Patient-reported outcomes with nivolumab in advanced solid cancers

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Declaration of interest

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Abstract

Patients with recurrent or metastatic cancer commonly suffer from debilitating toxicity associated with conventional treatment modalities, as well as disease-related symptoms, often with a concomitant negative impact on health-related quality of life (HRQoL). Patient-reported outcomes (PROs) provide important insights into the patient experience in clinical trials. Nivolumab is a programmed death-1 receptor inhibitor that extends survival in patients with recurrent or metastatic disease in multiple tumor types. In this review, we summarize published PRO analyses from eight phase II−IV clinical trials with nivolumab for the treatment of melanoma, non-small cell lung cancer, renal cell carcinoma (RCC), and squamous cell carcinoma of the head and neck (SCCHN). Symptom burden, physical functioning, and HRQoL were measured using generic, cancer-specific, and tumor type–specific validated PRO instruments. Nivolumab showed sustained stabilization across all tumor types and, in some cases, clinically meaningful improvement in HRQoL, whereas standard of care therapies often led to deteriorations. Exploratory analyses found a positive correlation between baseline HRQoL scores and overall survival in RCC, and between baseline HRQoL scores and healthcare resource utilization in SCCHN, suggesting that patient-reported symptoms at treatment initiation may have clinical value. In the era of value-based oncology care, stakeholders are increasingly interested in PRO findings to guide clinical, regulatory, and reimbursement decisions. However, missing data remain a significant challenge in PRO analyses, including in nivolumab trials. Future clinical trials in immuno-oncology should incorporate PRO data collection, including beyond treatment discontinuation or trial completion to assess the long-term effects of treatment on HRQoL.

Keywords:

Melanoma

Nivolumab

Non-small cell lung cancer

Patient-reported outcomes

Renal cell carcinoma

Head and neck cancer

Highlights

- PROs reported from eight nivolumab trials in four types of advanced cancer
- PROs were assessed using generic, cancer-specific, and tumor type–specific measures
- Nivolumab generally sustained/improved HRQoL, and improved functioning
- Nivolumab benefits versus chemotherapy or targeted therapy seen across tumor types
- PROs may be a differentiating factor between PD-1 inhibitors and other treatments

Introduction

Evaluation of novel therapies in oncology should include not only clinical outcomes, but also patient-reported outcomes (PROs) that reflect patients' perceptions of their physical, mental, and social health status, without interpretation by a clinician or another intermediary (1). PROs assess health-related quality of life (HRQoL) or components that contribute to HRQoL such as disease-related or treatment-related symptoms and typical daily functioning, incorporating the patient's voice to provide a holistic understanding of patient experiences beyond conventional clinical endpoints. PRO findings can help patients, oncologists, payers, and regulators evaluate the tolerability and benefits of therapies comprehensively, and provide additional differentiation between treatment options. While patients with cancer rank survival as their highest priority, they also value HRQoL during and after treatment (2). Although advances have been made in clinical outcomes, well-being during initial treatment and throughout cancer survivorship remains a critical unmet need for patients (3).

The majority of systemic treatments for advanced cancers have remained fundamentally palliative. Furthermore, conventional treatments cause debilitating toxicity that negatively affects HRQoL in most patients, including those without clinical benefits. HRQoL assessment is especially important for immunotherapies that may require longer treatment durations and, for some patients, may enable long-term survival beyond historic benchmarks. Patients may also value the "hope" of improved survival potentially provided by novel therapies (4).

Immune checkpoint blockade is an effective therapeutic strategy that harnesses the immune system to generate an antitumor response (5). Nivolumab and ipilimumab are antibodies that bind to the immune-modulating programmed death-1 (PD-1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) receptors, respectively, blocking ligand interaction and downstream signaling pathways. This disrupts the negative regulation of T-cell function, potentially resulting in an antitumor effect. Nivolumab, alone or in combination with ipilimumab, prolongs survival and is currently approved in a number of cancers (6).

Immune checkpoint inhibitors have safety profiles distinct from those of cytotoxic and targeted therapies, which may translate into HRQoL benefits. PD-1 inhibitors typically cause fewer and less severe treatment-related adverse events (TRAEs) compared with conventional chemotherapies, although immune-related adverse events (AEs) can occur, requiring monitoring and specialized management to prevent serious complications (7). In the initial nivolumab trials, grade 3-4 immune-related AEs of colitis were reported in 1%−17% of patients, followed by diarrhea (1%−11%), rash (<1%−5%) and hypophysitis (<1%−3%). TRAEs tended to be low-grade; those most commonly reported were fatigue, nausea, rash, diarrhea, pruritis, and decreased appetite. Grade 3 or 4 anemia or neutropenia, which are common toxicities associated with chemotherapy, were reported in <1%−2% of patients treated with nivolumab (8-15).

PROs have been included as secondary or exploratory endpoints in nivolumab clinical trials across multiple tumor types, providing a unique opportunity to evaluate the impact of nivolumab on HRQoL in patients with highly symptomatic, advanced cancers.

PRO instruments and assessments in the nivolumab trials

PROs are collected by administering questionnaires that are scored and quantitatively analyzed to evaluate patients' symptoms, functioning, or general well-being. Numerous PRO instruments have been designed using robust methodologies, focusing on a disease, condition, or overall health status, and psychometrically validated in the target patient population to ensure relevance, consistency, sensitivity, and correlation with other measures (16, 17). The PROs used in nivolumab trials reviewed here included a generic HRQoL measure, the EuroQoL five dimensions (EQ-5D) 3-level version (18-20), and at least one cancer-specific measure (Table 1). The cancer-specific measures were the general cancer European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (21), as well as the tumor type–specific Lung Cancer Symptom Scale (LCSS) for non-small cell lung cancer

(NSCLC) (22, 23), the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) for renal cell carcinoma (RCC) (24), and the EORTC 35-Question Head and Neck Cancer-Specific Module (EORTC QLQ-H&N35) for squamous cell carcinoma of the head and neck (SCCHN) (25, 26).

In the nivolumab trials described, PROs were collected prior to treatment initiation and at multiple time points during treatment and follow-up, enabling assessment of changes over time. This review focuses on data collected during treatment, with exceptions noted in the text. During study visits, patients completed questionnaires prior to physician contact, treatment dosing, or any procedures. The timing of assessments differed by trial; therefore, comparisons across trials at specific time points were not always possible, although general trends were assessed. Completion rates were calculated for each PRO measure based on the proportion of patients alive in the study at that time. In some trials, adjusted completion rates representing the proportion of patients with a baseline assessment and at least one post-baseline assessment were reported.

PRO data were assessed using descriptive statistics within each treatment arm, comparing scores during treatment to baseline scores and between treatment arms at specific time points. Longitudinal changes from baseline within and between arms were assessed with mixed-effects models for repeated measures (MMRM). Time to deterioration or improvement in HRQoL, defined based on clinically meaningful change in score, was determined using Kaplan-Meier methodology. A clinically meaningful change in score represents a treatment benefit or harm perceptible by the patient and significant enough to warrant a modification to the patient's clinical management. Changes in scores are also often interpreted relative to the minimally important difference (MID), which is the smallest difference in score that patients perceive as beneficial or detrimental, and is established by extensive anchor-based and/or distribution-based quantitative analyses (18, 27-29). Clinical relevance and the MID vary by patient

population and clinical context of treatment, such that a PRO instrument can have more than one MID or a range of MID estimates (Table 1).

All studies included in this review were conducted in accordance with the ethical principles defined by Declaration of Helsinki. All patients provided informed written consent prior to study enrollment.

Results of PRO assessments in nivolumab trials

Nearly all patients (98%−100%) included in the initial nivolumab trials were categorized as high-functioning at baseline by either Eastern Cooperative Oncology Group performance status score (0−1) or Karnofsky performance score (≥70), across tumor types (8-15). This review presents published PRO data from eight nivolumab studies, predominantly randomized phase III trials, in four advanced solid cancers: melanoma, NSCLC, RCC, and SCCHN (Table 2). Key PRO data are summarized in Table 3 and discussed by tumor type below.

Melanoma

CheckMate 066 was a randomized, double-blind, phase III trial that compared nivolumab with dacarbazine in patients with treatment-naive metastatic melanoma with wild-type *BRAF* (10). Nivolumab was associated with a significant survival benefit and lower risk of high-grade toxicity compared with dacarbazine. PROs were included in the trial as secondary (EORTC QLQ-C30) and exploratory (EQ-5D) endpoints (30).

Questionnaire completion rates for both questionnaires at baseline were 70% for the nivolumab arm and 65% for the dacarbazine arm, and remained similar to baseline throughout treatment when adjusted for patients alive. A high attrition rate in the dacarbazine arm, likely because of disease progression or death, resulted in small sample sizes after week 13 (n ≤ 41), limiting comparative HRQoL analysis between arms to early time points.

Patients receiving nivolumab maintained HRQoL levels at or above baseline over time, with clinically meaningful improvements in EQ-5D utility index (UI) and visual analog scale (VAS) scores at multiple time points. Patients receiving dacarbazine had no significant or clinically meaningful changes in EQ-5D UI and VAS scores from baseline. Nivolumab significantly delayed time to deterioration in EQ-5D UI relative to dacarbazine; however, for the cancer-specific EORTC QLQ-C30 scales, no significant differences within or between arms occurred at any time point.

A pattern mixture model (PMM) sensitivity analysis of missing data found no significant interaction between treatment and dropout except for the EQ-5D VAS longitudinal analysis, suggesting that missing data may have muted the magnitude of the improvement in EQ-5D VAS scores among patients treated with nivolumab.

CheckMate 067, a randomized, double-blind, phase III trial in treatment-naive patients with metastatic melanoma, compared nivolumab plus ipilimumab with each agent alone (11, 13). Single-agent nivolumab and nivolumab plus ipilimumab showed greater efficacy than single-agent ipilimumab. Combination therapy was associated with higher rates of grade 3–4 TRAEs versus each single-agent therapy, potentially diminishing HRQoL. PROs were included in this trial as secondary (EORTC QLQ-C30) and exploratory (EQ-5D) endpoints (31).

Adjusted questionnaire completion rates for the EORTC QLQ-C30 and EQ-5D at baseline were between 82% and 87% in each of the three treatment arms. Completion rates remained ≥50% in all arms for both questionnaires through week 67.

HRQoL was maintained relative to baseline in the single-agent nivolumab and nivolumab plus ipilimumab arms, with no clinically meaningful difference versus single-agent ipilimumab. Subgroup analyses were conducted among patients with mutated *BRAF*, wild-type *BRAF*, complete response (CR) or partial response (PR), grade 3–4 AEs, and treatment discontinuation for any reason or due to AEs. There were no significant deteriorations in the single-agent nivolumab or nivolumab plus ipilimumab arms in any of these subgroups, except for EORTC

QLQ-C30 Global Health score in the nivolumab plus ipilimumab arm at week 17, and for EQ-5D VAS score at 4 weeks (follow-up visit 1) and 16 weeks (follow-up visit 2) after the last dose of treatment among patients receiving nivolumab plus ipilimumab who discontinued due to AEs. In the wild-type *BRAF* subgroup, those treated with nivolumab had a clinically meaningful improvement at weeks 31–37.

Nivolumab plus ipilimumab also demonstrated greater clinical activity and increased frequency of grade 3−4 TRAEs versus single-agent ipilimumab in CheckMate 069, a randomized, double-blind, phase II trial in treatment-naive patients with advanced melanoma (9). PROs were included as secondary (EORTC QLQ-C30) and exploratory (EQ-5D) endpoints (32).

Questionnaire completion rates at baseline were 65% (EORTC QLQ-C30) and 64% (EQ-5D) for the nivolumab plus ipilimumab arm, and 79% (EORTC QLQ-C30) and 77% (EQ-5D) for the ipilimumab arm, and remained stable throughout treatment except for a reduction at week 13 with nivolumab plus ipilimumab (48%). PRO data were analyzed between baseline and week 25 of treatment, beyond which small patient numbers precluded analysis.

Throughout the analysis period, patients treated with nivolumab plus ipilimumab and single-agent ipilimumab maintained HRQoL at baseline levels. There were no clinically meaningful changes in either treatment arm for any of the EORTC QLQ-C30 scales nor the EQ-5D outcomes. Cox proportional hazards regression analyses revealed no significant differences between treatment arms in the hazards for time to improvement or deterioration (as defined by scale MID or clinically important difference, applied at the individual patient level).

A PMM analysis assessing the impact of dropout patterns on longitudinal changes showed that, in most cases, early (last assessment weeks 7 or 13) or late (last assessment week 19 or later) dropout did not impact MMRM results. However, for the EORTC QLQ-C30 physical functioning scale, early dropout in both treatment arms was associated with deterioration.

Non-small cell lung cancer

In the randomized, open-label, phase III CheckMate 017 trial, nivolumab significantly prolonged overall survival (OS) compared with docetaxel in previously treated patients with locally advanced or metastatic squamous cell NSCLC (14). This trial included an analysis of the proportion of patients with disease-related symptom improvement by week 12 using the LCSS as a secondary endpoint (33).

Adjusted LCSS completion rates were 69% (nivolumab) and 63% (docetaxel). At week 12, a similar proportion of patients in the nivolumab (20%) and docetaxel (22%) arms had clinically meaningful symptom improvement, as measured by the LCSS Average Symptom Burden Index (ASBI). However, at later time points, patients continuing on nivolumab showed reduced symptom burden over time, whereas those receiving docetaxel had stabilized or worsened symptoms.

LCSS ASBI score changes from baseline in the nivolumab arm indicated clinically meaningful improvements between weeks 42 and 84, whereas no significant or clinically meaningful changes were observed in the docetaxel arm. A longitudinal analysis showed that ASBI score ($p = 0.028$) and its fatigue component ($p < 0.001$) were significantly better in patients treated with nivolumab than in those who received docetaxel; there was an improvement in cough in the nivolumab arm that was statistically significant ($p < 0.001$) and clinically meaningful. Analyses of time to deterioration based on MID revealed significantly slower deterioration in anorexia ($p = 0.009$), symptom distress ($p = 0.026$), interference with activity level ($p = 0.004$), and global HRQoL ($p = 0.007$) among patients who received nivolumab versus those who received docetaxel.

Analyses of the LCSS 3-Item Index revealed statistically significant improvements compared with baseline in the nivolumab arm at weeks 24, 42–54, and 66, but clinically meaningful deterioration in the docetaxel arm at weeks 30 and 36. Statistically significant

improvements were observed for patients treated with nivolumab versus docetaxel at weeks 30–54. Longitudinal analysis showed that, based on the MID, nivolumab significantly slowed time to deterioration in the LCSS 3-Item Index compared with docetaxel ($p = 0.005$).

Similar trends were observed with the EQ-5D. Adjusted EQ-5D completion rates were higher for nivolumab (72%) compared with docetaxel (64%). At week 12, completion rates were similar for both treatment arms (nivolumab, 70%; docetaxel, 71%). By week 42, scores in EQ-5D UI among patients receiving nivolumab were more favorable than mean scores reported for a general US population (34), whereas throughout treatment, scores for patients receiving docetaxel were similar to the norm for a lung cancer population (18) (Fig. 1). For the EQ-5D VAS, patients who received nivolumab had clinically meaningful improvements from baseline and achieved mean scores exceeding that of the general population at weeks 48 and 60, whereas those receiving docetaxel maintained a level of health consistent with that of patients with lung cancer, with no clinically meaningful changes. Nivolumab significantly delayed time to deterioration versus docetaxel for both the EQ-5D UI ($p = 0.006$) and VAS ($p = 0.008$), with the curves beginning to separate before 2 months.

Nivolumab has also demonstrated significantly longer OS and a favorable safety profile compared with docetaxel in advanced, previously treated non-squamous NSCLC in CheckMate 057, a randomized, open-label, phase III trial (8). Improvement in disease-related symptoms by week 12 was assessed as a secondary endpoint using the LCSS (35). Overall health status, assessed using the EQ-5D, was an exploratory objective (36). Questionnaire completion rates were generally similar between the nivolumab and docetaxel arms at baseline (EQ-5D: 84% vs. 80%; LCSS: 82% vs. 77%) and at week 12 (EQ-5D: 77% vs. 80%; LCSS: 77% vs. 76%).

The rate of disease-related symptom improvement by week 12, defined as a ≥10-point decrease from baseline in LCSS ASBI score at any time from randomization to week 12, was similar in both arms: 18% with nivolumab and 20% with docetaxel. Nivolumab was associated with a brief worsening in ASBI score at week 4 ($p = 0.033$), followed by significant

improvements from weeks 16 to 54, with clinically meaningful improvements in cough from weeks 36 to 48. Docetaxel was associated with worsening in ASBI score relative to baseline at week 9 ($p = 0.018$), after which ASBI scores indicated stable symptoms. Numerical between-arm differences in ASBI score changes from baseline were observed in favor of nivolumab from week 12 (first common PRO assessment time point) throughout treatment. An MMRM longitudinal analysis showed improvements from baseline in the nivolumab arm for fatigue ($p = 0.032$) and cough ($p = 0.046$), and deterioration from baseline in the docetaxel arm for ASBI ($p = 0.001$), fatigue ($p < 0.001$), and dyspnea ($p < 0.001$); however, changes were not clinically meaningful. Time to deterioration in ASBI score ($p = 0.002$) and most of its individual components was delayed with nivolumab versus docetaxel, with Kaplan-Meier curves separating at approximately 2 months.

At common assessment time points with >10 patients (to week 48), between-arm differences in the change from baseline in LCSS 3-Item Index score were significant at weeks 24 and 30, favoring nivolumab over docetaxel. There was a clinically meaningful improvement in HRQoL at week 48 in the nivolumab arm. Time to deterioration in the LCSS 3-Item Index ($p < 0.001$) and its components was slower with nivolumab versus docetaxel, with Kaplan-Meier curves also separating at approximately 2 months.

Apart from a worsening at week 4 ($p = 0.008$) in the nivolumab arm that was not clinically meaningful, neither arm exhibited statistically significant changes in EQ-5D UI scores from baseline. Patients treated with nivolumab exhibited clinically meaningful improvements from baseline in EQ-5D VAS scores at weeks 24 and 36; there were no significant differences between arms for any on-treatment assessments.

Longitudinal and time-to-deterioration analyses showed no differences between treatment arms for the EQ-5D UI. However, an MMRM analysis for the EQ-5D VAS showed a significant improvement from baseline with nivolumab ($p = 0.021$) and no changes with docetaxel; between-arm differences favored nivolumab ($p = 0.002$). Time to deterioration based

on the EQ-5D VAS was delayed with nivolumab versus docetaxel (p = 0.032), with Kaplan-Meier curves separating at approximately 4 months.

In a community-based phase IIIb/IV trial (CheckMate 153) of nivolumab in patients with previously treated stage IIIB/IV squamous or non-squamous NSCLC, PROs were assessed as secondary endpoints using the LCSS and EQ-5D instruments (37). Based on the available data from this ongoing trial, LCSS ASBI and 3-Item Index scores remained stable from baseline to week 6, then improved steadily though week 30. Subgroup analyses showed that patients with PR (no patients had a CR) had improvements in LCSS ASBI scores from baseline to week 6. After week 6, all response-evaluable groups (PR, stable disease, and progressive disease) trended toward improvement. For the LCSS 3-Item Index, all three response groups had improvements from weeks 6 to 18. There were no HRQoL differences between programmed death ligand 1 (PD-L1) non-expressers (<1%), expressers (≥1%), and indeterminate expressers, based on LCSS ASBI or 3-Item Index scores.

Both EQ-5D UI and VAS scores improved over time with nivolumab treatment, with significant improvements from weeks 12 to 24. EQ-5D VAS scores showed clinically meaningful improvements from weeks 18 to 30, approaching the United States population norm by week 30. Subgroup analyses showed an improvement trend between baseline and week 18 among patients with PR and stable disease, with a clinically meaningful improvement at week 18 for the PR group. There were no differences between PD-L1 non-expressers, expressers, and indeterminate expressers for the EQ-5D VAS, while current/former smokers with squamous histology and non-smokers with non-squamous histology had clinically meaningful improvements from baseline at week 18. Patients regardless of age, as well as those with an Eastern Cooperative Oncology Group performance status of 0–1, showed improvements in mean EQ-5D VAS score. Patients with a performance status of 2 had lower EQ-5D VAS scores at baseline but showed improvements from week 6 onwards (38).

Renal cell carcinoma

In CheckMate 025, a randomized, open-label, phase III trial in previously treated patients with advanced RCC, nivolumab improved OS versus everolimus, an mTOR inhibitor (12). PROs were assessed as exploratory endpoints using the FKSI-DRS questionnaire and EQ-5D (39). Adjusted baseline completion rates were 89% in the nivolumab arm and 86–87% in the everolimus arm.

Patients treated with nivolumab had improved FKSI-DRS scores relative to baseline from weeks 20–104, whereas in patients treated with everolimus, scores deteriorated relative to baseline between weeks 4–32 and 60–64 (Fig. 2), with significant differences between treatment arms. Scores were improved with nivolumab versus everolimus for all nine individual FKSI-DRS items. Longitudinal MMRM showed that patients receiving everolimus experienced clinically meaningful deterioration from baseline through week 84, whereas scores remained stable during the same period for patients receiving nivolumab. A higher proportion of patients treated with nivolumab (55%) had clinically meaningful improvements versus patients treated with everolimus (37%) ($p < 0.0001$). Using a more stringent scoring threshold (MID of ≥3 points), 41% of patients treated with nivolumab had clinically meaningful improvements versus 28% of patients treated with everolimus ($p = 0.0002$). Median time to improvement was shorter in patients treated with nivolumab versus everolimus.

EQ-5D UI and VAS scores improved from baseline to week 104 with nivolumab, whereas deterioration occurred with everolimus. With the EQ-5D UI, there was no significant difference between the treatment arms in the proportion of patients who had clinically meaningful improvement, or in the hazard ratios for time to improvement. However, more patients had clinically meaningful improvements in EQ-5D VAS scores with nivolumab (53%) versus everolimus (39%) ($p = 0.0001$). Time to improvement, as assessed with the EQ-5D VAS, was 6.5 months with nivolumab and 23.1 months with everolimus ($p = 0.070$).

An exploratory analysis suggested that OS was positively correlated with PROs based on the FKSI-DRS, EQ-5D UI, and EQ-5D VAS (39, 40). Median OS was longest in patients with high baseline scores (above the median) and improvements from baseline, and shortest in patients with low baseline scores (below the median), suggesting that baseline PRO scores could to be prognostic indicators of clinical outcomes.

Squamous cell carcinoma of the head and neck

CheckMate 141 was a phase III randomized, open-label trial of nivolumab versus investigator's choice (IC) of single-agent chemotherapy (cetuximab, docetaxel, or methotrexate) in recurrent or metastatic platinum-refractory SCCHN (15). Treatment with nivolumab resulted in longer OS and was associated with fewer grade 3–4 AEs compared with IC. HRQoL was assessed as an exploratory endpoint using EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D (41).

Questionnaire completion rates were 80% for nivolumab (all questionnaires) and 74–75% for IC at baseline, and precipitously decreased over time. Owing to small sample sizes (n < 10) in the IC arm, analyses comparing treatment arms were not conducted beyond week 15. An analysis of missing data showed that, generally, patients who had only completed a baseline assessment had lower functioning and higher symptom burden than patients who also completed questionnaires during treatment. Before dropout, both EORTC questionnaire scores remained stable in the nivolumab arm but declined in the IC arm, suggesting that estimates of treatment differences might be conservative.

Through week 15 of treatment, patients treated with nivolumab had stable EORTC QLQ-C30 scale scores, whereas patients receiving IC had statistically significant and clinically meaningful worsening in physical, role, cognitive, and social functioning, as well as fatigue, dyspnea, insomnia, and appetite loss. There was no evidence of a differential benefit with nivolumab versus IC based on tumor PD-L1 expression status (<1% vs. ≥1%) or human

papillomavirus status (positive vs. negative). Nivolumab significantly delayed the time to deterioration versus IC for global health status; physical, role, cognitive, and social functioning; and symptoms of fatigue, dyspnea, insomnia, and appetite loss.

With the EORTC QLQ-H&N35, patients treated with nivolumab also had stable scores through week 15 of treatment, whereas patients receiving IC had statistically significant and clinically meaningful worsening in sensory, social eating, social contact, and mouth-opening (trismus-related) problems, sticky saliva, feeling ill, painkiller use, and weight loss. In addition, nivolumab significantly delayed the time to deterioration versus IC for pain, sensory, social contact, and mouth-opening problems. There was no evidence of a differential benefit across tumor human papillomavirus status and PD-L1 expression subgroups.

EQ-5D VAS scores showed that patients treated with nivolumab experienced clinically meaningful improvements from baseline to week 15, in contrast with clinically meaningful deteriorations in the IC arm. The difference between arms at week 15 was statistically significant ($p = 0.037$), clinically meaningful, and favored nivolumab. EQ-5D UI scores were similar for the two treatment arms with no statistically significant nor clinically meaningful differences observed within or between arms at weeks 9 and 15.

An exploratory analysis found that some HRQoL measures correlated with healthcare resource utilization (HCRU; frequency of physician office visits, hospital outpatient visits, emergency department visits, hospital admissions, or other visits) (42). Higher baseline EORTC QLQ-C30 global health status ($p = 0.040$), cognitive functioning ($p = 0.012$), and social functioning ($p = 0.011$) were associated with lower total HCRU event frequency, while higher symptom burden was associated with more frequent total HCRU events. These correlations suggest that baseline HRQoL scores may be useful in identifying patients at risk of high HCRU.

Discussion

PRO data reported across CheckMate clinical trials in melanoma, NSCLC, RCC, and SCCHN show that treatment with nivolumab stabilizes or improves HRQoL and symptom burden in patients with advanced cancer while providing clinical benefits, whereas comparators, both conventional chemotherapy and targeted agents, are more often associated with HRQoL deterioration. In addition, nivolumab delays time to symptom deterioration in multiple tumor types.

The positive effect of nivolumab on PROs combines amelioration of disease-related symptoms and lower treatment toxicity reflecting nivolumab's distinct mode of action, which does not involve direct cytotoxicity. Cytotoxicity of chemotherapy is not cancer-selective and results in AEs that can impact HRQoL. Although better tolerated, targeted agents are also associated with HRQoL-affecting AEs. Like nivolumab, ipilimumab's mechanism of action relies on the generation of a T cell–mediated immune antitumor response. While immune-related AEs are very common in patients treated with immunotherapies, particularly an anti–CTLA-4 antibody, the overall AE profiles of immuno-oncology agents are favorable compared with chemotherapy and targeted therapy (7). HRQoL, symptoms, and functioning assessed using PROs are an important part of the patient experience and may be a critical differentiating factor between PD-1 inhibitors and other treatments.

In some instances, HRQoL advantages with nivolumab were observed prior to clinical benefits, potentially owing to currently undefined effects on circulating factors (e.g. cytokines/chemokines) that mediate symptoms and affect functioning. It is also possible that, in open-label trials, patients' knowledge of received therapy affected their perception of the treatment and their HRQoL (43).

Relevance and limitations of PRO assessments

Reporting the patient perspective is becoming particularly important in the development of therapies that may require longer duration of treatment. For some indications, PROs may

distinguish between available therapies when comparative clinical data are not available, enabling physicians and patients to make informed therapeutic decisions. PROs have prognostic capacity, which could be useful for tailoring therapeutic approaches to patient needs (39, 40, 42). Collection of PROs in routine clinical practice, while still infrequent, leads to more effective patient-centered care, improved patient-physician communication and patient satisfaction, and has been linked to extended survival (44-47).

There is increasing demand to demonstrate value, particularly for novel therapeutic approaches that have high direct costs. Value frameworks encompassing benefits, toxicity, and cost of therapy are used to quantify the net value of cancer therapies, enabling comparisons, formulary prioritization, and cost-effectiveness assessments. Although the value framework designed by the Institute for Clinical and Economic Review uses quality-adjusted life years (48), and that of the European Society for Medical Oncology enables optional weighting of efficacy outcomes based on HRQoL (49), most do not yet require the inclusion of PROs in their metrics; this has been recognized as a limitation of the current models and will be addressed in future versions (50-52). It is expected that PROs will increasingly be included in health technology assessments, which will impact reimbursements, pricing negotiations, and market access (53).

Stakeholders including regulatory bodies have started to commit to more patient-focused cancer drug development and the inclusion of PROs in oncology clinical trials (albeit not as primary endpoints) (54). The importance of PROs is reflected in the updated US Food and Drug Administration (FDA) and European Medicines Agency drug approval processes (1, 55). PRO findings are encouraged (but not required) to be included as part of the regulatory approval submission package, both in the United States and in Europe, and data collected rigorously using appropriate, reliable, and validated instruments can be included in product labels (54). Nevertheless, between 2010 and 2014, only three of the 40 newly approved anticancer drugs reviewed by the FDA had PRO-related labeling, demonstrating the challenges of integrating PRO assessments in clinical trials and in the oncology drug approval process (56). Guidelines

for reporting clinical trial data promote transparent and accurate reporting of PROs, in an effort to facilitate interpretation of these complex data and their limitations, which are further compounded by factors such as the unblinded nature of many oncology studies (57, 58).

Based on experience with PROs as additional endpoints in nivolumab trials, questionnaire completion rates remain a major area for improvement in order to generate robust data and conduct accurate analyses. Missing PRO data are common in oncology clinical trials, impacting confidence intervals and statistical power. Analyses become particularly difficult in cases of imbalanced missing data between trial arms such that the patient groups are no longer comparable, and may reflect differing clinical benefits. To mitigate the impact of missing data, analyses for handling missing data should be preplanned and tailored to each trial design and assessment characteristics. Missing data should be explored to evaluate the reasons for dropout and, depending on the assessment, adjustment methods such as imputation procedures, PPMs, and selection models can be used (1, 43, 55, 59). The analytic plan for missing data should be fully reported, along with a detailed methodology of PRO collection and analysis, baseline PRO results, and other study limitations, per the Consolidated Standards of Reporting Trials (CONSORT) PRO extension, which provides guidance for authors of publications describing PRO data from clinical trials (57, 60, 61).

PRO completion rates could be improved by increasing patient and physician awareness of the value of PROs in clinical trials, as these assessments are sometimes viewed as less important and less robust than clinical outcomes. While patients generally consider PRO questionnaires to be useful, few clinicians have experience conducting HRQoL assessments, citing limited resources, uncertainty about the measure to use, and a perceived lack of impact on patient care (62, 63). In addition, the inclusion of PRO assessments in clinical trials is time-consuming and logistically difficult, often resulting in the deprioritization of PRO endpoints.

Members of the clinical study team should be trained to ensure PROs are properly administered and collected; detailed instructions should include their purpose and significance

for the study (64). Participating patients should receive clear instructions, and the importance of honest, independent, and complete responses should be conveyed (64). The burden of PRO assessments could be reduced through electronic data collection instead of using paper questionnaires. Tablets, smartphones, or telephone-based interactive voice-response systems would improve data accuracy and completion rates (65). Additionally, PROs should be assessed beyond treatment discontinuation (e.g. in association with survival follow-up); this is particularly important for therapies that provide durable responses and long-term survival.

A limitation of existing cancer-specific PRO measures is that these instruments were not designed to evaluate immune-based therapies and may not fully capture the benefits and tolerability of these therapies. New or updated cancer-specific measures covering the symptomatic AEs of immunotherapies are needed. Relevant items from the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) could be incorporated in immuno-oncology clinical trial endpoints, although the PRO-CTCAE may not be sufficiently comprehensive in its current form to encompass all immune-related AEs (66, 67).

Conclusions

HRQoL results from eight clinical trials in four cancer types demonstrate that nivolumab treatment generally results in stabilized or improved PROs compared with deteriorations observed with the trial comparators. Transparent, accurate, and complete reporting of the patient perspective using PROs is important in patient-focused cancer drug development and encouraged for inclusion in clinical trials by the regulatory authorities in the United States and Europe.

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Tables

Table 1

PRO instruments used in nivolumab studies.

Focus of measure	Scale	Components	Scoring and direction	MID[a] in patients with cancer
General cancer	EORTC QLQ-C30 (21)	Global health and functioncal domains: • Global health status/HRQoL scale (2 items) • Physical functioning (5 items) • Role functioning (2 items) • Emotional functioning (4 items) • Cognitive functioning (2 items) • Social functioning (2 items)	Ranges from 0 to 100 Higher score = better HRQoL	10[b] and/or domain-specific MIDs (27, 28)
		Symptom domains: • Pain (2 items) • Nausea and vomiting (2 items) • Fatigue (3 items) • Dyspnea • Insomnia • Appetite loss • Constipation • Diarrhea • Financial difficulties	Ranges from 0 to 100 Higher score = higher symptom burden	

Cancer type–specific	EORTC QLQ-H&N35 (25, 26)	Multi-item scales: • Pain • Sensory problems • Social contact problems • Swallowing • Social eating problems • Speech problems • Reduced sexuality Single-item scales: • Teeth • Opening mouth • Dry mouth • Sticky saliva • Coughing • Feeling ill • Painkiller use • Nutritional supplements • Use of a feeding tube • Weight loss • Weight gain	Ranges from 0 to 100 Higher score = higher symptom burden	10[c]
	FKSI-15 (24)	• Work • Enjoy life • Bothered by side effects	Ranges from 0 (no symptoms) to 36 (worst symptoms)	2–3

	• Worry condition will worsen • Appetite • Sleep	Higher score = higher symptom burden	
	FKSI-DRS • Energy • Pain • Weight loss • Bone pain • Fatigue • Dyspnea • Cough • Fevers • Hematuria		
LCSS (22, 23)	ASBI • Anorexia • Fatigue • Dyspnea • Pain • Hemoptysis • Cough	Ranges from 0 to 100 on a VAS Higher score = higher symptom burden	10
	3-Item Index • Symptom distress • Interference with activity level	3 items combined on a scale of 0 to 300 Higher score = better HRQoL	30

		• HRQoL		
Overall health	3-level EQ-5D (19, 68)	EQ-5D UI • Mobility • Self-care • Usual activities • Pain/discomfort • Anxiety/depression	Patient responses converted to a vector and weighted using the UK preference-weighting algorithm (69) to provide an aggregate measure of a respondent's health state value to society, on a scale from 0 (dead) to 1 (full health)	0.08
		EQ-5D VAS Single VAS representing health state today	Ranges from 0 (worst state imaginable) to 100 (best health state imaginable)	7

Abbreviations: ASBI, Average Symptom Burden Index; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; EORTC QLQ-H&N35, EORTC 35-Question Head and Neck Cancer-Specific Module; EQ-5D, EuroQoL five dimensions; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; HRQoL, health-related quality of life; LCSS, Lung Cancer Symptom Scale; MID, minimally important difference; UI, utility index; VAS, visual analog scale.

[a] MID is defined within each instrument.

[b] Clinically important difference, not necessarily MID.

[c] Also commonly accepted as the clinically important difference.

Table 2

Summary of clinical outcomes from nivolumab studies reporting PRO measures.

Indication	Melanoma			Lung			RCC	SCCHN
Trial	066 NCT01721772	067 NCT01844505	069 NCT01927419	017 NCT01642004	057 NCT01673867	153 NCT02066636	025 NCT01668784	141 NCT02105636
Phase	III	III	II	III	III	IIIb/IV	III	III
Blinding	Double-blind	Double-blind	Double-blind	Open-label	Open-label	N/A	Open-label	Open-label
Treatments	Nivo vs. DTIC	Nivo vs. nivo + ipi vs. ipi	Nivo + ipi vs. ipi	Nivo vs. docetaxel	Nivo vs. docetaxel	Nivo	Nivo vs. everolimus	Nivo vs. IC (cetuximab, docetaxel, or methotrexate)
Median OS	NR (nivo), 10.8 mo (DTIC)	NR (nivo + ipi), 37.6 mo (nivo), 19.9 mo (ipi)	Not reported	9.2 mo (nivo), 6.0 mo (docetaxel)	12.2 mo (nivo), 9.4 mo (docetaxel)	Not yet published	25.0 mo (nivo), 19.6 mo (everolimus)	7.5 mo (nivo), 5.1 mo (IC)
Median PFS	5.1 mo (nivo), 2.2 mo (DTIC)	11.5 mo (nivo + ipi), 6.9 mo (nivo), 2.9 mo (ipi)	*BRAF* WT: NR (nivo + ipi), 4.4 mo (ipi) *BRAF* mut: 8.5 mo (nivo + ipi), 2.7 mo (ipi)	3.5 mo (nivo), 2.8 mo (docetaxel)	2.3 mo (nivo), 4.2 mo (docetaxel)	Not yet published	4.6 mo (nivo), 4.4 mo (everolimus)	2.0 mo (nivo), 2.3 mo (IC)
ORR	40.0% (nivo) 13.9% (DTIC)	57.6% (nivo + ipi), 43.7% (nivo), 19.0% (ipi)	BRAF WT: 61% (nivo + ipi), 11% (ipi)	20% (nivo), 9% (docetaxel)	19% (nivo), 12% (docetaxel)	Not yet published	25% (nivo), 5% (everolimus)	13.3% (nivo), 5.8% (IC)

			BRAF mut: 52% (nivo + ipi), 10% (ipi)					
Any grade TRAEs	74.3% (nivo), 75.6% (DTIC)	95.5% (nivo + ipi), 82.1% (nivo), 86.2% (ipi)	91.5% (nivo + ipi), 93.5% (ipi)	58% (nivo), 86% (docetaxel)	69% (nivo), 88% (docetaxel)	Not yet published	79% (nivo), 88% (everolimus)	58.9% (nivo), 77.5% (IC)
Grade 3–4 TRAEs	11.7% (nivo), 17.6% (DTIC)	55.0% (nivo + ipi), 16.3% (nivo), 27.3% (ipi)	54.2% (nivo + ipi), 23.9% (ipi)	7% (nivo), 55% (docetaxel)	10% (nivo), 54% (docetaxel)	Not yet published	19% (nivo), 37% (everolimus)	13.1% (nivo), 35.1% (IC)
PRO instruments	EQ-5D EORTC QLQ-C30	EQ-5D EORTC QLQ-C30	EQ-5D EORTC QLQ-C30	EQ-5D LCSS	EQ-5D LCSS	EQ-5D LCSS	EQ-5D FKSI-DRS	EQ-5D EORTC QLQ-C30 EORTC QLQ-H&N35
PRO assessment schedule	• At baseline • Q6W on treatment • At follow-up visits 1 and 2	• At baseline • At weeks 1 and 5 of every 6-week cycle for the first 6 mo • Then Q6W up to week 79 • At follow-up visits 1 and 2	• At baseline • Q6W for the first 6 mo of the study	• At baseline • Q4W (nivo) and Q3W (docetaxel) for the first 6 mo of the study, then Q6W • At follow-up visits 1 and 2	• At baseline • Q4W (nivo) and Q3W (docetaxel) for the first 6 mo of the study, then Q6W • At follow-up visits 1 and 2	• At baseline • Q6W for the first year of the study, then Q4W for the duration of treatment • At follow-up visits 1 and 2 (EQ-5D only)	• At baseline • Q4W on treatment • At follow-up visits 1 and 2 • At survival visits (EQ-5D only)	• At baseline • At week 9 then Q6W on treatment
PRO endpoints	Secondary (EORTC QLQ-	Secondary (EORTC QLQ-	Exploratory	Secondary (disease-related	Secondary (disease-related	Exploratory	Exploratory	Exploratory

	C30) and exploratory (EQ-5D)	C30) and exploratory (EQ-5D)		symptom improvement rate by week 12) and exploratory (EQ-5D)	symptom improvement rate by week 12) and exploratory (EQ-5D)			
Primary publication(s)	Robert et al. N Engl J Med 2015 (10)	Larkin et al. N Engl J Med 2015 (11) Wolchok et al. N Engl J Med 2017 (13)	Postow et al. N Engl J Med 2015 (9)	Brahmer et al. N Engl J Med 2015 (14)	Borghaei et al. N Engl J Med 2015 (8)	–	Motzer et al. N Engl J Med 2015 (12)	Ferris et al. N Engl J Med 2016 (15)
PRO publication(s)	Long et al. Ann Oncol 2016 (30)	Schadendorf et al. Eur J Cancer 2017 (31)	Abernethy et al. J Clin Oncol 2015 (32)	Reck et al. J Thorac Oncol 2017 (33)	Gralla et al. J Clin Oncol 2016 (35); Reck et al. Ann Oncol 2016 (36)	Schwartzberg et al. Eur J Cancer 2015 (37); Spigel et al. J Thorac Oncol 2016 (38)	Cella et al. Lancet Oncol. 2016 (39); Grimm Oncol Ther 2017 (40)	Harrington et al. Lancet Oncol 2017 (41)

Abbreviations: *BRAF* mut, *BRAF* V600 mutation-positive tumors; *BRAF* WT, *BRAF* wild-type tumors; DTIC, dacarbazine; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; EORTC QLQ-H&N35, EORTC 35-Question Head and Neck Cancer-Specific Module; EQ-5D, EuroQoL five dimensions; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; IC, investigator's choice of methotrexate, docetaxel, or cetuximab; ipi, ipilimumab; LCSS, Lung Cancer Symptom Scale; N/A, not applicable; nivo, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TRAEs, treatment-related adverse events.

Table 3

Summary of PRO score changes within and between arms.

Tumor type	Study	Tx arm	n	Baseline completion rates (%)	Change from baseline (within arm)		Difference between arms
					Statistically significant	Clinically meaningful[a]	Statistically significant
Melanoma	066	Nivo	210	EQ-5D: 70 QLQ-C30: 70	EQ-5D UI: ↑ wk 7–49 EQ-5D VAS: ↑ wk 25, 31, 37 QLQ-C30: none	EQ-5D UI: ↑ wk 37, 61, 67 EQ-5D VAS: ↑ wk 31, 37, 49, 55, 61 QLQ-C30: none	EQ-5D UI: favoring nivo, wk 7 EQ-5D VAS: none QLQ-C30: none
		DTIC	208	EQ-5D: 65 QLQ-C30: 65	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: none	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: none	
	067	Nivo	316	*EQ-5D: 84.5* *QLQ-C30: 85.1*	EQ-5D UI: ↑ wk 13 onward EQ-5D VAS: none QLQ-C30: NS	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: none	EQ-5D UI: NS EQ-5D VAS: ipi worse than nivo, wk 7–13, 19–23, ipi worse than nivo + ipi, wk 11, 19 QLQ-C30: NS
		Nivo + ipi	314	*EQ-5D: 87.2* *QLQ-C30: 87.3*	EQ-5D UI: ↓ wk 7, ↑ to baseline wk 13 EQ-5D VAS: none QLQ-C30: ↓ wk 7 role functioning, fatigue, appetite loss	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: ↓ wk 7 role functioning, fatigue, appetite loss	
		Ipi	315	*EQ-5D: 81.9* *QLQ-C30: 82.2*	EQ-5D UI: ↓ wk 7, ↑ to baseline wk 19 EQ-5D VAS: ↓ wk 5-23	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: none	

				QLQ-C30: NS			
	069	Nivo + ipi	95	EQ-5D: 64.2 QLQ-C30: 65.3	EQ-5D UI: ↓ wk 7 EQ-5D VAS: none QLQ-C30: ↑ emotional functioning	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: none	NS
		Ipi	47	EQ-5D: 76.7 QLQ-C30: 78.7	EQ-5D UI: ↓ wk 7 EQ-5D VAS: none QLQ-C30: ↑ emotional functioning	EQ-5D UI: none EQ-5D VAS: none QLQ-C30: none	
NSCLC	017	Nivo	135	EQ-5D: 81.5 LCSS: 77.8	EQ-5D UI: ↑ wk 20, 24, 42, 48, 54, 66 EQ-5D VAS: ↑ wk 12, 20, 24, 30, 36, 48, 66 LCSS ASBI: ↑ wk 16–54 LCSS 3-II: ↑ wk 24, 42–54, 66	EQ-5D UI: ↑ wk 42-66, 78 EQ-5D VAS: ↑ wk 24–48, 60-72, 84 LCSS ASBI: ↑ wk 42–84 LCSS 3-II: ↑ wk 42–84	EQ-5D UI: favoring nivo, wk 48, 54 EQ-5D VAS: favoring nivo, wk 12, 48 LCSS ASBI: favoring nivo, wk 30–42 LCSS 3-II: favoring nivo, wk 30–54
		Doc	137	EQ-5D: 76.6 LCSS: 78.1	EQ-5D UI: none EQ-5D VAS: none LCSS ASBI: none LCSS 3-II: ↓ wk 30–36	EQ-5D UI: ↓ wk 36 EQ-5D VAS: none LCSS ASBI: ↓ wk 36 LCSS 3-II: ↓ wk 30–36	
	057	Nivo	292	EQ-5D: 83.6 LCSS: 82.2	EQ-5D UI: ↓ wk 4 EQ-5D VAS: ↓ wk 4, ↑ wk 16–36 LCSS ASBI: ↓ wk 4, ↑ wk 16–54 LCSS 3-II: ↓ wk 4, ↑ wk 16-36, 48	EQ-5D UI: none EQ-5D VAS: ↑ wk 24, 36 LCSS ASBI: none LCSS 3-II: none	EQ-5D UI: none EQ-5D VAS: none LCSS ASBI: favoring nivo, wk 12, 24, 30, 42

		Doc	290	EQ-5D: 80.0 LCSS: 76.6	EQ-5D UI: none EQ-5D VAS: none LCSS ASBI: ↓ wk 9 LCSS 3-II: none	EQ-5D UI: none EQ-5D VAS: none LCSS ASBI: none LCSS 3-II: none	LCSS 3-II: favoring nivo, wk 24, 30
	153	Nivo	620[b]	EQ-5D: NS LCSS: NS	EQ-5D UI: ↑ wk 12–24 EQ-5D VAS: ↑ wk 12–24 LCSS ASBI: NS LCSS 3-II: NS	EQ-5D UI: none EQ-5D VAS: ↑ wk 18–30 LCSS ASBI: none LCSS 3-II: none	NA
RCC	025	Nivo	410	*EQ-5D: 88.9* *FKSI-DRS: 88.9*	EQ-5D UI: ↑ wk 28–92, 100 EQ-5D VAS: ↑ wk 8–116 FKSI-DRS: ↑ wk 20–104	EQ-5D UI: NS EQ-5D VAS: NS FKSI-DRS: NS	EQ-5D UI: favoring nivo, wk 8–12, 24–44, 52–68, 80 EQ-5D VAS: favoring nivo, wk 4–68, 76–80, 88–92 FKSI-DRS: favoring nivo, wk 4–76
		Ever	411	*EQ-5D: 86.6* *FKSI-DRS:86.4*	EQ-5D UI: ↓ wk 4–8 EQ-5D VAS: ↓ wk 4–16, 24, 32–36, 56 FKSI-DRS: ↓ wk 4–32, 60–64	EQ-5D UI: NS EQ-5D VAS: NS FKSI-DRS: ↓ wk 4-84	
SCCHN	141	Nivo	240	EQ-5D: 79.6 QLQ-C30: 79.6 QLQ-H&N35: 80.4	EQ-5D UI: NS EQ-5D VAS: NS QLQ-C30: NS QLQ-H&N35: NS	EQ-5D UI: none EQ-5D VAS: ↑ wk 15 QLQ-C30: none QLQ-H&N35: ↑ painkiller use, weight loss, wk 9; ↑ painkiller use, wk 15; ↓ weight gain[c], wk 9–15	EQ-5D UI: none EQ-5D VAS: favoring nivo, wk 15 QLQ-C30: favoring nivo, role, and social functioning, fatigue, dyspnea, diarrhea, appetite loss, wk 9; role, physical, cognitive, and social functioning, pain, fatigue, dyspnea, appetite loss, insomnia, wk 15
		IC	121	EQ-5D: 74.4 QLQ-C30: 75.2	EQ-5D UI: NS EQ-5D VAS: NS	EQ-5D UI: none EQ-5D VAS: ↓ wk 15	

	QLQ-H&N35: 75.2	QLQ-C30: NS QLQ-H&N35: NS	QLQ-C30: ↓ appetite loss, wk 9; ↓ physical, role, cognitive, social functioning, fatigue, dyspnea, insomnia, appetite loss, wk 15 QLQ-H&N35: ↓ sticky saliva, nutritional supplement use, weight gain[c], wk 9; ↓ sensory problems, social eating problems, social contact problems, mouth-opening, sticky saliva, feeling ill, painkiller use, weight loss, wk 15	QLQ-H&N35: favoring nivo, pain, sensory problems, nutritional supplement use, wk 9; favoring nivo, pain, sensory problems, social contact problems, mouth-opening problems, sticky saliva, coughing, feeling ill, painkiller use, weight loss, wk 15

Abbreviations: 3-II, 3-Item Index; ASBI, Average Symptom Burden Index; doc, docetaxel; DTIC, dacarbazine; EQ-5D, EuroQoL five dimensions; ever, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms; IC, investigator's choice of methotrexate, docetaxel, or cetuximab; ipi, ipilimumab; LCSS, Lung Cancer Symptom Scale; n, number of patients randomized; NA, not applicable; nivo, nivolumab; NS, not specified; NSCLC, non-small cell lung cancer; PRO, patient-reported outcome; QLQ-C30, EORTC Quality of Life Questionnaire Core 30; QLQ-H&N35, EORTC 35-Question Head and Neck Cancer-Specific Module; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; Tx, treatment; UI, utility index; VAS, visual analog scale.

↑ = improvement; ↓ = deterioration.

[a] Clinically meaningful change was defined as a change equal to or exceeding the MID of the scale.

[b] Number of patients included in PRO analysis (single-arm study).

[c] Per scale design, a decrease in score for weight gain indicates that patients experienced an increase in weight, which, for this patient population that is often affected by difficulties eating and by weight loss, can be viewed as a positive effect.

Italic text indicates adjusted completion rates calculated using the number of patients with non-missing PRO data at baseline and data from ≥1 post-baseline visit, divided by the number of patients in the study at each respective time point.

Figures

Fig. 1. Mean (95% confidence interval) on-treatment scores on EQ-5D 3-level version from CheckMate 017 (33). (A) EQ-5D utility index; (B) EQ-5D visual analog scale (VAS). Only time points that had data available for five or more patients in either treatment group are shown. Dashed lines represent the mean scores reported for a general United States population (34) and for a lung cancer population (18).

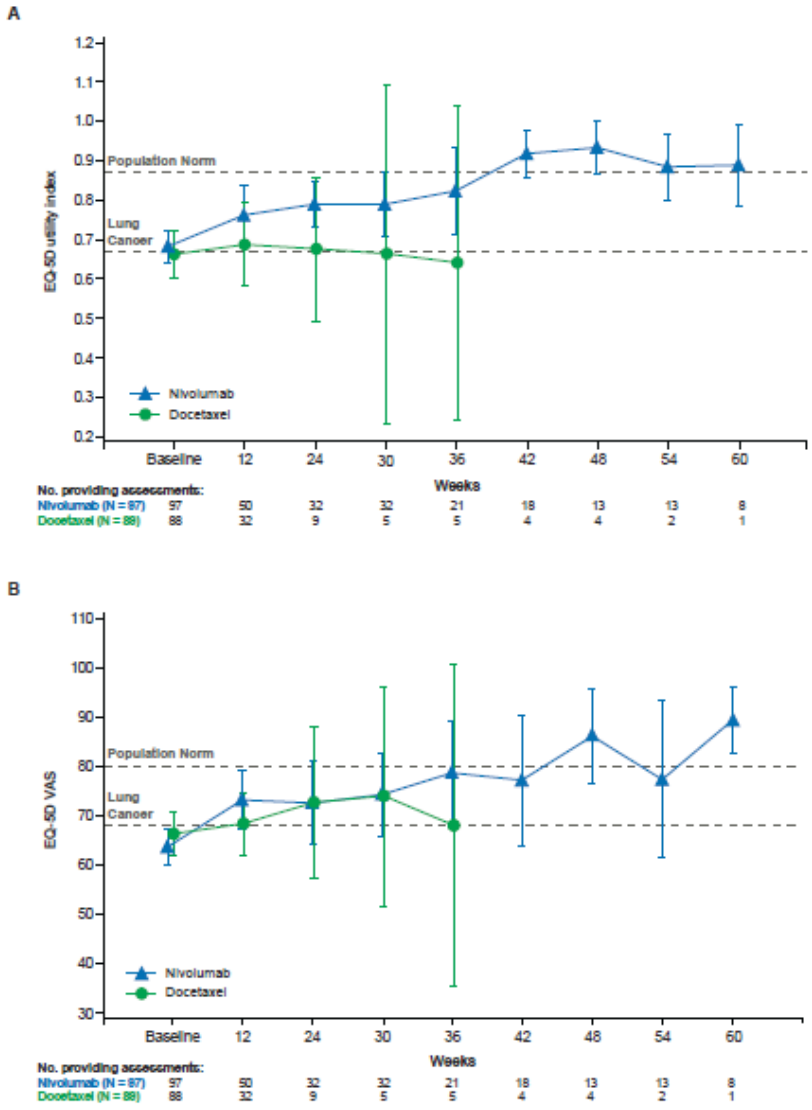

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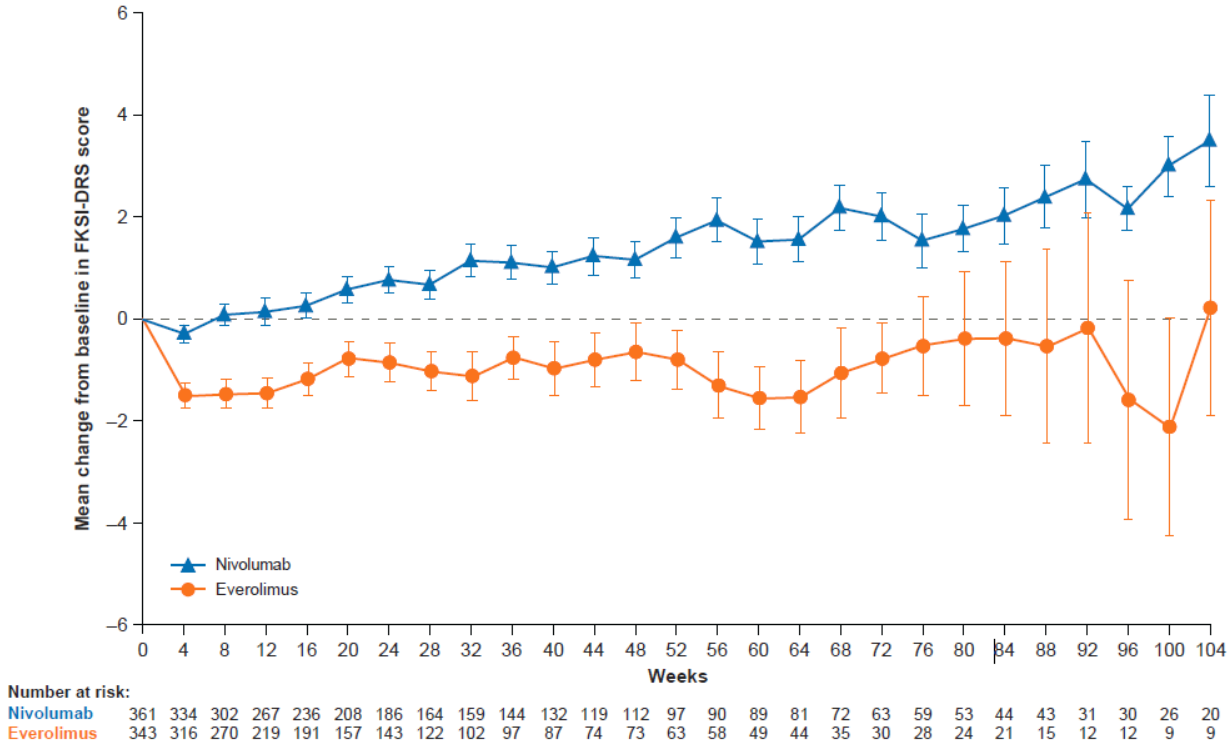
Fig. 2. Mean change from baseline in health-related quality of life (HRQoL) scores on Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS) from CheckMate 025 (39). Only time points where data were available for five or more patients are shown. Number at risk shows the number of randomized patients with baseline plus at least one post-baseline HRQoL assessment with non-missing patient-reported outcome data. Time 0 indicates baseline. Bars show standard error.



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