

Immune Checkpoint Inhibitors and Health-Related Quality of Life: A Systematic Review of the Current Literature

Mohamed H. Elshahidi

Faculty of Medicine, Mansoura University, Mansoura, Egypt

Abstract

Background: Over the past years, some immune checkpoint inhibitors (ICPIs) have been approved for clinical use in several malignancies. Examining the effects of ICPIs on the patients' health-related quality of life (HRQoL) may help clinicians in their decision-making process. **Aim:** The aim of this review is to summarize the current evidence about the effects of ICPIs on the patients' HRQoL. **Methods:** PubMed, Embase (via OvidSP), Web of Science, Scopus, and EBSCOhost were searched from their dates of inception to January 2018. Studies reporting the effects of ICPIs on the HRQoL using a valid questionnaire are included in the review. A narrative summary of the included studies was presented. **Results:** Sixteen studies met the specific inclusion criteria, which are as follows: seven about melanoma, three about renal cell carcinoma (RCC), one about metastatic Merkel-cell carcinoma (mMCC), two about squamous cell carcinoma of the head and neck, two about non-small-cell lung cancer (NSCLC), and one about colorectal cancer (CRC). In melanoma, more improvements in the global health status (GHS) were observed with pembrolizumab, ipilimumab 3 mg/kg, and pembrolizumab every 2 weeks than with ipilimumab, ipilimumab 10 mg/kg, and pembrolizumab every 3 weeks, respectively. However, no clinically significant differences were found when adding gp100 vaccine, using different doses of pembrolizumab or combining ICPIs. In RCC, the EQ-5D utility index and the time to deterioration were improved in the nivolumab groups than in everolimus groups. In squamous cell carcinoma of the head and neck, the GHS remained stable or improved with nivolumab. However, there was no significant difference in the time to deterioration between nivolumab and investigator's choice. In mMCC, a slight gain in the GHS was observed with avelumab. In NSCLC, improvements were observed in the symptoms scales and some of the functioning scales with pembrolizumab than chemotherapy. However, no difference was observed between them on emotional functioning. In CRC, some clinically meaningful improvements were observed in nivolumab plus ipilimumab. **Conclusion:** Due to the complexities in the longitudinal analysis of HRQoL data and some other concerns in the included studies designs, these results should be interpreted carefully.

PROSPERO registration number: CRD42018089311

Keywords: Cytotoxic T-lymphocyte-associated protein -4, health-related quality of life, immune checkpoint inhibitors, programmed death-1, programmed death-ligand 1, quality of life

INTRODUCTION

Rationale

Being the second leading cause of death worldwide, cancer accounts for 1 in 6 deaths with 8.8 million deaths in 2015.^[1] Moreover, cancer occurrence negatively affects the physical and social functioning of the patients, with psychological distress being common among them.^[2-5] Health-related quality of life (HRQoL) is defined as individual's satisfaction or happiness with domains of life insofar as they affect or are affected by health.^[6] HRQoL assessment includes the effect of diseases or treatments on the physical, social/role,

emotional, and cognitive functioning domains.^[7] Although clinical trials have principally considered overall survival and progress-free survival as their main endpoints, the importance of other patient-centered endpoints as HRQoL is increasingly being acknowledged.^[8,9] Incorporating HRQoL provides platform for shared clinical decision-making and personalize the treatment benefits from the patient's point of

Address for correspondence: Mohamed H. Elshahidi, Algomhorria Street, Mansoura, Dakahlia, Egypt. E-mail: mohamedelshahidi@students.mans.edu.eg

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Elshahidi MH. Immune checkpoint inhibitors and health-related quality of life: A systematic review of the current literature. *Mustansiriyah Med J* 2018;17:1-13.

Access this article online

Quick Response Code:



Website:
<http://www.mmjonline.org>

DOI:
10.4103/MJ.MJ_19_18

view.^[10,11] In 2006, the Food and Drug Administration (FDA) provided recommendations on the support of using HRQoL in the labeling claims.^[12]

Immune checkpoint inhibitors (ICPIs) are a group of drugs able to block the interaction of the inhibitory signals between the cancer cells and the immune cells.^[13] The cancer cell can deceive the immune system by expressing inhibitory molecules, for example, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2, that bind to T-cell receptor, for example, programmed death-1 (PD-1), and inhibit the immune response against it.^[14] Blocking these restraints have shown to unleash the immune response against the cancer cells and prolonging the overall survival in a subset of patients with certain types of cancer.^[15] In 2011, the FDA approved ipilimumab (Yervoy®), the first ICPI drug, targeting the inhibitor receptor cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), for the treatment of unresectable or metastatic melanoma.^[16] Since then, several ICPIs have been approved for NSCLC, head-and-neck squamous cell carcinoma, breast cancer, colorectal cancer (CRC), and advanced urothelial carcinoma.^[16] Despite their durable response, several immune-related adverse events (irAEs) including autoimmune colitis, hepatitis, endocrinopathies, arthralgia, and cutaneous adverse reactions were observed.^[17-21] Given the high cost of ICPIs and their associated irAEs, investigating the effects of ICPIs on the patients' HRQoL may assist in the clinical decision-making process.^[22,23]

Objective

This review aims to systematically search the literature and to summarize current evidence regarding the effects of ICPIs on the HRQoL.

METHODS

Guidelines

The Preferred Reporting Items for Systematic reviews and Meta-Analyses statement was used in reporting this systematic review.^[24]

Search strategy

The search process was carried out using the following search algorithm: ((((((((((((((PD-1 inhibitor) OR Pembrolizumab) OR Keytruda) OR Nivolumab) OR Opdivo) OR PD-L1 inhibitor) OR Atezolizumab) OR Tecentriq) OR Avelumab) OR Bavencio) OR Durvalumab) OR Imfinzi) OR CTLA-4 inhibitor) OR Ipilimumab) OR Yervoy)) AND (((((((("Quality of Life"[Mesh]) OR Quality of Life) OR Life quality) OR Health-Related Quality of Life) OR Health-Related Quality of Life) OR HRQOL) OR QoL) OR Hqol) OR Patient Reported Outcome).

Data sources

An electronic search of PubMed, Embase (via OvidSP), Scopus, Web of Science, and EBSCOhost was performed for articles published in them from their dates of inception to January 2018. Besides, the references of the included studies

were also hand-searched for pertaining studies. No language filter was applied.

Criteria for selecting studies

Screening of the retrieved citations was in two phases

Title and abstract screening then full-text reviewing. Records were screened for meeting the following criteria: (1) peer-reviewed, published article, (2) included an ICPI, and (3) used a valid HRQoL questionnaire. Proposals, reviews, and editorials studies not involving ICPI or studies using quality-adjusted life years as a measure in cost-utility analyzes were excluded from the review. In addition, abstracts were excluded due to the difficulty in appraising the study design and in extracting the data.

Data extraction

A data extraction form was designed to collect the following data

Study ID (first author, year of publication), type, population, interventions or arms, questionnaire, completion rate, analysis time-point, summary of the results, sensitivity analysis, and percentage of Grade 3–5 AEs.

Risk of bias and methodological quality assessments

The Cochrane risk of bias assessment tool was used in investigating the possible risk of bias in the included studies. It judges randomized trials based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data, and selective reporting.^[25] Furthermore, the methodological quality was appraised using a tool previously used in other systematic reviews of HRQoL.^[26,27] The criteria focus on aspects related to the study design were as follows: inclusion and exclusion, population characteristics, and statistical analyzes. Each study accesses a total of 14 points. Studies scoring $\geq 75\%$ were of high quality, $75\%–50\%$ were of moderate quality, and $\leq 50\%$ were of low quality.

Data synthesis

Due to the differences in the types of cancer that are included, no quantitative analysis was carried out. Summary of the included studies was presented in a narrative, qualitative method.

RESULTS

Study selection

The search algorithm reached 1493 citations. After duplicate removing, title and abstract screening, and full-text reviewing, 16 reports were included in the narrative synthesis by cancer type [Figure 1].

Melanoma

Seven studies were found pertaining to the effect of ICPIs on HRQoL in patients with melanoma^[28-34] [Tables 1 and 2]. Two studies were open-label, and five studies were double-blind. HRQoL and patient-reported outcomes were considered secondary endpoints in three studies. Most studies included

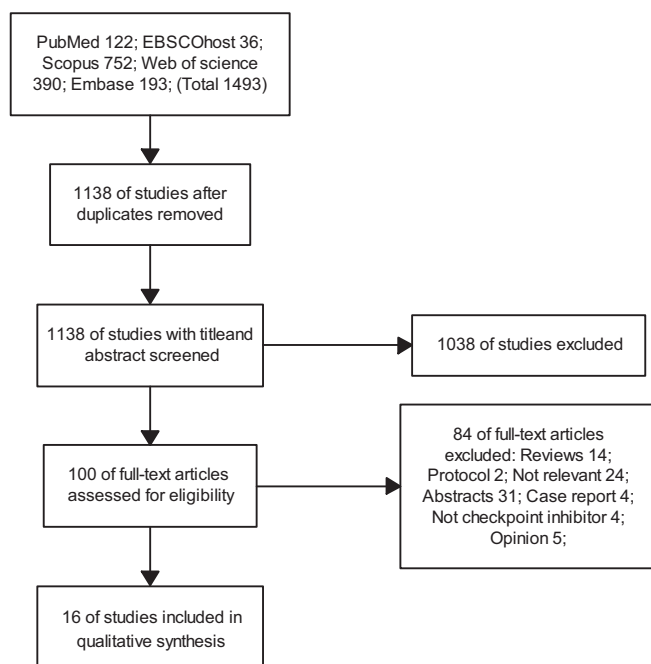


Figure 1: PRISMA flow diagram of the search process conducted on January 30th, 2018

patients with Stage III or IV melanoma. One study included patients without BRAF mutation only, and another study included patients with BRAFV600 mutation. Most studies tested the effect of one ICPI against another ICPI, dacarbazine, placebo, or investigator's choice. One study investigated the effect of combining two ICPIs, nivolumab (a PD-1 inhibitor) plus ipilimumab (a CTLA-4 inhibitor) at different doses. All studies used the EORTC QLQ-C30 questionnaire, and four of them used the EQ-5D questionnaire. None of them included a melanoma-specific questionnaire. The total number of patients included in them was 5025. The completion rate at baseline differed among them; however, it decreased in all of them over time. The analysis of the mean change from baseline in the global health status (GHS) scale of the EORTC QLQ-C30 was calculated in most of them at week 12. The mean change in the GHS scale decreased more with ipilimumab than with pembrolizumab (a PD-1 inhibitor). In addition, the decrease in GHS score was more in the arm receiving pembrolizumab every 3 weeks than the group receiving it every 2 weeks. Similarly, high dose (10 mg/kg) of ipilimumab resulted in more decrease in the mean change of the GHS score than low dose (3 mg/kg). In addition, combining ipilimumab with Gp 100 peptide vaccine resulted in no or little improvements. Different doses of pembrolizumab showed no difference in the mean change in the GHS score. However, pembrolizumab showed less decrease in the mean change of GHS score than chemotherapy. In combining nivolumab plus ipilimumab, no clinical meaningful change was observed than monotherapy. No significant difference was observed in the functional scales between groups receiving different doses of pembrolizumab. Moreover, pembrolizumab was associated with improvement in the emotional functioning scale. Both dacarbazine and

nivolumab were associated with stable function and symptoms. A small change was observed in the groups receiving pembrolizumab than the groups receiving chemotherapy. Furthermore, in the group receiving combination ICPIs, deterioration was observed in the fatigue, appetite, and symptoms scales than monotherapy. Using the EQ-5D scale, high dose of ipilimumab was associated with more decrease in the utility index. A significant difference in the utility index was neither observed between nivolumab and dacarbazine nor between combination ICPIs and monotherapy ICPI. However, the time to deterioration was shorter in the chemotherapy group than in the pembrolizumab group. In addition, high dose of ipilimumab and combination ICPIs were associated with high percentage of Grade 3–5 AEs than low dose of ipilimumab and monotherapy, respectively. Furthermore, more AEs were more in the dacarbazine group than the nivolumab group.

Renal cell carcinoma

Three studies examining the effects of ICPIs on HRQoL in patients with renal cell carcinoma were found^[35-37] [Table 3]. Two studies were open-label, and one was single-arm, nonrandomized study. They included nivolumab either alone or versus everolimus (an inhibitor of mammalian target of rapamycin). All of them used the disease-specific questionnaire. None of them investigated the effect of combining ICPIs. The total number of the patients included in them was 1290. The time to deterioration was improved in the nivolumab groups. In addition, Grade 3–5 AEs were more among the nivolumab groups than everolimus.

Squamous cell carcinoma of the head and neck

Two studies were identified^[38,39] [Tables 4 and 5]. Both reports were open-label and Phase III studies. They included nivolumab versus investigator's choice or standard of therapy. The total number of included patients was 722. GHS in the nivolumab groups remained stable or improved. The functional scales showed improvements favoring the nivolumab groups. The EQ-5D questionnaire showed improvements in the nivolumab groups. In addition, Grade 3–5 AEs were less among the nivolumab groups. However, there is no significant change in the time to deterioration.

Non-small cell lung cancer

Two studies were identified^[40,41] [Tables 4 and 5]. The two studies were reports from Phase III trials, one was double-blind trial, and the other was open-label. They investigated nivolumab or pembrolizumab versus docetaxel or investigator's choice. None of them includes combinations of ICPIs. Both of them used the disease-specific scale. The total number of included patients was 571. In the GHS scores, there were some improvements in the pembrolizumab group than investigator's choice. In addition, pembrolizumab improved some functional scores than chemotherapy including physical functioning, role functioning, and social functioning. However, there was minimal decrease in the cognitive functioning scale among the pembrolizumab group than chemotherapy. In addition, the effects of pembrolizumab and chemotherapy on

Table 1: Characteristics of the included studies about melanoma

Study ID	Type	Population	Interventions	Questionnaire	Patients number	Completion rate	GHS/QoL change from baseline	QLQ-C30 functional scale	QLQ-C30 symptoms scale
KEYNOTE-006 Petrella <i>et al.</i> , 2017 ^[28]	International, randomized (1:1:1), controlled, open-label, Phase III. PROs were an exploratory endpoint	Ipilimumab-naïve advanced melanoma who received one or no prior therapies	Pembrolizumab 10 mg/kg either every 2 weeks (Q2W) or every 3 weeks (Q3W) or to receive four doses of ipilimumab 3 mg/kg Q3W	EORTC LQ-C30 and EuroQoL EQ-5D	Pembrolizumab Q2W (n=270), pembrolizumab Q3W (n=266), and ipilimumab (n=240)	99% at baseline, 98% for pembrolizumab. (Q2W), 95% for pembrolizumab (Q3W), 93% for ipilimumab. 79% for pembrolizumab (Q2W), 85% for pembrolizumab (Q3W), 74% for ipilimumab at week 12	Pembrolizumab (Q2W): -1.9 (-4.86-1.01), Pembrolizumab (Q3W): -2.5 (-5.32-0.37), Ipilimumab -10.0 (-13.16--6.85)	Ipilimumab was associated with decreases in all function scale scores, whereas pembrolizumab was associated with improvement in emotional functioning. No significant difference between the pembrolizumab arms	There is small increase in the fatigue, pain, dyspnea, appetite loss, and diarrhea than those receiving ipilimumab. Slight improvements were found in nausea, vomiting and insomnia in the Pembrolizumab arms than in the Ipilimumab arms
Ascierto <i>et al.</i> , 2017 ^[29]	International, randomized (1:1), double-blind, Phase III, HRQoL was a secondary end-point	Patients with untreated or previously treated unresectable stage III or IV melanoma, without previous treatment with BRAF inhibitors or immune checkpoint inhibitors	Ipilimumab 10 mg/kg or 3 mg/kg	EQ-5D, EORTC QLQ-C30	Ipilimumab 10 (n=365), Ipilimumab 3 (n=362)	88% for both arms at the baseline, 29%-32% at end of treatment	For the 10 mg/kg group was -13.26 (95% CI: -17.57--8.95) and for the 3 mg/kg was -8.07 (-11.46--4.68)	-	-
CheckMate 066 Long <i>et al.</i> , 2016 ^[30]	International, randomized, double-blind, Phase III, PRO was an exploratory endpoint	Treatment-naïve patients who had metastatic melanoma without a BRAF mutation	Nivolumab 3 mg/kg versus dacarbazine 1000 mg/m ²	QLQ-C30, EQ-5D	nivolumab (n=210) or dacarbazine (n=208)	70% for the nivolumab arm and 65% for the dacarbazine arm	Modest change in the nivolumab that was not significant	Remained stable in both groups	
Revciki <i>et al.</i> , 2012 ^[31]	Randomized (3:1:1), double-blind, Phase III	Unresectable stage III or IV melanoma patients	Ipilimumab plus gp100, versus ipilimumab alone, versus gp 100 alone	EORTC QLQ-C30	Ipilimumab plus gp100 (n=403), ipilimumab alone (n=137), and gp100 alone (n=136) treatment arms	95% at baseline, and 61%-65% at week 12 for the three arms	No change or a little impairment across EORTC QLQ-C30 global health status, function, and symptom subscales		

Contd...

Table 1: Contd...

Study ID	Type	Population	Interventions	Questionnaire	Patients number	Completion rate	GHS/QoL change from baseline	QLQ-C30 functional scale	QLQ-C30 symptoms scale
KEYNOTE-002 Schadendorf <i>et al.</i> , 2016 ^[32]	International, randomized (1:1:1), open-label, Phase II	Unresectable Stage III or IV melanoma, disease progression after two or more prior ipilimumab doses, and previous BRAF and/or MEK inhibitor therapy (BRAFFV600 mutant only)	Pembrolizumab 2 or 10 mg/kg every 3 weeks (Q3W) or investigator-choice chemotherapy	EORTC QLQ-C30	Pembrolizumab 2 mg/kg (n=180), pembrolizumab 10 mg/kg (n=181), or chemotherapy (n=179)	93%-96% at baseline across groups, 76.6%-82.3% at week 12	-2.6 (-6.15-0.96) for pembrolizumab 2 mg/kg, -2.6 (-5.99-0.89) for pembrolizumab 10 mg/kg, and -9.1 (-12.86--5.39) for chemotherapy	Small change was observed with minimal difference between the two pembrolizumab groups	QLQ-C30 symptoms
CheckMate 067 Schadendorf <i>et al.</i> , 2017 ^[33]	Randomized (1:1:1), double-blind, Phase III, PRO was a secondary endpoint	Stage III (unresectable) or stage IV melanoma with no prior systemic treatment	Nivolumab 3 mg/kg every 2 weeks (Q2W); nivolumab 1 mg/kg Q3W plus ipilimumab 3 mg/kg Q3W for 4 doses, followed by nivolumab 3 mg/kg Q2W; or ipilimumab 3 mg/kg Q3W for 4 doses	QLQ-C30, EQ-5D	316 to nivolumab (313 treated), 314 to nivolumab plus ipilimumab (313 treated), and 315 to ipilimumab (311 treated)	85.1% for nivolumab, 87.3% for nivolumab plus ipilimumab, and 82.2% for ipilimumab	No clinically meaningful changes were observed in any treatment group while on treatment	Clinically meaningful deterioration was observed at week 7 for nivolumab + ipilimumab for role functioning as well as the fatigue and appetite loss symptom scales	QLQ-C30 symptoms
EORTC 18071 Coens <i>et al.</i> , 2017 ^[34]	International, randomized (1:1), double-blind, Phase III, HRQoL was a secondary endpoint	Stage III cutaneous melanoma	Ipilimumab versus placebo	EORTC QLQ-C30	475 in the ipilimumab group and 476 in the placebo group	94% at baseline, 80% at week 10	The difference between the two groups was not clinically significant, however, improvements were observed in ipilimumab	Diarrhea and insomnia were improved in the ipilimumab arm	QLQ-C30 symptoms

GHS: Global health status, QoL: Quality of life, CI: Confidence interval, PRO: Patient-reported outcomes, QLQ-C: QoL questionnaire core

Table 2: Characteristics of the included studies about melanoma

Study ID	EQ-5D utility score	Deterioration	Disease-specific questionnaire	Analysis time-point	Sensitivity analysis	Percentage of grade 3-5 AE	Quality score
KEYNOTE-006 Petrella <i>et al.</i> , 2017 ^[28]	Pembrolizumab Q2W and ipilimumab arms was 0.08; pembrolizumab Q3W and ipilimumab arms was 0.08	Deterioration was observed in (pembrolizumab Q2W, 31%; pembrolizumab Q3W, 29%; and ipilimumab, 44%)	No	Week 12	Yes	Pembrolizumab (Q2W) 13.3%; and pembrolizumab (Q3W) 10.1%; ipilimumab 19.9%	14
Ascierto <i>et al.</i> , 2017 ^[29]	Mean change in the index in the 10 mg/kg group was -0.09 (95% CI: -0.12--0.06) and for the 3 mg/kg group was -0.05 (-0.08--0.02), mean change in the VAS for the 10 mg/kg group was -8.54 (95% CI: -12.86--4.22) and for the 3 mg/kg group was -2.11 (-6.28-2.06)	-	No	Week 12	No	34% in the 10 group, 18% in the 3 groups	13
CheckMate 066 Long <i>et al.</i> , 2016 ^[30]	There were also no significant differences between the treatment arms at any time point		No	Week 13		11.7% in nivolumab and 17.6% in dacarbazine	14
Revicki <i>et al.</i> , 2012 ^[31]	-	-	No	Week 12	Yes	-	12
KEYNOTE-002 Schadendorf <i>et al.</i> , 2016 ^[32]	-	31.8% for pembrolizumab 2 mg/kg, 26.6% for 10 mg/kg, and 38.3% for chemotherapy	No	Week 12	No	20 (11%) patients in the pembrolizumab 2 mg/kg group, 25 (14%) in the pembrolizumab 10 mg/kg group, and 45 (26%) in the chemotherapy group	13
CheckMate 067 Schadendorf <i>et al.</i> , 2017 ^[33]	No clinically meaningful changes were observed in any group while on treatment in any time point		No	-	No	55% combination therapy and 27% monotherapy	13
EORTC 18071 Coens <i>et al.</i> , 2017 ^[34]	-	-	No	Week 10	No	52% discontinued ipilimumab due to adverse effects	14

CI: Confidence interval, VAS: Visual analog scale

emotional functioning were similar. In the symptoms scales, the pembrolizumab generally showed improvements than the investigator's choice group. In the utility index score, the mean change between ICPIs groups and docetaxel or investigator's choice was nearly similar. Regarding time to deterioration, the ICPIs arms showed improvements and prolonged the time to deterioration than the docetaxel or investigator's choice arms. Besides, the disease-specific scales favored ICPIs arm. Moreover, AEs were less among ICPIs groups.

Colorectal cancer

Only one study met the inclusion criteria^[42] [Tables 4 and 5]. It was a single-arm study including 119 patients with DNA mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) metastatic colorectal cancer mCRC. The study included the combination of nivolumab and ipilimumab for four doses then nivolumab every 2 weeks. It showed statistically and clinically significant mean change from baseline in the questionnaire scores. It considered a mean change ≥ 10 points to be clinically significant.

Merkel-cell carcinoma

After full-texting reviewing, a Phase II, single-arm study was included^[43] [Tables 4 and 5]. It studied the effect of avelumab (a PD-L1 inhibitor) on HRQoL of 88 patients with metastatic Merkel-cell carcinoma. Small gain in the mean change from baseline in the HRQoL scale scores was observed.

Risk of bias and methodological quality assessment

According to the Cochrane risk of bias assessment tool, most of the included studies have low risk of bias in the following categories: random sequence generation, incomplete data reporting, and selecting reporting [Figures 2 and 3]. However, high risk of bias was observed in allocation concealment and blinding of participants and personnel, mostly due to the open-label design of some of the included studies. Moreover, according to the quality assessment tool, all of the included studies were of high quality, scoring ≥ 10 points [Tables 2, 3 and 5].

Table 3: Characteristics of the included studies about renal cell carcinoma

Study ID	Type	Population	Interventions	Questionnaire	Patients number	Completion rate	EQ-5D utility scale	Time to deterioration	FKSI-DRS scales	Disease specific time-point analysis	Sensitivity analysis	Percentage of grade 3-5 AE	Quality score	
CheckMate 025 Cellia <i>et al.</i> , 2016 ⁽³⁵⁾	International, randomized (1:1), open-label, phase III, HRQoL was an exploratory endpoint	Patients with advanced renal cell carcinoma	Nivolumab 3 mg/kg or everolimus	FKSI-DRS and EQ-5D	Nivolumab (n=410), everolimus (n=411)	88% in the nivolumab, 84% in the everolimus at baseline	Difference between two groups in the utility index 0.04, 95% CI 0.02-0.07, P=0.0003	Time to improvement was short in the nivolumab group	In the FKSI-DRS, 55% of nivolumab patients showed improvement in the mean change from baseline than 37% in the everolimus	Yes	Week 104	Yes	19% in the nivolumab, 37% in the everolimus	14
CheckMate 025 Escudier <i>et al.</i> , 2017 ⁽³⁶⁾	Single-arm study	Patients with advanced Renal cell carcinoma beyond progression	Nivolumab 3 mg/kg	FKSI-DRS	406	-	-	Improvements were observed	Improvements were observed	Yes	-	No	-	13
CheckMate 025 Tomita <i>et al.</i> , 2017 ⁽³⁷⁾	International, randomized (1:1), open-label, phase III, HRQoL was an exploratory endpoint	Patients with advanced renal cell carcinoma, Japanese	Nivolumab 3 mg/kg or everolimus	FKSI-DRS	37 nivolumab, 26 everolimus	<90% on average except for week 8, 36	-	-	Generally equal to or slightly exceeded baseline values at every assessment in the nivolumab arm	Yes	-	No	78% in nivolumab, 100% in everolimus	14

FKSI-DRS: Functional Assessment of Cancer Therapy--Kidney Symptom Index--Disease-Related Symptoms, CI: Confidence interval

Table 4: Characteristics of the included studies about squamous cell carcinoma of the head and neck, colorectal cancer, and Merkel carcinoma

Study ID	Type	Population	Interventions	Questionnaire	Number of patient	Completion rate	GHS/QoL change from baseline	Functional scales	Symptoms scales	EQ-5D utility score	Time to deterioration	Disease-specific scale
CheckMate 141 Harrington <i>et al.</i> , 2017 ^[38]	International, randomized (2:1) open-label, Phase III, PRO was an exploratory end-point	Patients with recurrent or metastatic squamous cell carcinoma of the head and neck who progressed within 6 months after platinum-based chemotherapy	Nivolumab 3 mg/kg, or investigator's choice of methotrexate, docetaxel, or cetuximab	QLQ-C30, EORTC QLQ-H, and N35, EQ-5D	Nivolumab (240), investigator's choice (121)	At baseline, 74%-80%	Significant improvements were observed in physical functioning, role functioning, cognitive functioning, social functioning, fatigue, dyspnea, insomnia, appetite	VAS mean change in the nivolumab versus investigator's choice is 7.3 versus -7.8	Was not significantly different	Adjusted mean change in the nivolumab group -4.1-15.3, for the investigator choice -26.8-13.4. clinically meaningful worsening at week 15 was seen in no domains in the nivolumab group		
Ferris <i>et al.</i> , 2016 ^[39]	Randomized (2:1) open-label, phase III, HRQoL was a secondary endpoint	Recurrent squamous-cell carcinoma of the head and neck	Nivolumab 3 mg/kg versus standard therapy	QLQ-C30, EORTC QLQ-H, and N35, EQ-5D	240 in nivolumab and 121 in standard therapy	-	Among patients treated with nivolumab, these measures remained nearly stable or showed slight improvements					
CheckMate 017 Reck <i>et al.</i> , 2018 ^[41]	International, randomized, open-label, Phase III, PRO was a secondary end-point	Patients with advanced squamous NSCLC with disease progression during or after one prior platinum-containing chemotherapy regimen	Nivolumab (3 mg/kg intravenously every 2 weeks) versus docetaxel (75 mg/m ² intravenously every 3 weeks)	LCSS, EuroQoL EQ-5D	Nivolumab (n=135) or docetaxel (n=137)	Baseline was 77.8% in the nivolumab group and 76.6% in the docetaxel group				Similar between two arms during week 12, 24. After week 30, utility index scores improved in nivolumab	Deterioration was non-significant in LCSS ASBI at week 12. However, it was significant, favoring nivolumab, in LCSS 3-IGI, the EQ-5D utility index, and the EQ-5D VAS	Clinically significant improvement was observed in five of the six symptom scales of LCSS (loss of appetite, fatigue, cough, dyspnea, and pain)

Contd...

Table 4: Contd...

Study ID	Type	Population	Interventions	Questionnaire	Number of patient	Completion rate	GHS/QoL change from baseline	Functional scales	Symptoms scales	EQ-5D utility score	Time to deterioration	Disease-specific scale
KEYNOTE-024 Brahmer <i>et al.</i> , 2017 ⁽⁴⁰⁾	International, randomized (1:1), open-label, phase III, PRO was an exploratory end-point	Treatment-naive, stage IV NSCLC	200 mg every 3 weeks pembrolizumab versus investigator's choice	EORTC QLQ-C30, QLQ-LC13, EQ-5D-3L	Pembrolizumab (n=151), chemotherapy/investigator's choice (n=148)	Baseline was 96% in the pembrolizumab arm, 93% in the chemotherapy arm. At week 15, 72% at the pembrolizumab arm, 62% at the chemotherapy arm	Pembrolizumab: 6.9 (3.3-10.6), chemotherapy: -0.9 (-4.8 to 3.0)	In the physical functioning, role functioning, and social functioning in the pembrolizumab arm than in the chemotherapy arm. Minimal decrease in the cognitive functioning scale in the pembrolizumab arm than in the chemotherapy. similar improvement in the emotional functioning scale between the two arms	In the physical functioning, role functioning, and social functioning in the pembrolizumab arm than in the chemotherapy arm. Minimal decrease in the cognitive functioning scale in the pembrolizumab arm than in the chemotherapy. similar improvement in the emotional functioning scale between the two arms	The difference in the change of the VAS between the two arms was not significant	Deterioration was observed in 31% of the pembrolizumab arm and 39% in the chemotherapy arm	Pembrolizumab seemed better than chemotherapy in most QLQ-13 scales
CheckMate-142 Overman <i>et al.</i> , 2018 ⁽⁴²⁾	International, non-randomized, open-label, phase II, PRO was a secondary end-point	Patients with recurrent CRC or mCRC assessed as dMMR and/or MSI-H	Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg	QLQ-30, EQ-5D	119	At baseline, 94%-97%, to 90% at week 13	Statistically significant and clinically meaningful improvements were observed in patient-reported outcomes, including functioning, symptoms, and quality of life					
Kaufman <i>et al.</i> , 2018 ⁽⁴³⁾	International, phase II	Stage IV MCC, who have received at least one line of chemotherapy for the treatment of mMCC	10 mg/kg of avelumab	FACT-M, EQ-5D	88	Around 81% for both scales, at baseline. around 61% for both scales at week 7				Small change in the utility index was observed		30% decrease in tumor size correlated with 5.5-point change from baseline in the FACT-M

GHS: Global health status, QoL: Quality of life, PRO: Patient-reported outcomes, VAS: Visual analog scale, QLQ-C: QoL questionnaire core

Table 5: Characteristics of the included studies about squamous cell carcinoma of the head and neck, colorectal cancer, and Merkel carcinoma

Study ID	Disease-specific questionnaire	Analysis time-point	Sensitivity analysis	Percentage of grade 3-5 AE	Quality score
CheckMate 141 Harrington <i>et al.</i> , 2017 ^[38]	Yes	Week 15	No	13% of patients treated with nivolumab compared with 35% of those treated with investigator's choice	14
Ferris <i>et al.</i> , 2016 ^[39]	Yes	Week 15	No	3.1% in the nivolumab group versus 35.1% in the standard-therapy group	12
CheckMate 017 Reck <i>et al.</i> , 2018 ^[41]	Yes	Week 12	No	7% in the nivolumab, 55% in the docetaxel group	14
Keynote-024 Brahmer <i>et al.</i> , 2017 ^[40]	Yes	Week 15	No	26.6% in pembrolizumab versus 53.3% in chemotherapy	14
CheckMate-142 Overman <i>et al.</i> , 2018 ^[42]	No	Week 13	No	-	11
Kaufman <i>et al.</i> , 2018 ^[43]	Yes	Week 7	No	In 45% of the patients	14

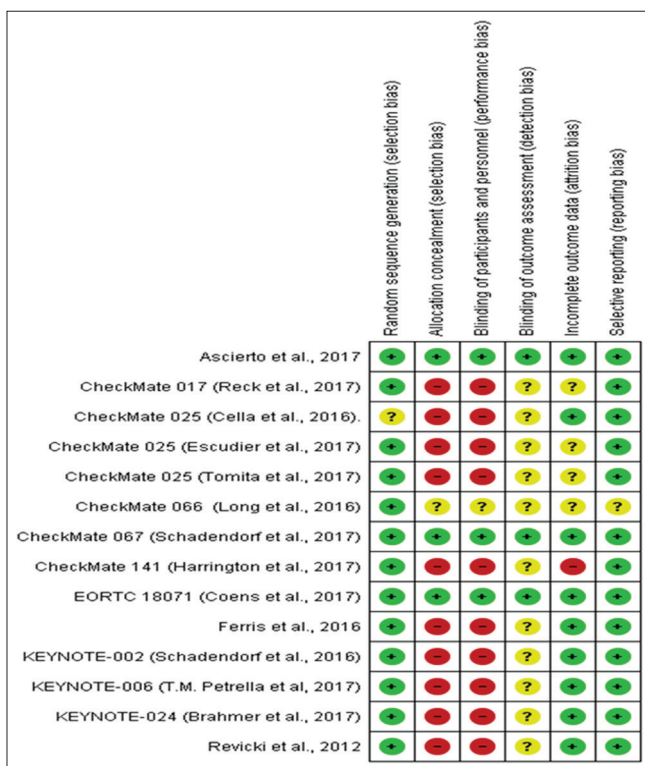


Figure 2: Risk of bias summary: judgments about each risk of bias item for each included study

Questionnaire and sensitivity analysis

Out of the 16 included studies, eight studies used a disease-specific questionnaire. Summary of the included questionnaires is provided [Table 6].^[44-50] The GHS scale uses a mean change ≥ 10 points in showing a clinically meaningful improvement. Only two included studies used a different mean change to demonstrate clinically meaningful improvement.

DISCUSSION

The evolution of ICPI have reconstructed the regimens of treatments of metastatic malignancies.^[51] Reports from clinical

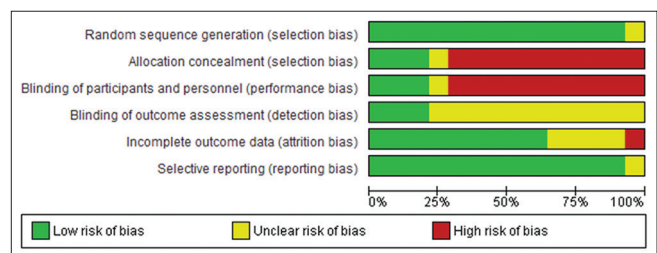


Figure 3: Risk of bias graph: judgments about each risk of bias item presented as percentages across all included studies

trials presenting the improvements in progression-free survival and overall survival of these drugs are promising about the future of this remarkable treatment technique.^[52] Despite these encouraging results, irAEs including dermatologic, endocrine, and hepatotoxic effects restraint enjoying their pros.^[53] In the past, the most clinical trials in oncology have considered overall survival and progression-free survival as their traditional endpoints. However, as tools and methods have evolved, assessing HRQoL in oncology trials has been on the rise.^[54,55] This helps to advise the clinicians about the effectiveness of the treatments from the patients' perspectives and equips the patients with the information to personalize their treatment choices.^[56] Despite their successful impact on the tumor, only certain groups of patients continued responding to them, and the others develop irAEs necessitating the discontinuation of the therapy.^[57-59] This growing body of evidence shows the importance of selecting patients appropriately for receiving ICPIs.^[60,61] HRQoL may aid in investigating the groups most likely to respond well to ICPIs. Although the included studies generally have showed, when comparing with chemotherapy or investigator's choice, that HRQoL remained stable or improved, some concerns should be highlighted in interpreting these results. First, according to the risk of bias summary, most of the studies lack allocation concealment and blinding. This may predispose to selection and performance biases which may have affected the results of them. Second, some ICPIs' HRQoL reports are found in the form of abstracts during the screening process. Moreover, there are some ongoing ICPIs trials that have

Table 6: Summary of the included questionnaires

Questionnaire	Type	Domains
EORTC QLQ-C-30	Generic	functional scales (physical, role, emotional, cognitive and social functioning), a global health status/QoL scale, and symptoms scales/items (fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) ^[44]
EuroQoL EQ-5D	Generic	It consists of a descriptive system and a VAS. The descriptive system contains five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analog scale. The scores can be finally converted into single summary index number (utility) reflecting preferability ^[45]
LCSS	Specific	Patient scale: Symptoms, total symptomatic distress, activity status, overall QoL Observer scale: Symptoms ^[46]
Lung Cancer Module (QLQ-LC13)	Specific	Assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis ^[47]
FKSI-DRS	Specific	Nine symptom-specific questions that address lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fevers, and hematuria ^[48]
FACT-M	Specific	Physical, social/family, emotional, functional well-beings ^[49]
EORTC QOL module for head-and-neck cancer (QLQ-H and N35)	Specific	Seven multiitem symptom scales (pain, sensory problems, social contact problems, swallowing, eating problems, speech problems, and reduced sexuality) and 11 single-item symptom scales (nutritional supplement use, mouth opening problems, teeth problems, coughing, painkiller use, weight loss, weight gain, sticky saliva, feeding tube, dry mouth, and feeling ill) ^[50]

QoL: Quality of life, EORTC: European Organization for Research and Treatment of Cancer, QLQ-C: QoL questionnaire core, LCSS: Lung Cancer Symptom Scale, FKSI-DRS: Functional Assessment of Cancer Therapy—Kidney Symptom Index- Disease-Related Symptoms, FACT-M: Functional Assessment of Cancer Therapy - Melanoma

not reported their HRQoL results. Thus, the presented evidence of these included studies should be interpreted carefully.^[62] Third, minimal clinically important differences (MCIDs) of ≥ 10 points used in some questionnaire has been reported years ago, and thus, using the same clinically meaningful threshold currently bears some limitations in interpreting these studies from a clinical point of view.^[63] Only two studies have included a sensitivity analysis for using ≥ 15 points as their MCIDs. Finally, in some of the included studies, as the number of patients decrease, the remaining number of patients continuing the therapy showed improvements in their health status. This also may support the idea of patient selection for ICPI therapy.

CONCLUSION

The review has summarized the present evidence regarding the HRQoL associated with immune-checkpoint inhibitors. The effects of therapy differ according to the type of tumor being involved. Considering their costly price and sometimes serious irAEs, this information may aid clinician in their decision-making process when considering ICPIs. However, due to the complexities associated with the longitudinal analyzes of HRQoL data, these results should be interpreted carefully. Moreover, future reports from ongoing trials are to be watched.

Limitation

The review results are limited by the limitations of the primary clinical trials included in it. Moreover, gray literature, for example, Google Scholar, has not been searched.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- World Health Organization. Cancer. WHO. Available from: <http://www.who.int/mediacentre/factsheets/fs297/en/>. [Last accessed on 2018 Feb 20].
- Boini S, Brianc¸on S, Guillemin F, Galan P, Hercberg S. Impact of cancer occurrence on health-related quality of life: A longitudinal pre-post assessment. *Health Qual Life Outcomes* 2004;2:4.
- Lee GL, Pang GS, Akhileswaran R, Ow MY, Fan GK, Wong CC, *et al*. Understanding domains of health-related quality of life concerns of Singapore Chinese patients with advanced cancer: A qualitative analysis. *Support Care Cancer* 2016;24:1107-18.
- Bottomley A. The cancer patient and quality of life. *Oncologist* 2002;7:120-5.
- Ryan H, Schofield P, Cockburn J, Butow P, Tattersall M, Turner J, *et al*. How to recognize and manage psychological distress in cancer patients. *Eur J Cancer Care (Engl)* 2005;14:7-15.
- Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA* 1995;273:59-65.
- Osoba D. Health-related quality of life and cancer clinical trials. *Ther Adv Med Oncol* 2011;3:57-71.
- Fiteni F, Westeel V, Pivot X, Borg C, Vernerey D, Bonnetain F. Endpoints in cancer clinical trials. *J Visc Surg* 2014;151:17-22.
- Punt CJ, Buyse M, Köhne CH, Hohenberger P, Labianca R, Schmol HJ, *et al*. Endpoints in adjuvant treatment trials: A systematic review of the literature in colon cancer and proposed definitions for future trials. *J Natl Cancer Inst* 2007;99:998-1003.
- Sztankay M, Giesinger JM, Zubernigg A, Krempler E, Pall G, Hilbe W, *et al*. Clinical decision-making and health-related quality of life during first-line and maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC): Findings from a real-world setting. *BMC Cancer* 2017;17:565.
- Kaplan RM. Health-related quality of life in patient decision making. *J Soc Issues* 1991;47:69-90.
- U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: Patient-reported outcome measures: Use in medical product development to support labeling claims: Draft guidance. *Health Qual Life Outcomes* 2006;4:79.

13. Granier C, De Guillebon E, Blanc C, Roussel H, Badoual C, Colin E, *et al.* Mechanisms of action and rationale for the use of checkpoint inhibitors in cancer. *ESMO Open* 2017;2:e000213.
14. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. *Am J Clin Oncol* 2016;39:98-106.
15. Azoury SC, Straughan DM, Shukla V. Immune checkpoint inhibitors for cancer therapy: Clinical efficacy and safety. *Curr Cancer Drug Targets* 2015;15:452-62.
16. Mahmoudi M, Farokhzad OC. Cancer immunotherapy: Wound-bound checkpoint blockade. *Nat Biomed Eng* 2017;1:31.
17. Michot JM, Bigenwald C, Champiat S, Collins M, Carbone F, Postel-Vinay S, *et al.* Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *Eur J Cancer* 2016;54:139-48.
18. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. *JAMA Oncol* 2016;2:1346-53.
19. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: A systematic review. *Ann Oncol* 2017;28:2377-85.
20. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: A systematic review of case reports. *PLoS One* 2016;11:e0160221.
21. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, *et al.* Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 2018;36:1714-68.
22. Andrews A. Treating with checkpoint inhibitors-figure \$1 million per patient. *Am Health Drug Benefits* 2015;8:9.
23. Braschi-Amirfarzan M, Tirumani SH, Hodi FS Jr., Nishino M. Immune-checkpoint inhibitors in the era of precision medicine: What radiologists should know. *Korean J Radiol* 2017;18:42-53.
24. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med* 2009;6:e1000100.
25. Cochrane Handbook for Systematic Reviews of Interventions. Available from: <http://www.handbook-5-1.cochrane.org/>. [Last accessed on 2018 Feb 21].
26. Mols F, Vingerhoets AJ, Coebergh JW, van de Poll-Franse LV. Quality of life among long-term breast cancer survivors: A systematic review. *Eur J Cancer* 2005;41:2613-9.
27. Cornish D, Holterhues C, van de Poll-Franse LV, Coebergh JW, Nijsten T. A systematic review of health-related quality of life in cutaneous melanoma. *Ann Oncol* 2009;20 Suppl 6:vi51-8.
28. Petrella TM, Robert C, Richtig E, Miller WH Jr., Masucci GV, Walpole E, *et al.* Patient-reported outcomes in KEYNOTE-006, a randomised study of pembrolizumab versus ipilimumab in patients with advanced melanoma. *Eur J Cancer* 2017;86:115-24.
29. Ascierto PA, Del Vecchio M, Robert C, Mackiewicz A, Chiarion-Sileni V, Arance A, *et al.* Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: A randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2017;18:611-22.
30. Long GV, Atkinson V, Ascierto PA, Robert C, Hassel JC, Rutkowski P, *et al.* Effect of nivolumab on health-related quality of life in patients with treatment-naïve advanced melanoma: Results from the phase III checkMate 066 study. *Ann Oncol* 2016;27:1940-6.
31. Revicki DA, van den Eertwegh AJ, Lorigan P, Lebbe C, Linette G, Ottensmeier CH, *et al.* Health related quality of life outcomes for unresectable stage III or IV melanoma patients receiving ipilimumab treatment. *Health Qual Life Outcomes* 2012;10:66.
32. Schadendorf D, Dummer R, Hauschild A, Robert C, Hamid O, Daud A, *et al.* Health-related quality of life in the randomised KEYNOTE-002 study of pembrolizumab versus chemotherapy in patients with ipilimumab-refractory melanoma. *Eur J Cancer* 2016;67:46-54.
33. Schadendorf D, Larkin J, Wolchok J, Hodi FS, Chiarion-Sileni V, Gonzalez R, *et al.* Health-related quality of life results from the phase III checkMate 067 study. *Eur J Cancer* 2017;82:80-91.
34. Coens C, Suci S, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, *et al.* Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): Secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2017;18:393-403.
35. Cella D, Grünwald V, Nathan P, Doan J, Dastani H, Taylor F, *et al.* Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in checkMate 025: A randomised, open-label, phase 3 trial. *Lancet Oncol* 2016;17:994-1003.
36. Escudier B, Motzer RJ, Sharma P, Wagstaff J, Plimack ER, Hammers HJ, *et al.* Treatment beyond progression in patients with advanced renal cell carcinoma treated with nivolumab in CheckMate 025. *Eur Urol* 2017;72:368-76.
37. Tomita Y, Fukasawa S, Shinohara N, Kitamura H, Oya M, Eto M, *et al.* Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study. *Jpn J Clin Oncol* 2017;47:639-46.
38. Harrington KJ, Ferris RL, Blumenschein G Jr., Colevas AD, Fayette J, Licitra L, *et al.* Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): Health-related quality-of-life results from a randomised, phase 3 trial. *Lancet Oncol* 2017;18:1104-15.
39. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, *et al.* Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856-67.
40. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, *et al.* Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): A multicentre, international, randomised, open-label phase 3 trial. *Lancet Oncol* 2017;18:1600-9.
41. Reck M, Taylor F, Penrod JR, DeRosa M, Morrissey L, Dastani H, *et al.* Impact of nivolumab versus docetaxel on health-related quality of life and symptoms in patients with advanced squamous non-small cell lung cancer: Results from the CheckMate 017 study. *J Thorac Oncol* 2018;13:194-204.
42. Overman MJ, Lonardi S, Wong KY, Lenz HJ, Gelsomino F, Aglietta M, *et al.* Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/Microsatellite instability-high metastatic colorectal cancer. *J Clin Oncol* 2018;36:773-9.
43. Kaufman HL, Hunger M, Hennessy M, Schlichting M, Bharmal M. Nonprogression with avelumab treatment associated with gains in quality of life in metastatic Merkel cell carcinoma. *Future Oncol* 2018;14:255-66.
44. Questionnaires. EORTC. Available from: <http://www.groups.eortc.be/qol/eortc-qlq-c30>. [Last accessed on 2018 Feb 23].
45. EQ-5D Instruments – EQ-5D. Available from: <https://www.euroqol.org/eq-5d-instruments/>. [Last accessed on 2018 Feb 23].
46. Lung Cancer Symptom Scale. Available from: <http://www.qol.thoracic.org/sections/instruments/ko/pages/lcss.html>. [Last accessed on 2018 Feb 23].
47. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: A modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC study group on quality of life. *Eur J Cancer* 1994;30A: 635-42.
48. FKSI-DRS – Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms. Available from: <https://www.eprovide.mapi-trust.org/instruments/functional-assessment-of-cancer-therapy-kidney-symptom-index-disease-related-symptoms>. [Last accessed on 2018 Feb 23].
49. FACT-M – Functional Assessment of Cancer Therapy – Melanoma. Available from: <https://www.eprovide.mapi-trust.org/instruments/functional-assessment-of-cancer-therapy-melanoma>. [Last accessed on 2018 Feb 23].
50. EORTC QOL Module for Head and Neck Cancer (QLQ-H&N43) (Revision of EORTC QLQ-H&N35). EORTC. Available from: <http://www.groups.eortc.be/qol/eortc-qol-module-head-and-neck-cancer-qlq-hn43-revision-eortc-qlq-hn35>. [Last accessed on 2018 Feb 23].
51. Thallinger C, Füreder T, Preusser M, Heller G, Müllauer L, Höller C, *et al.* Review of cancer treatment with immune checkpoint inhibitors: Current concepts, expectations, limitations and pitfalls. *Wien Klin Wochenschr* 2018;130:85-91.

52. Spain L, Larkin J. Weighing up the pros and cons of immune checkpoint inhibitors in the treatment of melanoma. *Immunotherapy* 2016;8:677-9.
53. Kourie HR, Klastersky J. Immune checkpoint inhibitors side effects and management. *Immunotherapy* 2016;8:799-807.
54. Zikos E, Coens C, Ediebah DE, Quinten C, Greimel E, Flechtner H, *et al.* Health-related quality of life assessment in EORTC cancer clinical trials. *J Clin Oncol* 2012;30 Suppl 15:6090.
55. Efficace F, Osoba D, Gotay C, Sprangers M, Coens C, Bottomley A. Has the quality of health-related quality of life reporting in cancer clinical trials improved over time? Towards bridging the gap with clinical decision making. *Ann Oncol* 2007;18:775-81.
56. Bottomley A, Aaronson NK; European Organisation for Research and Treatment of Cancer. International perspective on health-related quality-of-life research in cancer clinical trials: The European organisation for research and treatment of cancer experience. *J Clin Oncol* 2007;25:5082-6.
57. Assi HI, Kamphorst AO, Moukalled NM, Ramalingam SS. Immune checkpoint inhibitors in advanced non-small cell lung cancer. *Cancer* 2018;124:248-61.
58. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: A systematic review. *Ann Intern Med* 2018;168:121-30.
59. Dijkstra KK, Voabil P, Schumacher TN, Voest EE. Genomics- and transcriptomics-based patient selection for cancer treatment with immune checkpoint inhibitors: A review. *JAMA Oncol* 2016;2:1490-5.
60. Sen S, Hess K, Hong DS, Naing A, Piha-Paul S, Janku F, *et al.* Development of a prognostic scoring system for patients with advanced cancer enrolled in immune checkpoint inhibitor phase 1 clinical trials. *Br J Cancer* 2018;118:763-9.
61. Choudhury N, Nakamura Y. Importance of immunopharmacogenomics in cancer treatment: Patient selection and monitoring for immune checkpoint antibodies. *Cancer Sci* 2016;107:107-15.
62. Solinas C, Gombos A, Latifyan S, Piccart-Gebhart M, Kok M, Buisseret L. Targeting immune checkpoints in breast cancer: An update of early results. *ESMO Open* 2017;2:e000255.
63. Singh J, Sloan JA, Johanson NA. Challenges with health-related quality of life assessment in arthroplasty patients: Problems and solutions. *J Am Acad Orthop Surg* 2010;18:72-82.