 9.8)
Appetite loss	8	–5.3 (–7.3, –3.4)	<.001	7	–1.3 (–4.7, 2)	6.4 (2.2–10.7)
Constipation	8	–2.0 (–3.9, –0.1)	.035	7	–0.9 (–2.9, 1)	2.0 (0.7–3.4)
Diarrhea	8	–3.6 (–5.1, –2)	<.001	7	–0.4 (–1.2, 0.4)	4.0 (1.4–6.5)
Financial difficulties	6	–2.3 (–4.1, –0.4)	.015	6	0 (–1.2, 1.2)	2.6 (0.9–4.4)
EQ-5D 3 L						
Utility index	7	0.047 (0.032–0.063)	<.001	5	0.019 (–0.015, 0.053)	–0.03 (–0.076, 0.017)
VAS	9	4.5 (3.2–5.7)	<.001	6	2.0 (–0.5, 4.5)	–3.9 (–6.2, –1.7)

Abbreviations: CI, confidence interval; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-3 L, EuroQol Five Dimensions Questionnaire 3 L; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30 items; QoL, Quality of Life; VAS, visual analog scale.

longer with PD-1/PD-L1 inhibitors. Taken together, these findings indicate that the patients treated with PD-1/PD-L1 inhibitors maintained HRQoL to a greater degree and had less symptom burden compared with those treated with standard-of-care therapy.

The observed changes in PROs within and between treatment groups did not meet the threshold for clinically meaningful change. For the EORTC QLQ-C30, a 10-point difference in score is widely considered clinically meaningful. However, smaller changes (5–10 points) might be clinically meaningful

CheckMate (nivolumab trial), IMvigor211 (atezolizumab trial), KEYNOTE (pembrolizumab trial).

Figure 3. Forest plot of hazard ratios for time from baseline to first deterioration in the Quality of Life Questionnaire Core 30 items on global health status and quality of life by the European Organisation for the Research and Treatment of Cancer. Abbreviations: CI, confidence interval; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Table 3. Time from baseline to first deterioration in PROs

PROs	No. of trials	HR (95% CI)	p value
EORTC QLQ-C30			
Function scales			
Global health status/QoL	5	0.72 (0.55–0.93)	.011
Physical functioning	4	0.70 (0.54–0.90)	.005
Role functioning	3	0.69 (0.57–0.84)	<.001
Emotional functioning	2	0.63 (0.45–0.89)	.008
Cognitive functioning	2	0.64 (0.48–0.86)	.003
Social functioning	2	0.60 (0.45–0.81)	.001
EORTC QLQ-C30 Symptom scales/items			
Fatigue	3	0.74 (0.55–1.00)	.049
Nausea and vomiting	2	0.51 (0.34–0.76)	.001
Pain	2	0.69 (0.52–0.91)	.008
Dyspnea	2	0.52 (0.38–0.71)	<.001
Insomnia	2	0.62 (0.45–0.84)	.003
Appetite loss	2	0.48 (0.35–0.66)	<.001
Constipation	2	0.63 (0.38–1.06)	.083
Diarrhea	2	0.74 (0.51–1.08)	.123
Financial difficulties	2	0.73 (0.50–1.07)	.111
EQ-5D 3 L			
Utility index	3	0.58 (0.46–0.74)	<.001
VAS	4	0.73 (0.62–0.86)	<.001

Abbreviations: CI, confidence interval; EORTC, European Organisation for the Research and Treatment of Cancer; EQ-5D-3 L, EuroQol Five Dimensions Questionnaire 3 L; HR, hazard ratio; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PRO, patient-reported outcome; QLQ-C30, Quality of Life Questionnaire Core 30 items; QoL, Quality of Life; VAS, visual analog scale.

depending on the treatment population and clinical context [36–38]. In our study, between-group differences in changes for the EORTC QLQ-C30 were in the range of “small” (5–10

points) for global health status/QoL, role and social functioning, fatigue, dyspnea, insomnia, and appetite loss. Within-group changes in the EORTC QLQ-C30 were “small” deteriorations for global health status/QoL, physical, role, cognitive and social functioning, fatigue, dyspnea, and appetite loss in the control group, whereas changes in the PD-1/PD-L1 inhibitor group were “trivial” for all scales and items. We interpret these results to mean that the PD-1/PD-L1 inhibitor group had a small but relevant improved HRQoL and symptoms compared with the standard-of-care therapy group.

Less deterioration in the HRQoL and symptoms with PD-1/PD-L1 inhibitors is likely to be driven by better disease control and safety profile. PD-1/PD-L1 inhibitors have been shown to produce durable responses and prolong progression-free survival [1]. Additionally, our previous meta-analysis found that PD-1/PD-L1 inhibitors were associated with a lower risk of any all- or high-grade toxicity, fatigue, anorexia, nausea, diarrhea, and constipation compared with chemotherapy [7]. These findings are consistent with the better scores on the PROs with PD-1/PD-L1 inhibitors. Interestingly, the CTCAE-based assessment did not show a difference in risk of dyspnea (relative risk [RR], 1.02; 95% CI, 0.80–1.29) or insomnia (RR, 0.98; 95% CI, 0.65–1.49) in our previous study [7], but based on the EORTC QLQ-C30, the PD-1/PD-L1 inhibitor group had the significantly less deterioration in these symptom scores in the current study. This suggests that clinicians’ assessment of patients’ symptoms may underestimate the symptoms experienced by patients and highlights the importance of PRO-based assessment. These PRO data are especially noteworthy, as the time to disease progression in these trials was significantly longer for patients on PD-1/PD-L1 therapy.

The results described here are affected by the characteristics of individual clinical trials that were included in this study. The strengths of the included studies are the randomized trial design and the prespecified PRO analysis plan. Nevertheless, there are some limitations. Most of the

studies used an open-label design, which could affect patients' responses to the PRO measures. As with other PRO studies in the literature, missing data due to disease progression and decline in patients' function may confound the results. In particular, these factors limit the analyses at later follow-up time points because of the smaller number of patients available. Considering this, most of the included trials assessed changes in PROs from baseline to up to 15 weeks' follow-up. Finally, the number of trials available for the TTD meta-analysis was small (2–5 trials depending on the PRO measure) even though we included the data from all available literature sources. Thus, these results should be interpreted with caution.

As more older adults and patients with poor ECOG PS are treated with PD-1/PD-L1 inhibitors, it will be important to evaluate PROs in this population. Notably, Revicki et al. evaluated differences in the EORTC QLQ-C30 outcomes in patients treated with ipilimumab by age group [39]. Patients aged ≥ 65 years reported more impairment in global health, social function, dyspnea, and diarrhea than those < 65 years. Moreover, CheckMate 153, a phase 3B/4 study of nivolumab in patients with advanced NSCLC, included patients aged ≥ 70 years ($n = 520$) and those with ECOG PS 2 ($n = 108$) [40]. In the recent update on this study, early data showed stable-to-improved PROs based on the Lung Cancer Symptom Scale and EQ-5D VAS. In our study, we could not assess the PRO data by age because this is a meta-analysis of study-level, not individual patient-level, clinical data. Additionally, the patients in our study were eligible for clinical trials and had good functional status (ECOG PS 0–1). Thus, the observed results may not be entirely applicable to the more general patient population. Further studies of PD-1/PD-L1 inhibitors in older and/or frail patients are warranted.

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CONCLUSION

In addition to the traditional efficacy and safety outcomes, PROs, including HRQoL and symptoms, are valuable for more comprehensive understanding of benefits and harms of treatment because they provide the patient's own experience with treatment. The framework proposed by the ASCO and the ESMO Magnitude of Clinical Benefit scale recommends including PROs in the parameters to assess the value of cancer treatments [10, 11]. Our study suggests that patients treated with PD-1/PD-L1 inhibitors maintained HRQoL to a greater degree and had less worsening in symptoms than those treated with standard-of-care therapy. Combined with the efficacy and safety data, the better HRQoL and symptom profile further supports the clinical benefit of PD-1/PD-L1 inhibitors in patients with advanced cancer.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

Kazuo Tamura: Ono, Kyowa-Kirin, Esai (H). The other authors indicated no financial relationships.

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