Special Series: Science in Action: Evidence and Opportunities for Palliative Care Across Diverse Populations and Care Settings

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Patient-Reported Outcomes for Cancer Patients Receiving Checkpoint Inhibitors: Opportunities for Palliative Care—A Systematic Review

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Abstract

Context. Immune checkpoint inhibitors (ICIs) are increasingly used to treat a variety of cancers, but comparatively little is known about patient-reported outcomes (PROs) and health-related quality of life (HRQoL) among patients receiving these novel therapies.

Objectives. We performed a systematic review to examine PROs and HRQoL among cancer patients receiving ICIs as compared to other anticancer therapies.

Methods. We systematically searched PubMed, CINAHL, Embase, Web of Science, and Scopus, using search terms representing ICIs, PROs, and HRQoL on August 10, 2018. Eligible articles were required to involve cancer patients treated with ICIs and to report PROs and/or HRQoL data.

Results. We screened 1453 references and included 15 publications representing 15 randomized controlled trials in our analysis. Studies included several cancer types (melanoma, lung cancer, genitourinary cancer, and head/neck cancer), used four different ICIs (nivolumab, pembrolizumab, atezolizumab, and ipilimumab), and compared ICIs to a wide range of therapies (chemotherapy, targeted therapies, other immunotherapy strategies, and placebo). Studies used a total of seven different PROs to measure HRQOL, most commonly the European Organisation for the Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30) ($n = 12$, 80%). PRO data were reported in a variety of formats and at a variety of time points throughout treatment, which made direct comparison challenging. Some trials ($n = 11$, 73%) reported PROs on specific symptoms. In general, patients receiving ICIs had similar-to-improved HRQoL and experiences when compared to other therapies.

Conclusion. Despite the broad clinical trials experience of ICI therapies across cancer types, relatively few randomized studies reported PROs and patient HRQoL data. Available data suggest that ICIs are well tolerated in terms of HRQoL compared to other anticancer therapies although the conclusions are limited by the heterogeneity of trial designs and outcomes. Currently used instruments may fail to capture important symptomatology unique to ICIs, underscoring a need for PROs designed specifically for ICIs. J Pain Symptom Manage 2019;58:137–156. © *2019 Published by Elsevier Inc. on behalf of American Academy of Hospice and Palliative Medicine.*

Key Words

Patient-reported outcomes, checkpoint inhibitors, quality of life, health-related quality of life, cancer

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Background

Cancer immunotherapy describes a broad group of therapies that are designed to harness the immune system to combat cancer growth and includes a class of drugs termed "immune checkpoint inhibitors" (ICIs). The mechanism of action of ICIs differs from that of cancer therapies that exhibit direct cytotoxic effects because ICIs block inhibitory T cell interactions and augment the host immune system's ability to recognize and destroy tumor cells. Since the initial FDA approval of ipilimumab for the treatment of metastatic melanoma in 2011, ICIs are increasingly used to treat a variety of advanced cancers. ICIs have FDA approval for use in lung cancer, kidney cancer, bladder cancer, head and neck cancer, lymphoma, liver cancer, cervical cancer, gastric cancer, and skin cancer and for all patients with tumors demonstrating microsatellite instability (so called "MSI high tumors"). Seven ICIs are currently in use in the U.S.: six antibodies target PD-1 or PDL-1—pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab—and one antibody targets CTLA-4—ipilimumab.

As a result of their mechanism of action, ICIs have a unique and unpredictable side effect profile. Symptoms typically associated with cytotoxic chemotherapies (such as nausea, anorexia, vomiting, peripheral neuropathy, and alopecia) are rare among patients receiving ICIs. On the other hand, immune-related side effects (also often called immune-related adverse events or IRAEs) are relatively common. These can range from easily managed and fairly mild side effects, including rash, fatigue, or hypothyroidism, to more severe complications including myocarditis, adrenal insufficiency, neurologic disorders, pneumonitis, and colitis; side effects can be life threatening in a small fraction of patients.[1]

Published reports of cancer therapeutic clinical trials typically report on safety and tolerability through a discussion of drug-related adverse events (AEs) that are collated and reported by clinicians. Recognizing the need to incorporate the patient's voice in reporting of treatment-related toxicity, researchers have proven the value of giving patients editorial control over the process by incorporating validated instruments, generally referred to as patient-reported outcomes (PROs) in their design of trial protocols. This information has been shown to be complementary and not redundant to clinician AEs in a number of cancer clinical trials.[2–5] Cancer clinical trials now routinely include PROs to further illustrate the tolerability of novel cancer therapies,[6] but little is known about the usefulness of traditional PROs in capturing the lived experience and symptomatology of patients receiving ICIs.

As the use of ICI therapy increases, palliative care clinicians will increasingly be consulted to address complex and challenging symptom management for this population. The purpose of this systematic review was to identify and summarize existing PRO and health-related quality of life (HRQoL) data among cancer patients receiving ICIs, as compared to standard cancer therapies, with a goal of identifying opportunities for improving the patient experience and quality of life for patients receiving ICIs. The PICOTS question appears in Table 1.

Methods

Search Strategy

We systematically searched five databases: PubMed, CINAHL, Embase, Web of Science, and Scopus databases for articles published up to August 10, 2018. The search used keywords and medical subject headings representing checkpoint inhibitor immunotherapeutics and patient-reported outcomes or quality of life, such as "patient-reported outcome measures," "quality of life," "checkpoint inhibitor" and individual drug names. Peer-reviewed publications from major immune checkpoint inhibitor clinical trials and references from included studies were hand searched and assessed using the same protocol. Appendix details the search strategy for PubMed and with that search strategy then adapted to the other four databases. Note that in the time since this search, an additional ICI has been FDA approved (cemiplimab), but it was not specifically examined in our search strategy. The study was registered on Prospero (ID # CRD42018104718).

Study Selection

We downloaded the search results into Proquest® Refworks software (Ann Arbor, MI) and then into the Covidence Web-based software platform (Melbourne, Australia) for systematic reviews.[7,8] Duplicates were removed. Eligible studies were screened based on the inclusion and exclusion criteria in Table 1. The titles and abstracts and then the full texts of articles were independently reviewed by two members of the study team (from among E. T. H., S. S., J. D., B. G., R. A. A., L. S.) with discrepancies adjudicated through group discussion. We reported our results following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[9]

Data Extraction

For each article meeting criteria to undergo data extraction, at least two members of the study team (from among E. T. H., S. S., J. D., B. G.) abstracted independently the following data (when available): trial

Table 1
Study Eligibility Criteria

PICOTS question: Among patients with cancer, how do checkpoint inhibitors as compared to other chemotherapeutics impact reported outcomes and quality of life?
Population—Patients with cancer
Intervention—Checkpoint inhibitor therapy (specifically CTLA-4 and PD-1 antibody therapies including pembrolizumab, nivolumab, avelumab, atezolizumab, durvalumab, ipilimumab, tremelimumab)
Comparator—Other anticancer therapy (chemotherapy, targeted therapy, placebo, or checkpoint inhibitor therapy)
Outcome(s)—Any reported outcomes related to quality of life (either qualitative or quantitative)
Timing—After treatment
Setting(s)—Inpatient or outpatient

Inclusion criteria
- Participant received checkpoint inhibitor therapy
- Either prospective or retrospective study design is acceptable
- Evaluated outcomes of quality of life or related to quality of life
- Cancer patients
- Inpatient/outpatient facilities
- Systematic reviews

Exclusion criteria
- Single case reports, case series
- "Gray literature"—abstracts, non–peer-reviewed publications
- Narrative reviews
- The study did not involve patients with cancer
- The study did not involve therapy with checkpoint inhibitors
- There were no original data reported (e.g., commentary)
- There were no qualitative or quantitative outcomes relating to quality of life.

design, PRO measures used, clarification of nature of PRO end points, study inclusion/exclusion criteria, baseline characteristics of study populations, treatment details of the intervention and control arms, and summary data of PROs reported in the manuscripts. All extracted data with discrepancies were reviewed and adjudication was performed by group consensus.

Data Synthesis

Results from the identified trials were presented in a tabular summary and summarized in a qualitative synthesis. Meta-analysis was not possible due to the varied detail and content of PROs and the heterogeneity of disease states and comparator treatment arms.

Quality Appraisal

The methodological quality of all included studies was assessed by two members of the study team (E. T. H., S. S., J. D., B. G.) independently using the Cochrane Collaboration Risk-of-Bias Tool Version 1.0.10.[10] Reviewers assessed each of the seven criteria as low, high, or unclear. Disagreements were adjudicated by consensus between the two reviewers.

Results

The database searches generated 1565 records, and an additional 75 references were identified by hand searching (Fig. 1). After duplicates were removed, we screened the abstracts of 1453 articles for inclusion/exclusion criteria. The abstract review resulted in 86 articles for full manuscript screening, which yielded a total of 15 unique references reporting on PRO data for patients receiving checkpoint inhibitors.

Of the 15 studies, all described randomized controlled clinical trials published between 2012 and 2018 with 14 of 15 manuscripts published since 2016 (Tables 2 and 3). All studies were conducted in multiple countries and disclosed funding support by pharmaceutical sponsors. The clinical trials involved patients with a variety of advanced cancer types including melanoma ($n = 8$), lung cancer ($n = 3$), genitourinary cancer ($n = 3$), and head and neck cancer ($n = 1$). Comparator therapies in these studies included cytotoxic chemotherapy ($n = 8$), other immunotherapy strategies including checkpoint inhibitors and vaccines ($n = 4$), targeted therapies ($n = 2$), and placebo ($n = 1$). The majority of studies enrolled patients with unresectable or metastatic cancer to receive palliative ICI therapy ($n = 13$), whereas two studies examined ICIs as adjuvant therapies (after surgical removal of all known disease with goal to increase the likelihood of cure). In 13 of the 15 studies, detailed PROs were presented in a separate manuscript from the primary treatment efficacy manuscript, whereas in two studies, the PRO data were presented only in the primary treatment efficacy manuscript. Ten of the 15 studies were open-label, and the remaining five studies were blinded to patients and clinicians.

Several PRO instruments were used and comprised a combination of general cancer and cancer type–specific instruments. The most commonly utilized PRO instruments were the European Organisation for the Research and Treatment of Cancer (EORTC) core quality of life questionnaire (EORTC

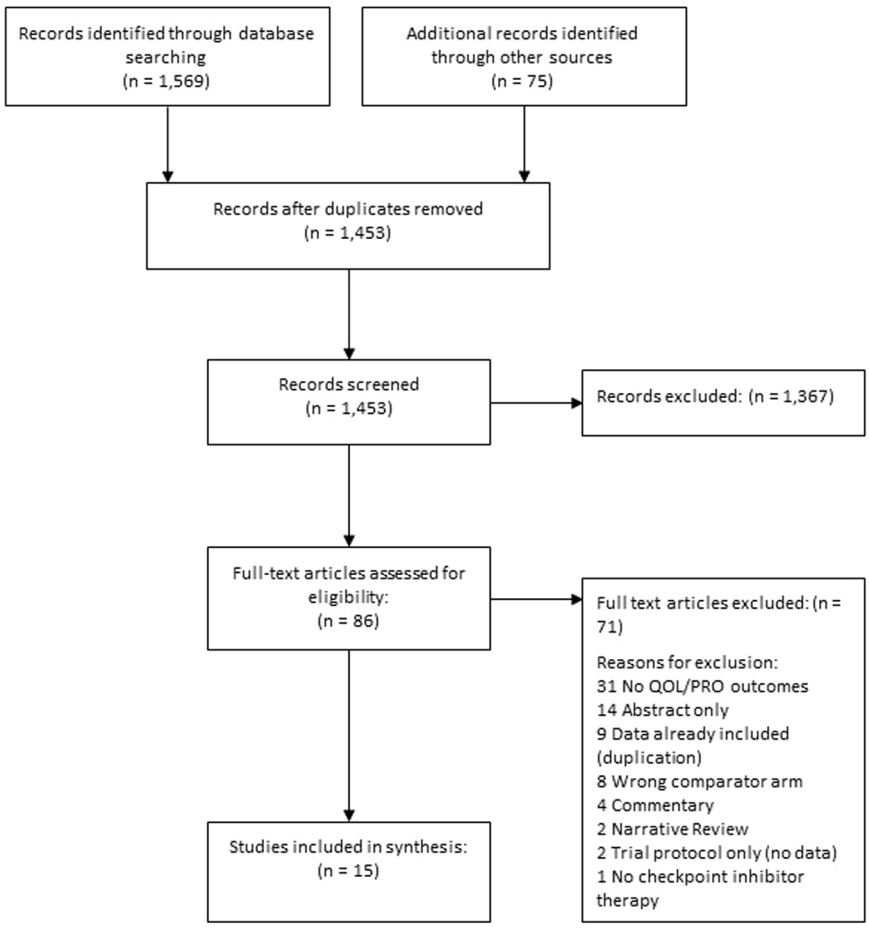

Fig. 1. PRISMA diagram.[9]

QLQ-C30) (n = 12, 80%) and EuroQOL EQ-5D (n = 10, 67%).[11–13] Disease-specific scales were reported in several studies. Two trials used EORTC lung cancer–specific questionnaire module (EORTC QLQ-LC13) and several other disease-specific quality of life outcome measures were reported in a single trial: Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19), Lung Cancer Symptom Scale (LCSS), and EORTC head and neck module (EORTC QLQ-H&N35).[14–20]

All studies reported global health status/HRQoL compared to baseline at various time points compared across treatment groups. Eleven studies reported data on specific symptoms compared between ICI and control arms. Most commonly, this consisted of the symptom subscores of the EORTC QLQ-C30 questionnaire, which are fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea. Although the data were presented in a heterogenous format and used different measures and time points for analysis, conclusions of the studies were that checkpoint inhibitor therapies compared favorably to the other therapies studied in terms of global health status (Table 4) and across several symptoms (Table 5).

Among review of the subset of trials that compared immunotherapy to an alternative immunotherapy strategy, most trials found no significant differences in HRQoL between treatment strategies although one study suggested that pembrolizumab may result in less detrimental impact on HRQoL than ipilimumab.[21]

Baseline PRO completion rates and compliance with subsequent evaluations were reported in most of the trials and varied widely. We found that this was true both for the baseline PRO assessment (~60–99%) and later assessments (Weeks 12–24 ranging from ~50 to >90% depending on the trial).

Risk of Bias/Quality Assessment of Included Studies

The results of our risk of bias/quality assessment are shown in Table 6. The domains found to be most at risk for bias were Blinding of Participants and Personnel and Blinding of Outcome Assessors in

Table 2
Study Design of Included Trials

First Author	Primary Efficacy Publication (if Applicable)	Study Name	Funding	Study Design	Key Inclusion/ Exclusion Criteria[a]	Treatment Arms
Melanoma trials						
Schadendorf 2016[40]	Ribas 2015[41]	Keynote-002	Merck & Co., Inc.	Open-label, randomized controlled trial (1:1:1), $N = 540$ pts PROs were prespecified, exploratory end points	Inclusion: Unresectable Stage III or Stage IV melanoma Prior ipilimumab treatment Prednisone dose 10 mg/day or less for at least two weeks before the first dose of study drug Exclusion: Active brain metastases or carcinomatous meningitis Active autoimmune disease Known history of HIV infection Active hepatitis B or C virus infection History of Grade 4 ipilimumab-related adverse events or Grade 3 ipilimumab-related adverse events lasting longer than 12 weeks	A) Pembrolizumab 10 mg/kg IV q 3 weeks B) Pembrolizumab 2 mg/kg IV q 3 weeks C) Investigators choice of chemotherapy (carboplatin/paclitaxel IV OR carboplatin IV OR paclitaxel IV OR dacarbazine IV OR temozolomide PO)
Long 2016[42]	Robert 2015[43]	Checkmate 066	Bristol-Myers Squibb	Double-blind, randomized (1:1), controlled trial $N = 418$ pts PROs were prespecified secondary or exploratory end points	Inclusion: Unresectable, previously untreated Stage III or IV melanoma without a BRAF mutation. Tumor tissue available for biomarker analysis Exclusion: Active brain metastases Uveal melanoma History of serious autoimmune disease	A) Nivolumab 3 mg/kg IV q 2 weeks + placebo IV q 3 weeks B) Dacarbazine 1000 mg/m^2 IV q 3 weeks + placebo IV q 2 weeks
Weber 2017[44]	Same	Checkmate 238	Bristol-Myers Squibb/Ono Pharmaceutical	Double-blind, randomized controlled trial $N = 906$ pts PROs were prespecified, secondary end points	Inclusion: Age 15+ Stage IIIB, IIIC, or IV melanoma Complete regional lymphadenectomy or resection was required within 12 weeks before randomization. Exclusion: Ocular/uveal melanoma	A) Nivolumab 3 mg IV q 2 weeks + placebo IV q 3 weeks × 4 doses, then q 12 weeks B) Ipilimumab 10 mg/kg IV q 3 weeks × 4 doses, then q 12 weeks + placebo IV q 3 weeks

(*Continued*)

Table 2
Continued

First Author	Primary Efficacy Publication (if Applicable)	Study Name	Funding	Study Design	Key Inclusion/ Exclusion Criteria[a]	Treatment Arms
					History of autoimmune disease Previous nonmelanoma cancer without complete remission for more than three years Systemic use of glucocorticoids Previous systemic therapy for melanoma.	
Revicki 2012[45]	Hodi 2010[46]	MDX010−20	Medarex and Bristol-Myers Squibb	Double-blind, randomized controlled trial $N = 676$ pts Unclear if PRO end points were prespecified	Inclusion: Life expectancy of at least four months Positive status for HLA-A*0201 Stage III or IV melanoma Had received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or IL-2. No systemic treatment in the previous 28 days. Exclusion: Prior cancer from within less than five years Primary ocular melanoma Autoimmune disease Active, untreated CNS metastases Treatment with any non-study anticancer therapy or immunosuppressive agent Long-term use of systemic corticosteroids.	A) Ipilimumab 3 mg/kg IV + placebo IM q 3 weeks × 4 doses B) Ipilimumab 3 mg/kg IV + gp100 vaccine IM q 3 weeks × 4 doses C) Gp100 vaccine IM + placebo IV q 3 weeks × 4 doses
Petrella 2017[21]	Robert 2015[47]	KEYNOTE-006	Merck & Co., Inc.	Open-label, randomized controlled trial $N = 776$ pts PROs were prespecified, secondary end points	Inclusion: Unresectable Stage III or IV melanoma 0−1 prior systemic therapies Tumor sample available for PDL-1 testing Exclusion: Ocular melanoma Active brain metastases	A) Pembrolizumab 10 mg/kg IV q 2 weeks B) Pembrolizumab 10 mg/kg IV q 3 weeks C) Ipilimumab 3 mg/kg IV q 3 weeks × 4 doses

					History of serious autoimmune disease	
Schadendorf 2017[28]	Larkin 2015[29]	Checkmate 067	Bristol-Myers Squibb	Double-blind, randomized controlled trial $N = 803$ pts PROs were secondary and exploratory end points	Inclusion: No prior systemic treatment Unresectable Stage III or Stage IV melanoma Exclusion: Active brain metastases Ocular melanoma Autoimmune disease requiring steroids or immunosuppression within 14 days of treatment	A) Nivolumab 3 mg/kg IV q 2 weeks B) Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg IV q 3 weeks followed by nivolumab 3 mg/kg q 2 weeks C) Ipilimumab 3 mg/kg q 3 weeks × 4 doses
Larkin 2018[48]	Weber 2015[49]	Checkmate 037	Bristol-Myers Squibb	Open-label, randomized controlled trial $N = 405$ pts PROs were secondary and exploratory outcomes	Inclusion: Unresectable Stage III/IV melanoma Exclusion: Treatment with either corticosteroids (>10 mg daily prednisone) or other immunosuppressive medications within 14 days Active, known, or suspected autoimmune disease Active brain metastasis or leptomeningeal metastasis Ocular melanoma	A) Nivolumab 3 mg/kg IV q 2 weeks B) Investigators choice of chemotherapy (dacarbazine 1000 mg/m^2 IV OR carboplatin (AUC 6) IV + paclitaxel 175 mg/m^2 IV) q 3 weeks
Coens 2017[31]	Eggermont 2015[30,50]	EORTC 18071	Bristol-Myers Squibb	Double-blind, randomized controlled trial $N = 951$ pts PROs were secondary, prespecified end points	Inclusion: Complete resection of Stage III melanoma with histologically confirmed melanoma metastatic to lymph node Randomization within 12 weeks of surgery Exclusion: Prior therapy for melanoma except surgery Autoimmune disease Unknown primary, ocular, or mucosal melanoma Use of systemic corticosteroids	A) Ipilimumab 10 mg/kg IV q 3 weeks × 4 doses, followed by q 3 months for up to three years B) Placebo IV q 3 weeks × 4 doses, followed by q 3 months for up to three years
Lung cancer trials						
Bordoni 2018[51]	Rittmeyer 2017[52]	OAK	F. Hoffmann-La Roche Ltd., Genentech, Inc.	Open-label, randomized controlled trial $N = 850$ pts PROs were prespecified, secondary end points	Inclusion: Squamous or nonsquamous NSCLC Life expectancy >12 weeks Received one to two previous cytotoxic chemotherapy regimens	A) Atezolizumab 1200 mg IV q 3 weeks B) Docetaxel 75 mg/m^2 IV q 3 weeks

(*Continued*)

Table 2
Continued

First Author	Primary Efficacy Publication (if Applicable)	Study Name	Funding	Study Design	Key Inclusion/ Exclusion Criteria[a]	Treatment Arms
					Exclusion: Active or untreated CNS metastases History of autoimmune disease Prior therapy with docetaxel	
Reck 2018[53]	Brahmer 2015[54]	Checkmate 017	Bristol-Myers Squibb	Open-label, randomized, controlled trial $N = 272$ pts PROs were secondary and exploratory end points	Inclusion: Stage IIIB or IV squamous-cell NSCLC Disease recurrence after one prior platinum-containing regimen Exclusion: Autoimmune disease Symptomatic interstitial lung disease Systemic immunosuppression Prior docetaxel therapy. More than one systemic therapy for metastatic disease	A) Nivolumab 3 mg/kg IV q 2 weeks B) Docetaxel 75 mg/m^2 q 3 weeks
Brahmer 2017[55]	Reck 2016[56]	KEYNOTE-024	Merck & Co.	Open-label, randomized controlled trial $N = 299$ pts PROs were prespecified, exploratory end points	Inclusion: Stage IV NSCLC Life expectancy >3 months No previous systemic chemotherapy for metastatic disease PD-L1 tumor proportion score of 50% or greater Exclusion: NO EGFR/ALK mutation/ translocation Prior systemic therapy Received immunosuppressive therapy less than three days before the first dose of treatment Presence of untreated CNS metastases or carcinomatous meningitis	A) Pembrolizumab 200 mg IV q 3 weeks B) Platinum-based chemotherapy (choice of five regimens) IV q 3 weeks x 4–6 cycles

					Active autoimmune disease that had required systemic treatment in the past two years Interstitial lung disease Active hepatitis B or C, or tuberculosis	
Genitourinary cancer trials						
Motzer 2018[57]	Same	Checkmate 214	Bristol-Myers Squibb/Ono Pharmaceutical	Open-label, randomized, controlled trial $N = 827$ pts PROs were exploratory end points	Inclusion: Previously untreated renal cell carcinoma with clear cell component KPS at least 70 Exclusion: CNS metastasis Autoimmune disease Glucocorticoid or immunosuppressant use	A) Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg IV q 3 weeks × 4 doses, then nivolumab 3 mg/kg IV q 2 weeks B) Sunitinib 50 mg PO daily with 28 days on, 14 days off
Vaughn 2018[58]	Bellmunt 2017[59]	Keynote 045	Merck Sharp & Dohme Corp.	Open-label randomized controlled trial $N = 542$ pts PROs were predefined exploratory end points	Inclusion: ECOG 0–2 Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra with predominantly transitional-cell features by histology Progression after platinum-based chemotherapy for advanced disease or recurrence within 12 months Received two or fewer lines of systemic chemotherapy Exclusion: Known additional malignancy that is progressing or requires active treatment Known active central nervous system (CNS) metastases and/or carcinomatous meningitis Active autoimmune disease requiring systemic treatment Active cardiac disease Interstitial lung disease or active noninfectious pneumonitis HIV, active hepatitis B/C	A) Pembrolizumab 200 mg IV q 3 weeks B) Docetaxel (75 mg/m^2) OR paclitaxel (175 mg/m^2) OR vinflunine (320 mg/m^2) IV q 3 weeks

(*Continued*)

Table 2
Continued

First Author	Primary Efficacy Publication (if Applicable)	Study Name	Funding	Study Design	Key Inclusion/ Exclusion Criteria[a]	Treatment Arms
Cella 2016[60]	Motzer 2015[61]	Checkmate 025	Bristol-Myers Squibb	Open-label, randomized controlled trial $N = 706$ pts PROs were prespecified secondary end points	Inclusion: Advanced renal cell carcinoma with a clear-cell component KPS of at least 70% Received one or two anti-angiogenic therapies for advanced renal cell carcinoma No more than three total previous regimens of systemic therapy, including cytokines and cytotoxic chemotherapy drugs Exclusion: Previous treatment with an mTOR inhibitor Disorder requiring treatment with glucocorticoids equivalent to >10 mg of prednisone daily CNS metastasis	A) Nivolumab 3 mg/kg IV q 2 weeks B) Everolimus 10 mg PO daily
Head and neck cancer trials						
Harrington 2017[62]	Ferris 2016[63]	CheckMate141	Bristol-Myers Squibb	Open-label, randomized, controlled trial $N = 361$ pts PROs were exploratory end points	Inclusion: Recurrent or metastatic SCCHN (oral cavity, pharynx, larynx), Stage III/IV, not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy) Tumor progression or recurrence within six months of last dose of platinum therapy Exclusion: Known HIV, hepatitis B/C virus infection Active brain metastases Autoimmune disease Systemic immunosuppression	A) Nivolumab 3 mg/kg IV q 2 weeks B) Investigators choice of chemotherapy (methotrexate 40–60 mg/m^2 IV OR cetuximab 250 mg/m^2 IV (after loading dose) OR docetaxel 30–40 mg/m^2 IV) weekly

PROs = patient-reported outcomes.
[a]Except where noted above, the trials all contained 1) the following inclusion criteria: age 18+, Performance Status Eastern Cooperative Oncology Group (ECOG) Score 0–1 and 2) the following exclusion criteria: treatment with prior checkpoint inhibitor immunotherapy.

Table 3
Descriptive Data of Included Trials

Variable	*N* (%)
Year of publication	
2012	1 (7)
2016	3 (20)
2017	6 (40)
2018	5 (33)
Experimental arm	
PD-1 antibody	
Nivolumab	6 (40)
Pembrolizumab	4 (27)
PDL-1 antibody	
Atezolizumab	1 (7)
CTLA-4 antibody	
Ipilimumab	2 (13)
Combined PD-1/CTLA-4	
Nivolumab/ipilimumab	2 (13)
Comparator arm	
Chemotherapy	8 (53)
Immunotherapy (including checkpoint inhibitor)	4 (27)
Targeted therapy	2 (13)
Placebo	1 (7)
Cancer type	
Melanoma	8 (53)
Lung cancer	3 (20)
Genitourinary cancers	3 (20)
Head and neck cancer	1 (7)
Timing of therapy	
Adjuvant	2 (13)
Unresectable/metastatic	13 (87)

open-label clinical trials. There were often insufficient data in the trial protocols to assess the risk of bias due to Selective Outcome Reporting and Incomplete Outcome data.

Discussion

This systematic review summarizes the PROs collected during randomized controlled trials of ICIs. We identified significant heterogeneity in the PRO instruments used in data collection, as well as in reported outcomes. Our data suggest that patients receiving ICIs experience similar-to-improved HRQoL compared to patients receiving other treatments for advanced cancer (such as chemotherapy, targeted therapies, other immunotherapies, or placebo). Patients treated with ICIs also appeared more likely to maintain their pretreatment HRQoL than those treated with other therapies. These are significant findings as these therapies are being increasingly utilized across tumor types and are being investigated for earlier stage disease. Regarding specific symptoms, there is some evidence to suggest that patients might have less fatigue and dyspnea with ICIs compared to chemotherapy, although this finding was highly variable in magnitude and was not consistent across studies. Differences among other symptoms across therapies were not generally clinically significant. It was difficult to generalize symptom experiences with ICIs across cancer types owing to the small numbers of trials within each disease.

Incorporating PROs in cancer clinical trials is essential because they provide direct and meaningful assessments of the lived experience of patients receiving the treatment being studied. A growing body of literature supports significant differences in frequency and severity when symptoms of cancer and cancer treatment are measured and reported by patients as compared to managing clinicians.[3–5,22–24] In a recent systematic review summarizing 28 articles across a variety of cancer types, Atkinson et al. reported moderate, at best, concordance between adverse events measured by clinicians using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and adverse events reported by patients through PROs, and across a wide variety of symptoms including both global HRQoL scales and for discrete symptoms (e.g., nausea, pain).[2] This has led to efforts to create patient-reporting mechanisms for adverse events (e.g., Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events™—PRO-CTCAE[25–27]) with the goal to more accurately capture patient experiences.

Given this trend toward incorporating PROs in cancer clinical trials, it is interesting to note that the studies reported here found relatively high rates of AEs in patients treated with ICIs as measured by clinicians using CTCAE despite the corresponding PROs generally not showing major decreases in HRQoL or symptom scales. For instance, in the Checkmate-067 trial, patients with advanced or metastatic melanoma treated with combination ICI therapy (ipilimumab and nivolumab) discontinued therapy owing to toxicity more often than those receiving ICI monotherapy with ipilimumab or nivolumab alone (36% vs. 15% or 8%, respectively). Severe side effects were relatively common in the combination ICI group (10% Grade 3–4 diarrhea, 8% Grade 3–4 colitis, and 5% Grade 3–4 rash) though PRO data presented from that trial did not show clear differences between the three groups (combination therapy or monotherapy with either agent) in the HRQoL analysis for global health assessed by multiple PRO instruments.[28,29] Schadenforf et al. examined HRQoL specifically among patients experiencing serious (Grades 3–4) adverse events and found no clear or consistent trend of diminished HRQoL in this subpopulation.[28] Similarly in the EORTC 18071 trial of ipilimumab versus placebo, more than half (52%) of the patients in the ipilimumab arm discontinued treatment owing to adverse events and severe side effects were again common (15% Grade 3–4 diarrhea/colitis, 7% Grade 3–4 endocrinopathies); yet, the mean decrease in global HRQoL in the ipilimumab group did not exceed the minimally clinically significant

Table 4

Patient-Reported Outcomes Reported in Immunotherapy Trials

First Author	PRO Instruments Used	Outcomes Reported in Trial	Results [95% CI][a]	Findings
Melanoma trials				
Schadendorf 2016[40]	EORTC QLQ-C30	Change from baseline to Week 12 in EORTC QLQ-C30 global health scale (GHS) score (least squares mean)	Pembro 2 mg/kg = −2.6 [−6.15, 0.96] Pembro 10 mg/kg = −2.6 [−5.99, 0.89] ICC = −9.1 [−12.86, −5.39]	Baseline GHS scores were similar between the groups, but the chemotherapy group had a statistically significant larger decline over the 12 weeks' time period compared with pembrolizumab (either dose). More patients treated with chemotherapy experienced a ≥10 point reduction in GHS/HRQoL (38% vs. 32%).
Long 2016[42]	EORTC QLQ-C30 EQ-5D 3 L	Mean (SE) change from baseline in EORTC QLQ-C30 GHS Mean (SE) change from baseline in EQ-5D utility index scores Mean (SE) change from baseline in EQ-5D VAS scores Time to first deterioration of EORTC QLQ-C30 GHS/QoL score based on minimally important difference Time to first deterioration of EORTC QLQ-C30 physical functioning score based on minimally important difference.	Time to first deterioration of EORTC QLQ-C30 GHS based on minimally important difference Nivolumab—253 days [168, NR] Dacarbazine—155 days [106, 203] Time to first deterioration of EORTC QLQ-C30 physical functioning score based on minimally important difference Nivolumab—379 days [210, NR] Dacarbazine—194 days [125, 266]	Patients receiving nivolumab tended to maintain their GHS score during treatment compared to those receiving dacarbazine. An exploratory analysis showed a between-arm difference in favor of nivolumab on the EQ-5D utility index and clinically meaningful EQ-5D improvements from baseline at several time points for patients receiving nivolumab compared to dacarbazine.
Weber 2017[44]	EORTC QLQ-C30 EQ-5D	Mean change from baseline in EORTC QLQ-C30 GHS Mean change from baseline in EQ-5D utility index Mean change from baseline in EQ-5D VAS		QOL scores in the two groups remained close to baseline values without any clinically meaningful changes with respect to score on Global Health Status, any individual scales, or on the EQ-5D measurements (data not shown in manuscript). Ipilimumab had a larger decrease from baseline in global health status than nivolumab on the EORTC QLQ-C30 instrument, although this was not felt to exceed the clinically meaningful threshold.
Revicki 2012[45]	EORTC QLQ-C30	Change in EORTC QLQ-C30 baseline to 12 weeks for GHS	Ipilimumab = −8.8 Ipilimumab + gp100 vaccine = −7.4 gp100 vaccine = −10.4	There were no differences between treatment arms in the primary QoL outcomes as measured in change from baseline to Week 12 with the EORTC QLQ-C30.
Petrella 2017[21]	EORTC QLQ-C30 EQ-5D	Change from baseline to Week 12 in the GHS score of the EORTC QLQ-C30 by LS mean % Patients with deterioration in EORTC QLQ-C30 GHS scores at Week 12 Analysis of change from baseline of GHS at Week 12 by progressive disease status using LS mean	Change from baseline to Week 12 in the global health status score of the EORTC QLQ-C30 by LS mean Pembro q 2 weeks = −1.9 [−4.86, 1.01] Pembro q 3 weeks = −2.5 [−5.32, 0.37] Ipi = −10 [−13.16, −6.85] % Patients with deterioration in EORTC QLQ-C30 GHS scores at Week 12 Pembro q 2 weeks = 31.1%	Pembrolizumab was associated with smaller worsenings in PROs than ipilimumab from baseline to Week 12 for several different functional and symptom scales. The absolute change in GHS among patients receiving pembrolizumab at 12 weeks compared to baseline was not felt to be clinically meaningful while the magnitude of

			Pembro q 3 weeks = 29.3% Ipi = 44.2%	decrease in GHS score among those receiving ipilimumab was felt to be clinically meaningfully worse. Fewer patients receiving pembrolizumab "deteriorated" (>10 point change in GHS/QOL) during the course of therapy compared to ipilimumab.
Schadendorf 2017[28]	EORTC QLQ-C30 EQ-5D WPAI:GH	Change in baseline in GHS (EORTC QLQ-C30) Change in baseline (EQ-5D Utility Index) Change in baseline (EQ-5D VAS)		HRQoL was maintained in all treatment groups with little clinically meaningful change noted in EORTC QLQ-C30 and EQ-5D assessments.
Larkin 2018[48]	EORTC QLQ-C30 EQ-5D	Change in GHS (EORTC QLQ-C30)		Patients treated with nivolumab appeared to have no significant change in overall HRQoL as measured by EORTC QLQ-C30. The chemotherapy group demonstrated a decrease in the QLQ-C30 score at 12 and 24 weeks. It is not clear from the manuscript if these findings were statistically significant between groups. HRQoL as measured by EQ-5D Utility Index did not change significantly for patients receiving nivolumab but did show "a clinically significant decrease" for patients in the ICC group at 12 weeks (actual data not presented).
Coens 2017[31]	EORTC QLQ-C30	EORTC QLQ-C30 GHS average during induction (ADI) and after induction (AAI) Descriptive GHS by timepoint	Average GHS score during induction (ADI) Mean (SD) Ipilimumab = 72.96 (17.82) Placebo = 77.32 (17.36) Average GHS score after induction (AAI) Ipilimumab = 72.32 (18.6) Placebo = 76.48 (17.52)	Global health status was decreased with ipilimumab compared to placebo. The effect was statistically significant, but not felt by the authors to be of a clinically significant magnitude. Ipilimumab-treated patients had significantly worse outcomes for specific symptoms (diarrhea, insomnia, fatigue).
Lung cancer trials				
Bordoni 2018[51]	EORTC QLQ-C30 EORTC QLQ-LC13	Time (months) to deterioration in physical functioning (EORTC QLQ-C30) Time (months) to deterioration in role function (EORTC QLQ-C30) Time (months) to deterioration in GHS (EORTC QLQ-C30) Mean change from baseline in physical function (EORTC QLQ-C30) Mean change from baseline in role function (EORTC QLQ-C30) Mean change from baseline in GHS (EORTC QLQ-C30)	Time (months) to deterioration in physical functioning (EORTC QLQ-C30)—median, 95% CI Atezolizumab = NE [13.2, NE] Docetaxel = 6.7 [5.1, NE] Time (months) to deterioration in role function (EORTC QLQ-C30) Atezolizumab = 11.4 [7.1, 18.2] Docetaxel = 5.1 [4.2, 7.7] Time (months) to deterioration in HRQoL (EORTC QLQ-C30) Atezolizumab = 16.2 [10.8, NE] Docetaxel = NE [5.7, NE]	Patients receiving atezolizumab had a trend toward prolonged time to deterioration in physical and role functioning compared to those receiving docetaxel. Mean changes from baseline in physical functioning scale, role functioning scale, and HRQoL appeared similar between treatment groups although summary statistics were not provided.
Reck 2018[53]	LCSS EQ-5D	Mean (SE) change from baseline in LCSS Average Symptom Burden Index (ASBI)	Mean (SE) change from baseline in LCSS Average Symptom Burden Index (ASBI)	Similar fractions of patients (~20%) in both treatment arms exhibited disease-related symptom improvement at Week

(*Continued*)

Table 4
Continued

First Author	PRO Instruments Used	Outcomes Reported in Trial	Results [95% CI][a]	Findings
		Mean (SE) change from baseline in LCSS Three-Item Global Index (3-IGI) Mean (SE) change from baseline in EQ-5D utility index scores Mean change from baseline in EQ-5D Visual Analog Scale (VAS) Time to first disease-related deterioration for LCSS ASBI (hazard ratio reports nivolumab vs. docetaxel) Time to first disease-related deterioration for LCSS 3-IGI (hazard ratio reports nivolumab vs. docetaxel) Time to first disease-related deterioration for EQ-5D utility index (hazard ratio reports nivolumab vs. docetaxel) Time to first disease-related deterioration for EQ-5D VAS (hazard ratio reports nivolumab vs. docetaxel)	Nivolumab = −4.4 (1.6) Docetaxel = 1.1 (2) Mean (SE) change from baseline in LCSS Three Item Global Index (3-IGI) Nivolumab = 9.9 (6.2) Docetaxel = −12.2 (7.9) Mean (SE) change from baseline in EQ-5D Utility Index scores Nivolumab = 0.053 (0.022) Docetaxel = 0.026 (0.03) Mean change from baseline in EQ-5D Visual Analog Scale (VAS) Mean (SD) Nivolumab = 3.6 (2.4) Docetaxel = −3.6 (2.8) Time to first disease-related deterioration for LCSS ASBI HR (nivo vs. docetaxel) 0.67 [0.43, 1.03] Time to first disease-related deterioration for LCSS 3-IGI HR (nivo vs. docetaxel) 0.57 [0.38, 0.85] Time to first disease-related deterioration for EQ-5D utility index HR (nivo vs. docetaxel) 0.55 [0.36, 0.84] Time to first disease-related deterioration for EQ-5D VAS HR (nivo vs. docetaxel) 0.59 [0.4, 0.87]	12. In exploratory analysis, the nivolumab group generally had decreased symptom burden while this was not observed in the docetaxel group. Time to first disease-related deterioration was longer among those receiving nivolumab.
Brahmer 2017[55]	EORTC QLQ-C30 EORTC QLQ-LC13 EQ-5D-3 L	Change from baseline to Week 15 in QLQ-C30 GHS score Time to deterioration in composite of cough, chest pain, and dyspnea (by QLQ-LC13)	Change from baseline to Week 15 in QLQ-C30 GHS/QOL score mean, 95% CI Pembrolizumab = 6.9 [3.3, 10.6] Platinum doublet chemotherapy = −0.9 [−4.8, 3] Time to deterioration (months) in composite of cough, chest pain, and dyspnea in QLQ-LC13 Pembrolizumab = NE [8.5, NE] Platinum doublet chemotherapy = 5 [3.6, NE]	Pembrolizumab was associated with improved HRQOL compared with platinum-based chemotherapy at 15 weeks. This magnitude (7.8 pts) was felt to be clinically significant. Treatment with pembrolizumab was associated with longer time to deterioration of a composite of symptoms (chest pain, cough, and dyspnea) than treatment with platinum doublet chemotherapy.
Genitourinary cancer trials				
Motzer 2018[57]	FKSI-19	Mean change from baseline in FKSI-19 score from Week 0 to Week 24	Mean change from baseline in FKSI-19 score from Week 0 to Week 24 (estimated from graph) Ipilimumab/nivolumab = 2 Sunitinib = −2	Examining change in HRQoL over six months of therapy, there was a statistically significant difference between the treatment groups, favoring preserved QoL in the nivolumab plus ipilimumab group.
Vaughn 2018[58]	EORTC QLQ-C30 EQ-5D	Time to deterioration in GHS (EORTC QLQ-C30) Mean change from baseline to Week 15 in GHS (EORTC QLQ-C30)	Time (months) to deterioration in HRQoL (EORTC QLQ-C30) Median Pembrolizumab = 3.5 Chemotherapy = 2.3	Pembrolizumab was associated with prolonged time to deterioration in GHS compared to chemotherapy and with preserved HRQoL at Week 15

		Change from Week 0 to Week 15 in EQ-5D Utility Score Change from Week 0 to Week 15 in EQ-5D VAS (visual analog score)	Mean change from baseline to Week 15 in HRQoL (EORTC QLQ-C30) Pembrolizumab = 0.69 [−2.4, 3.77] Chemotherapy = −8.36 [−11.84, −4.89] Change from Week 0 to Week 15 in EQ-5D Utility Score Pembrolizumab = −0.04 [−0.07, −0.01] Chemotherapy = −0.11 [−0.15, −0.08] Change from Week 0 to Week 15 in EQ-5D VAS (visual analog score) Pembrolizumab = 0.73 [−1.83, 3.29] Chemotherapy = −5.73 [−8.59, −2.87]	compared to chemotherapy. A variety of other measures shown in the manuscript showed relative stability over time for the pembrolizumab arm but worsening over time for the chemotherapy arm.
Cella 2016[60]	FKSI-DRS EQ-5D	Change from baseline in HRQoL as assessed by FKSI-DRS % patients with clinically meaningful improvement in FKSI-DRS-based HRQoL	Change in baseline to Week 20 HRQoL as assessed by FKSI-DRS, mean (SD) Nivolumab = 0.6 (3.8) Everolimus = −1.5 (4.5) % patients experiencing clinically meaningful improvement in FKSI-DRS-based HRQoL Nivolumab = 55% Everolimus = 37% % patients experiencing clinically meaningful improvement in FKSI-DRS-based HRQoL (more stringent threshold >=3 pts) Nivolumab = 41% Everolimus = 28%	On average, HRQoL tended to improve modestly with nivolumab while patients receiving everolimus tended to have a decrease in HRQoL. More patients treated with nivolumab were felt to experience clinically meaningful improvement in HRQoL than those treated with everolimus. Descriptive statistics suggested that symptom burden was better in those treated with nivolumab all nine modalities of the FKSI-DRS (lack of energy, pain, weight loss, bone pain, fatigue, hematuria, dyspnea, cough, and fever).
Head and neck cancer trials				
Harrington 2017[62]	EORTC QLQ-C30 EORTC QLQ-H&N35 EQ-5D-3 L	Analysis of baseline GHS status compared to Week 9 and Week 15 GHS (EORTC QLQ-C30) Time to first clinically meaningful deterioration in GHS (EORTC QLQ-C30) Analysis of baseline status compared to Week 9 and Week 15 (EORTC H&N-C35) Analysis of baseline status compared to Week 9 and Week 15 (EQ-5D-3 L) Time to deterioration (months) EQ-5D-3 L		Nivolumab treatment was associated with stabilization of several measures of quality of life during the first 15 weeks of treatment and delayed time to deterioration for many EORTC QLQ 30 measures (global health status; physical role, cognitive, and social functioning; symptoms of fatigue, dyspnea, insomnia, and appetite loss) and EORTC QLQ-H&N 25 measures (pain, sensory problems, social contract problems, mouth opening problems) compared to nivolumab. Using the EQ-5D VAS scale, treatment with nivolumab was associated with a clinically meaningful improvement from baseline to Week 15 while those treated with ICC were noted to have a clinically meaningful deterioration.

PROs = patient-reported outcomes; HRQoL = health-related quality of life; ICC = investigators choice of chemotherapy.
[a]Note that a commonly used threshold to define a clinically meaningful change in HRQoL/GHS by EORTC QLQ-C30 is a ≥10 point difference.[64] This was also the definition used by several references.

Table 5
Comparison of (EORTC QLQ-C30) Symptom Scales Between ICI and Chemotherapy Treatment Arms

Study ID	ICI	Control	Statistical Analysis	Fatigue	Nausea and Vomiting	Pain	Dyspnea	Insomnia	Appetite Loss	Constipation	Diarrhea	Financial Difficulties
Melanoma trials												
Schadendorf 2016[40]	P[a]	ICC	Change from baseline to Week 12	=	=	=	=	=	=	=	=	NR
Long 2016[42]	N	DCB	Mixed-effects model for repeated measures; change from baseline mean	=	=	=	=	=	=	=	=	=
Lung cancer trials												
Bordoni 2018[51]	A	DOC	Differences in mean changes from baseline (LS mean per ANCOVA); Cycle 5 (also report Cycle 6)	NR	=	NR	NR	NR	NR	=	=	NR
Brahmer 2017[55]	P	ICC	Change from baseline to Week 15	=	=	=	=	=	=	=	=	=
GU cancer trial												
Vaughn 2018[58]	P	ICC		I[b]	=	=	I[b]	=	=	=	=	=
H&N cancer trial												
Harrington 2017[62]	N	ICC[c]	ANCOVA analyses Week 9 and Week 15	↑	=	=	↑	=	↑	=	↑*	=

ICI = immune checkpoint inhibitor; P = pembrolizumab; N = nivolumab; A = atezolizumab; DOC = docetaxel; DCB = dacarbazine; ICC = investigators choice of chemotherapy; I = ICI better than chemo (clinically meaningful difference), unclear if statistically significant, ↑ = ICI better than chemotherapy (clinically and statistically significant); = , neither nivolumab/chemotherapy clinically significantly better; NR = not reported.
[a]Pembrolizumab dose of 2 mg/kg used for analysis as this is the FDA-approved weight-based dosing. The study also tested a higher dose of 10 mg/kg, which is not included in this table.
[b]Magnitude in change of symptom score is estimated from graph. Estimates are these effects are >= 10 pts. Data provided were insufficient to determine if this was statistically significant.
[c]Note one choice of investigator's choice of therapy in this study is cetuximab, a monoclonal antibody, which is not considered chemotherapy.
*Statistically and clinically significant differences in diarrhea compared to baseline were only noted at week 9.

change, suggesting preserved quality of life, although significant deterioration in the individual symptoms of insomnia, fatigue, and diarrhea was noted.[30,31]

This discrepancy between assignment of severity in adverse event reporting by clinicians and information collected directly from patients is striking. The capability of ICIs to cause significant organ toxicity and symptom severity did not seem to have a measurable effect on patient self-reported assessment of HRQoL. Investigators in several studies reported here commented on possible explanations, including the possibility that the PROs utilized failed to capture HRQoL and specific symptom toxicities of patients treated with ICIs. These PROs were designed specifically to incorporate frequent chemotherapy-related toxicities and yet ICIs share few common toxicities with chemotherapy treatments. Thus, perhaps, it is not surprising that symptom scale scores on commonly used PROs may appear more favorable with ICIs. These PROs may also not even measure common ICI-related toxicities. For example, although pruritus has been reported in up to 20%−30% of patients receiving ICIs, it is not commonly listed on standardized PROs for cancer patients and thus is missed by most current assessment tools used in published ICI reports.[32] Given the broad range of possible symptoms and toxicities associated with ICIs, comprehensive assessment of patient-reported symptoms would likely either take the form of a broad survey of potential symptoms (such as PRO-CTCAE) or require the design and

Table 6
Quality of Randomized Controlled Trial Studies, as Assessed by Cochrane Review of Bias[10]

Study Reference (First Author, Year, Ref)	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Schadendorf 2016[40]	Low	Low	High	High	Unclear	Unclear	Low
Petrella 2017[21]	Low	Low	High	Low	Unclear	Unclear	Unclear
Harrington 2017[62]	Low	Low	High	Unclear	High	Low	Low
Weber 2017[44]	Low	Low	Low	Low	Unclear	Unclear	Unclear
Revicki 2012[45]	Low	Low	Low	Unclear	High	High	Unclear
Schadendorf 2017[28]	Low	Low	Low	Low	Unclear	Low	Low
Cella 2016[60]	Low	Low	High	Unclear	Unclear	Unclear	Unclear
Motzer 2018[57]	Low	Low	High	Unclear	Unclear	Unclear	Low
Long 2016[42]	Unclear	Low	Low	Unclear	Unclear	Low	Unclear
Coens 2017[31]	Low	Low	Low	Unclear	Unclear	Unclear	Low
Brahmer 2017[55]	Low	Low	High	Unclear	Low	Low	Low
Reck 2018[53]	Low	Low	High	Unclear	Low	Low	Low
Bordoni 2018[51]	Low	Low	High	High	Low	Unclear	Unclear
Vaughn 2018[58]	Low	Low	High	Unclear	Low	Low	Low
Larkin 2018[48]	Low	Low	High	Unclear	High	Unclear	Unclear

validation of new instruments designed specifically to capture ICI-specific toxicities.

Another important difference between ICI and chemotherapy is the timing of onset of side effects. Although some chemotherapy side effects fail to get better over time (e.g., chemotherapy-induced peripheral neuropathy), other symptoms tend to stabilize and often improve as time passes since the most recent therapy. By contrast, ICI side effects have sometimes been reported to occur late in the course of therapy, even months after the final dose.[33–36] Patient adherence to completing the PROs was observed to decrease consistently over time in our reviews, often with significant missing data. Thus, the ability to measure delayed toxicities or symptoms related to ICI therapy may be limited if those patients are not completing PROs later in the study period. Most studies in our review reported the compliance with PRO completion, but it was not possible to determine if late-onset toxicities from the immunotherapy may have been underreported owing to missing data.

Perhaps most importantly, this review suggests a need for a novel PRO for patients receiving ICIs. Existing, commonly used PROs (such as the EORTC QLQ-C30) provide information on a limited range of symptoms that may not adequately capture the symptomatology of patients receiving ICIs. The use of immunotherapy strategies in cancer is expanding rapidly and encompasses a range of treatments in addition to ICIs (e.g., CAR-T cells and vaccine approaches). This need is highlighted by the >1500 currently enrolling clinical trials (with goal enrollment of >50,000 patients) involving PD-1/PDL-1 antibodies, many of which are immunotherapy combinations.[37] As novel ICI agents are brought first into clinical trials and then into clinical practice, we need to be confident that we understand the toxicity profile and lived experience of patients receiving these therapies to provide appropriate advice and engage in shared decision making. However, existing PRO instruments appear to be insufficient to do so.

The clinical implications of this review specifically for palliative care clinicians and oncologists are that, in general, HRQoL appears similar-to-improved among patients receiving ICI therapy compared to other cancer therapies (Table 7). Data on patient experience of

Table 7
Summary of Key Results

- ICIs compare similarly to favorably to conventional chemotherapies in overall patient-reported HRQoL measures despite high rates of clinician-reported adverse events noted in clinical trials.
- Many existing PROs (including disease-specific symptom scales) do not adequately assess for many toxicities that patients receiving ICIs may experience.
- It is imperative that PROs that are sensitive to capture the symptom experience of patients receiving ICIs are developed, particularly as the oncology field moves toward ICI combinations and other immunomodulatory strategies.

ICI = immune checkpoint inhibitor; HRQoL = health-related quality of life; PROs = patient-reported outcomes.

specific symptoms are too heterogeneous to draw strong conclusions although it appears to be similar across commonly surveyed, limited symptom domains. The discrepancy between AEs and PROs in our review suggests that some PRO measures may not be sensitive to detect patients with significant toxicity or symptoms during treatment with ICI therapy. Given the heterogeneous nature of symptoms experienced among patients treated with ICIs, it is also vital for palliative care clinicians and oncologists to keep a broad mind when interviewing and evaluating a patient receiving these therapies. There is much that is still being learned about ICI therapy, side effects, and management. Management of commonly encountered adverse effects is complicated and has been recently reviewed in this journal, and consensus guidelines have recently been published.[38,39]

Our review has several limitations. Owing to the nature of our PICOTS question, we excluded descriptive studies without comparator treatment arms. There may be additional data in descriptive, noncomparative studies that were not identified or summarized in this review. Our study did not identify any references examining pediatric populations and thus is not intended to serve as a reference for pediatric populations. We observed significant heterogeneity in the studies across several domains (including type of cancer, specific ICI therapy used, comparator therapy, PRO instrument utilized, and symptom scales reported), and this limited the aggregation of the data and power of therapy/symptom associations. Missing PRO data were common across studies (as has been observed commonly in PRO studies), and the impact of the missing data on the findings is uncertain. It is also important to note that all studies in our analysis were funded by pharmaceutical companies. Nearly all patients in these studies were of high functional status (Eastern Cooperative Oncology Group 0−1). It is unclear how HRQoL is impacted by ICIs in patients with more compromised performance status, particularly because these frailer and more vulnerable patients would be more likely to receive palliative care consultation.

Conclusions

In this review of PROs in ICI trials of cancer patients, overall HRQoL ranged from similar to slightly improved among those receiving ICIs as compared to other cancer treatments. Commonly assessed symptom scales such as fatigue, gastrointestinal symptoms, and pain were comparable between ICI and other cancer therapies, even in the context of significant rates of high-grade IRAEs (as measured by clinicians) during the conduct of these trials. This relationship between clinician-reported AEs and PROs differs from that reported for conventional chemotherapy. The mechanisms for this are unclear, and further study will be needed to elucidate this apparent preserved patient-reported HRQOL in the setting of significant clinician-reported toxicity.

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Appendix

(("Patient Reported Outcome Measures"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Patient Outcome Assessment"[Mesh] OR ("Outcome Assessment (Health Care)"[Mesh] AND "self report" [Mesh]) OR "patient-reported outcome" OR "patient reported outcomes" OR "Quality of Life"[Mesh] OR "quality of life") AND ("Ipilimumab"[Mesh] OR Ipilimumab OR pembrolizumab OR nivolumab OR avelumab OR atezolizumab OR durvalumab OR tremelimumab OR "checkpoint inhibitor" [tiab] OR "checkpoint inhibitors" [tiab] OR "checkpoint inhibitor-based" [tiab] OR "check point inhibitor" OR "check point inhibitors" OR "CTLA-4 Antigen/antagonists and inhibitors"[Mesh] OR "Programmed Cell Death 1 Receptor/antagonists and inhibitors"[Mesh] OR “yescarta” OR “Axicabtagene ciloleucel” OR “kymriah” OR “CAR T” OR “CAR-T” OR “Chimeric antigen receptor“ OR “Tisagenlecleucel”)) NOT (animals [Mesh] NOT humans [Mesh])