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Quality-of-life outcomes in patients with advanced melanoma: A review of the literature

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Summary
For patients with metastatic melanoma, the emergence of immune checkpoint inhibitors and targeted BRAF and MEK inhibitors has markedly enhanced clinical outcomes compared with chemotherapy. However, these novel agents are also associated with unique sets of adverse events, and increased overall survival can lead to prolonged exposure to some novel agents. Therefore, clinical evaluation of these therapies has now included the analysis of health-related quality of life (HRQoL) in addition to more traditional efficacy and safety outcomes as a measure of patient perception of benefit. The current review focuses on HRQoL outcomes in clinical trials of immune checkpoint inhibitors and targeted therapies in patients with advanced and metastatic melanoma to inform healthcare providers about patient perception of HRQoL as a new perspective in treatment decision making.

KEYWORDS
immunotherapy, melanoma, quality of life, targeted therapy

1 | INTRODUCTION

Randomized clinical trials in oncology have largely focused on traditional efficacy endpoints such as overall and progression-free survival (PFS; Lipscomb, Gotay, & Snyder, 2007). An increasing number of oncology trials (Efficace et al., 2014) and studies conducted in real-world routine care settings (Basch et al., 2012) are including assessments of patients’ overall and health-related quality of life (HRQoL) in their designs, which provides an additional reference for clinical decision making (Bradly et al., 1997; US Department of Health and Human Services FDA Centers for Drug Evaluation and Research, Biologics Evaluation and Research, and Devices and Radiological Health, 2006; Yellen, Cella, Webster, Blendowski, & Kaplan, 1997).

Some aspects of patients’ HRQoL have been shown to be independent predictors of survival in advanced melanoma (Brandberg et al., 2013; Butow, Coates, & Dunn, 1999; Coates et al., 1993). Roughly one-third of patients with melanoma have reported clinically significant levels of distress (Cornish, Holterhues, van de Poll-Franse, Coebergh, & Nijsten, 2009). The lowest levels of HRQoL and overall personal health perception are usually observed in the acute survival phase that immediately follows the diagnosis and are partly attributable to worsening somatic symptoms, such as increased levels of pain, decreased levels of energy, and a higher level of physical and emotional stress affecting social activities (Al-Shakhli, Harcourt, & Kenealy, 2006; Ko, Maggard, & Livingston, 2003).

Over the past 6 years, the US Food and Drug Administration (FDA) has approved several novel agents for the treatment of metastatic melanoma that have enhanced survival but also introduced new challenges in terms of toxicity. Immune checkpoint inhibitors have been associated with immune-related adverse events (AEs), including colitis/diarrhea, dermatitis, hepatitis, nephritis, and endocrinopathies (Di Giacomo, Biagioli, & Maio, 2010; Hofmann et al., 2016). With respect to targeted therapies, BRAF and/or MEK inhibitors have been associated with gastrointestinal AEs and a number of cutaneous AEs, including squamous cell carcinoma and photosensitivity (Sosman et al., 2012), and dabrafenib with or without trametinib is associated with pyrexia (Long et al., 2014; Weber et al., 2012). Because long-term survival for patients with metastatic melanoma is...
becoming a realistic prospect and treatment duration for some therapies has been extended by favorable outcomes, consideration of HRQoL and symptoms is of particular importance.

This review aims to provide an overview of HRQoL in the era of novel therapies in the treatment of advanced melanoma as a means of providing insight for clinical decision making. We will discuss some of the currently available tools used to assess HRQoL in patients with melanoma and examine the recent clinical trials regarding HRQoL outcomes in patients with advanced and metastatic melanoma.

2 HRQoL ASSESSMENT TOOLS USED IN clinicaL trial settinGS

The US Centers for Disease Control and Prevention define HRQoL as “an individual’s or a group’s perceived physical and mental health over time” (Centers for Disease Control and Prevention, 2016). The majority of recent clinical trials in melanoma that assess HRQoL use the EORTC QLQ-C30 questionnaire (QLQ-C30; Aaronson et al., 1993; Groenvold, Klee, Sprangers, & Aaronson, 1997; Bjordal, Fossa, Bjordal, & Kaasa, 1995; Kaasa et al., 1995; Osoba et al., 1994; Osoba, Aaronson, Zee, Sprangers, & Velde, 1997). The use of the melanoma-specific Functional Assessment of Cancer Therapy—Melanoma (FACT-M) questionnaire, first validated in 2008 (Cormier et al., 2008), has only recently moved into clinical practice.

The QLQ-C30 form is a self-reported, 30-item questionnaire and includes five scales that address patients’ level of functioning (physical, role, cognitive, emotional, and social) as well as nine symptom scales or single-item questions (assessing fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties; Aaronson et al., 1993; European Organisation for Research and Treatment of Cancer, 2016). The overall score ranges from 0 to 100 points and has demonstrated consistent responses across populations with various cancers (Aaronson et al., 1993; Hjermstad et al., 1995; Kaasa et al., 1995; Osoba et al., 1994, 1997). In a validation study, a high level of overall agreement was observed between patient answers in the questionnaire and observer interpretations from detailed interviews using the QLQ-C30 questions in an open-ended format (Groenvold et al., 1997). The QLQ-C30 questionnaire has shown meaningful correlations with Eastern Cooperative Oncology Group (ECOG) performance status and degree of weight loss in patients with lung cancer (Ko et al., 2003).

Like the QLQ-C30, the Functional Assessment in Cancer Treatment—General (FACT-G) is considered a core questionnaire generalized for all cancers. Its modification, the FACT-M form, is a validated assessment tool that contains an additional block of melanoma-specific questions (Askew et al., 2009; Cormier, Davidson, Xing, Webster, & Cella, 2005; Cormier et al., 2008). Of 24 melanoma subscale questions, nine items are clearly related to surgical complications (Cormier et al., 2008). The FACT-M form differs from the QLQ-C30 in the way the items are formulated as statements rather than questions. These statements are emotionally colored and encourage patients to “reflect on their thoughts and feelings throughout” (Luckett et al., 2011). Another commonly used HRQoL questionnaire is the EuroQol EQ-5D form, which comprises five questions about pain and physical, social, and emotional well-being, as well as a visual analogue scale, which asks the patient to rate his or her health perception on a 0-to-100 scale.

Regardless of the assessment tool used, however, the magnitude of the change in score that is indicative of a clinically significant difference in QoL requires quantification to facilitate clinical interpretations. In a study that assessed minimally important differences (MIDs) in the QLQ-C30, researchers compared the changes in a given patient’s QLQ-C30 score and the same patient’s responses to a separate subjective significance questionnaire that used a 7-category scale ranging from “much worse” through “no change” to “much better.” The results indicated that a difference of 5–10 points was perceived by the patients as “a little change,” 10–20 points as “moderate change,” and >20 points as “very much” change in perceptions of patients in physical, emotional, and social functioning (Osoba, Rodrigues, Myles, Zee, & Pater, 1998). Regarding the FACT-M, MID ranges were between 1 and 9 points depending on the subscale analyzed (Askew et al., 2009). The MID for the generic EQ-5D instrument (Kind, 1996; Pickard, Neary, & Cella, 2007; Rabin & Charro, 2001) was determined to be similar across various cancer types at 0.08. The use of MIDs is highly encouraged by the FDA (US Department of Health and Human Services FDA Centers for Drug Evaluation and Research, Biologics Evaluation and Research, and Devices and Radiological Health, 2006).

3 IMMUNOTHERAPY

Several novel melanoma immunotherapy studies, described in Table 1 and Figure 1, included the patients’ perception of HRQoL in their outcomes (Abernethy et al., 2015; Long et al., 2016; Petrella et al., 2015; Revicki et al., 2012; Schadendorf, Long et al., 2015; Schadendorf et al., 2016).

The randomized, double-blind, Phase III MDX010-20 trial compared the efficacy of ipilimumab, gp100 vaccine, and a combination of both agents in patients with previously treated advanced melanoma (Revicki et al., 2012). The results from this trial demonstrated that ipilimumab could prolong survival while minimally impacting QoL, as measured by QLQ-C30 questionnaire subscales. Exceptions were noted in the symptom scores for fatigue, sleep disturbance, and appetite loss, all of which showed moderate impairment 12 weeks after treatment with ipilimumab.

Clinical trials of both currently approved anti-PD-1 checkpoint inhibitors, pembrolizumab and nivolumab, did include HRQoL outcomes while comparing those drugs with chemotherapy. The open-label, randomized, Phase II KEYNOTE-002 trial used the QLQ-C30 to compare two different doses of pembrolizumab with investigator’s choice of chemotherapy in patients previously treated with ipilimumab (Schadendorf et al., 2016). Overall, patients in the two pembrolizumab arms had better maintenance of HRQoL from baseline to week 12 compared with patients in the chemotherapy arm. Specifically, patients in the pembrolizumab arm reported less decline in global health status (−2.6) compared with patients in the chemotherapy arm (−9.1). The authors acknowledged the possibility of bias from the partial open-label design.
### TABLE 1  HRQoL in immunotherapy trials in patients with advanced melanoma

| Trial | Patients, N (% treatment naive) | Regimens (discontinuation due to AEs, %) | HRQoL Tool | Conclusions | Comments |
|-------|---------------------------------|------------------------------------------|------------|-------------|----------|
| **Monotherapy** | | | | | |
| MDX010-20 Phase III (Revicki et al., 2012) | 676 (0) | Ipi + gp100 (9) versus Ipi (13) or gp100 (4) | EORTC QLQ-C30 | During 12 weeks of therapy, Ipi did not significantly impair HRQoL | Double-blind study; all patients previously treated; HRQoL was a secondary endpoint |
| KEYNOTE-002 Phase II (Schadendorf et al., 2016) | 540 (<1) | Pembro 2 mg/kg Q3W (12); Pembro 10 mg/kg Q3W (13); chemotherapy (11) | EORTC QLQ-C30 | Patients in the Pembro arms maintained significantly (p < .05) higher global health status compared with patients in the chemo arm | Open-label trial in previously treated patients; HRQoL was an exploratory endpoint |
| KEYNOTE-006 Phase III (Petrella et al., 2015) | 773 (66) | Pembro 10 mg/kg Q2W (7); Pembro 10 mg/kg Q3W (10); Ipi (14) | EORTC QLQ-C30 | Patients in the Pembro arms showed more stable global health status and longer time to deterioration of HRQoL versus patients in the Ipi arm | Open-label trial; treatment-naive and previously treated patients; HRQoL was an exploratory endpoint |
| CheckMate 066 Phase III (Long et al., 2016) | 418 (100) | Nivo (7); DTIC (12) | EORTC QLQ-C30; EuroQol EQ-5 D | Patients in the Nivo arm maintained their global health status longer than patients in DTIC arm | Double-blind study in treatment-naive patients; EORTC QLQ-C30 score was a secondary endpoint, and EQ-5D score was an exploratory endpoint |
| **Combination Immunotherapy** | | | | | |
| CheckMate 069 Phase II (Abernethy et al., 2015; Hodi et al., 2016) | 142 (100) | Nivo + Ipi (55); Ipi (28) | EORTC QLQ-C30; EuroQol EQ-5D | Combination Nivo + Ipi showed similar HRQoL versus Ipi monotherapy but provided superior antitumor response | Double-blind trial in treatment-naive patients; HRQoL was a secondary endpoint |
| CheckMate 067 Phase III (Larkin et al., 2015; Schadendorf, Long et al., 2015) | 945 (100) | Nivo + Ipi (42); Nivo (10); Ipi (16) | EORTC QLQ-C30; EuroQol EQ-5D | Although patients in the Nivo + Ipi arm had a higher frequency of AEs, no clinically meaningful changes from baseline were observed in any treatment arm | Randomized, double-blind study in treatment-naive patients; EORTC QLQ-C30 was a secondary endpoint, and EQ-5D was an exploratory endpoint. The patients who discontinued treatment prior to the censoring event were not included in QoL analysis |

AE, adverse event; chemo, chemotherapy; DTIC, dacarbazine; EORTC, European Organisation for Research and Treatment of Cancer; gp100, glycoprotein 100; HRQoL, health-related quality of life; Ipi, ipilimumab; Nivo, nivolumab; Pembro, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks.

*Included assessments at the time of treatment discontinuation and during subsequent follow-up visits.
Nivolumab was compared with dacarbazine in the randomized, double-blind, Phase III CheckMate 066 trial of patients with treatment-naive BRAF wild-type metastatic melanoma (Long et al., 2016). Completion rates for the QLQ-C30 questionnaire (secondary outcome) and the EQ-5D (exploratory outcome) were approximately 65%-70% for both arms throughout the assessment period. Although the QLQ-C30 global health scores in both study arms showed a non-significant trend toward improvement compared with respective baseline scores, patients treated with nivolumab were significantly less likely to experience a deterioration of QLQ-C30 global health status compared with patients in the dacarbazine arm (HR [95% CI], 0.65 [0.46–0.92]; p = .014). Similar results were obtained from the EQ-5D questionnaire data. Overall, in comparison with chemotherapy, both anti-PD-1 drugs showed stable or slightly improved HRQoL and a prolonged time to deterioration in patients treated with immunotherapy.

The HRQoL impact of pembrolizumab and nivolumab has also been assessed in comparison with ipilimumab monotherapy in the randomized, open-label, Phase III KEYNOTE-006 trial (Petrella et al., 2015) and the randomized, double-blind, Phase III CheckMate 067 trial (Larkin et al., 2015; Schadendorf, Long et al., 2015), respectively. The analysis of QLQ-C30 global health status scores demonstrated significantly better preservation of HRQoL by both anti-PD-1 antibodies compared with ipilimumab (p < .01). In the case of pembrolizumab versus ipilimumab, this difference at 12 weeks reached clinically meaningful magnitude (~9.9 in ipilimumab and ~2.3 and ~2.6 in pembrolizumab Q2W and Q3W, respectively). The authors explain a significantly longer time to deterioration of global health status for patients in the pembrolizumab arm by pointing out a prolonged PFS and a lower incidence of high-grade toxicity associated with pembrolizumab compared with ipilimumab.

Treatment of patients with a combination of ipilimumab and nivolumab has resulted in an increased number of objective responses and prolonged median PFS compared with ipilimumab monotherapy and less so compared with nivolumab monotherapy, although the analysis was not powered to compare the combination with nivolumab alone (Hodi et al., 2016; Larkin et al., 2015). The randomized, double-blind, Phase II CheckMate 069 trial evaluated a combination of ipilimumab plus nivolumab followed by nivolumab monotherapy versus ipilimumab plus placebo followed by placebo only in patients with previously untreated metastatic melanoma (Abernethy et al., 2015; Hodi et al., 2016), while the much larger randomized, double-blind, Phase III CheckMate 067 trial also included a third arm of nivolumab monotherapy (Larkin et al., 2015; Schadendorf, Long et al., 2015). The latter trial demonstrated a statistically significant but clinically unimportant initial decline of QLQ-C30 global health status in all arms compared to baseline scores (−2.7 for nivolumab, −4.3 for nivolumab + ipilimumab, and −3.1 for ipilimumab at week 5; p ≤ .01). At the same time, no significant deterioration of the global health status was observed in the combination therapy group compared with either monotherapy group. The EQ-5D utility scores showed normalization of initial decline back to baseline by week 13 in the nivolumab and combination arms; however, in the ipilimumab arm, recovery of EQ-5D scores did not occur until week 19 (after the four cycles of ipilimumab therapy were already completed).

The rate of treatment-related grade 3/4 AEs was increased in patients in the combination group (55%) compared with the monotherapy group (16.3% in the nivolumab group and 27.3% in the ipilimumab group). This observation correlates with the rates of treatment discontinuation due to adverse events in all three arms (for the combination arms of each study, these rates were 55% and 42% for CheckMate 069 and CheckMate 067, respectively). Notably, patients...
**Table 2** HRQoL in targeted therapy trials in patients with advanced BRAF V600-mutant melanoma

| Trial                  | Patients, N (treatment naive, %) | Regimens (discontinuation due to AEs, %) | HRQoL Tool          | Conclusions                                                                 | Comments                                                                 |
|------------------------|----------------------------------|------------------------------------------|---------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| **Monotherapy**        |                                  |                                          |                     |                                                                             |                                                                           |
| BREAK-3                | 250 (100)a                        | Dabra (3); DTIC (3)                       | EORTC QLQ-C30b      | Patients in the Dabra arm had significantly (p < .05) higher scores in emotional functioning and several symptom domains compared with DTIC arm. No significant changes from baseline were observed in the global health perception scores in either arm. | Randomized, open-label study in primarily previously untreated patients with BRAF V600E-mutant advanced melanoma; HRQoL was an exploratory endpoint |
| METRIC                 | 273 (66)                          | Trame (NR); Chemo (NR)                   | EORTC QLQ-C30b      | Overall, patients in the Trame arm reported an improvement from baseline in global health perception (a non-significant difference compared with DTIC). The difference between the arms was significant (p < .05) for physical and role functioning in favor of the Trame arm. | Randomized, open-label study in patients with previously treated or treatment-naive advanced BRAF V600E/K-mutant melanoma; HRQoL was an exploratory endpoint |
| **BRAF + MEK Inhibitors** |                                  |                                          |                     |                                                                             |                                                                           |
| COMBI-d                | 423 (100)                         | Dabra + Trame (11); Dabra + placebo (6)  | EORTC QLQ-C30b      | Patients in the Dabra + Trame arm maintained an improvement from baseline in global health and majority of functional domains, a statistically (p < .05) better result compared with that of Dabra + placebo arm patients, for whom scores were mostly below the baseline. | Randomized, double-blind study in treatment-naive patients with BRAF V600E/K-mutant advanced melanoma; HRQoL was an exploratory endpoint |
| COMBI-v                | 704 (100)                         | Dabra + Trame (13); Vemu monotherapy (12)| EORTC QLQ-C30, EuroQol EQ-5D FACT-Mb | Combination Dabra + Trame provided significant (p < .05) and clinically meaningful improvement (positive difference from baseline) in global health and several functional and symptom domains compared with Vemu monotherapy (negative difference from baseline). | Randomized, open-label study in patients with BRAF V600E/K-mutant advanced melanoma; HRQoL was a prespecified exploratory endpoint |
| coBRIM                 | 495 (100)                         | Vemu + Cobi (14); Vemu + placebo (7)     | EORTC QLQ-C30       | Overall change from baseline in global health status was similar between arms. Improvements in social functioning, insomnia, fatigue, and pain symptom scores favored the combination arm. | Randomized, double-blind study in patients with BRAF V600-mutant advanced melanoma. Reported preliminary results only, with no formal statistical analysis; HRQoL was a secondary endpoint |
| COLUMBUS               | 577 (4)                           | Enco + Bini (8); Enco (12); Vemu (14)    | EORTC QLQ-C30, FACT-M | Maintenance of QoL was improved with Enco + Bini combination compared with Vemu alone and Enco alone. | Randomized, open-label trial. HRQoL is defined as secondary outcome and measured by time to 10% score deterioration from time of randomization (without subsequent improvement) or death. No raw scores publicly available |

Bini, binimetinib; Chemo, chemotherapy; Cobi, cobimetinib; Dabra, dabrafenib; DTIC, dacarbazine; Enco, encorafenib; EORTC, European Organisation for Research and Treatment of Cancer; FACT-M, Functional Assessment of Cancer Therapy—Melanoma; HRQoL, health-related quality of life; IL-2, interleukin-2; NR, not reported; Trame, trametinib; Vemu, vemurafenib.

aPrior treatment with IL-2, surgery, or radiotherapy was allowed.

bIncluded assessments at the time of disease progression and 4–6 weeks after progression.
who discontinued treatment early were not included in the presented interim QoL analysis.

4 | BRAF AND MEK INHIBITORS

The introduction of novel BRAF and MEK inhibitors and their combinations has enhanced survival in patients with BRAF V600-mutant metastatic melanoma (Ascierto et al., 2016; Chapman et al., 2011; Flaherty et al., 2012; Hauschild et al., 2012; Larkin et al., 2014; Long et al., 2014, 2015; Robert et al., 2015). HRQoL has been assessed in a number of trials evaluating the efficacy and safety of BRAF inhibitors, MEK inhibitors, or their combination; results have been outlined in Table 2 and Figure 1.

Two trials that included HRQoL compared BRAF inhibitor dabrafenib and MEK inhibitor trametinib with chemotherapy (dacarbazine or paclitaxel). The randomized, open-label, Phase III METRIC trial showed significant (p < .05) and clinically meaningful improvements from baseline favoring the trametinib arm for physical, role, and social functioning, and a number of symptom scores at week 6 and/or 12 (Schadendorf et al., 2014). The improvement in the global health score in the trametinib group did not reach statistical significance, compared chemotherapy arm scores. The randomized, open-label, Phase III BREAK-3 trial showed survival and HRQoL advantages for dabrafenib, demonstrating statistically significant and clinically meaningful improvement from baseline in the emotional functional domain and several gastrointestinal symptom scores (Groß et al., 2014; Hauschild et al., 2012). The patients in the dacarbazine group who crossed over to the dabrafenib arm upon disease progression demonstrated clinically meaningful improvement in the overall global health dimension and in all functional and symptom scores following crossover compared with scores documented at progression. These results further support the enhanced HRQoL in patients with BRAF-mutant advanced melanoma treated with inhibitors of the mitogen-activated protein kinase (MAPK) pathway compared with those treated with chemotherapy.

The blockade of two steps of the MAPK pathway with concurrent administration of BRAF and MEK inhibitors has enhanced the overall survival of patients with BRAF V600E/K-mutant unresectable or metastatic melanoma while maintaining a safety profile comparable with that of BRAF inhibitor monotherapy. Two randomized Phase III trials, COMBI-d and COMBI-v, reported HRQoL results in patients treated with combination dabrafenib + trametinib in comparison with a BRAF inhibitor alone (dabrafenib or vemurafenib; Schadendorf, Amonkar et al., 2015; Grob et al., 2015; Robert et al., 2015). The QLQ-C30 global health status scores were consistently and significantly higher starting from week 8 in patients treated with the combination regimen compared with those treated with BRAF inhibitor monotherapy. The majority of functional domains and the pain scores also statistically and clinically significantly favored patients receiving the combination. Interestingly, in the COMBI-d trial, the fatigue and insomnia scores trended in favor of the combination arm, while gastrointestinal symptom scores (nausea and vomiting, diarrhea, and constipation) trended in favor of the dabrafenib plus placebo arm, observations that are consistent with the known safety profile.

Similar to dabrafenib plus trametinib, the combination of vemurafenib plus cobimetinib has demonstrated improved efficacy versus vemurafenib monotherapy in the randomized, double-blind, Phase III coBRIM trial (Dreno et al., 2015; Larkin et al., 2014). Although no clinically meaningful difference was observed between arms in the mean change in global health status from baseline on the QLQ-C30 questionnaire, a higher percentage of patients in the combination arm reported clinically meaningful score improvements from baseline in social function and in the insomnia, fatigue, and pain symptom scores compared with the vemurafenib monotherapy arm (Dreno et al., 2015).

The open-label, Phase III COLUMBUS trial aimed to compare the safety and efficacy of combination encorafenib plus binimetinib with encorafenib and vemurafenib monotherapies (Dummer et al., 2016). Patients in the combination arm had a higher objective response rate and prolonged median PFS. The rate of overall AEs and grade 3/4 events was similar between treatment arms. Patients in the combination arm had better maintenance of HRQoL versus either monotherapy arm as assessed by both the FACT-M and QLQ-C30 tools.

Taken together with the results of previously discussed trials, these data further support the HRQoL advantage of the combination of BRAF and MEK inhibitors over BRAF inhibitor monotherapy in the treatment of patients with BRAF V600-mutant metastatic melanoma.

5 | DISCUSSION

With the discovery of new therapeutic targets and immunologic checkpoints in melanoma, as well as the presence of multiple drugs from the same class, the choice of therapy becomes especially challenging for clinician and patient. Currently, several different drugs are approved as first-line single-agent or combination therapy for newly diagnosed unresectable BRAF-mutant melanoma. Although no strong evidence is available to favor one drug over another as frontline treatment, the current National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology supports the use of the combination of BRAF and MEK inhibitors when there is a need for early clinical response (NCCN, 2016). This recommendation could mean, in real-world clinical practice, that BRAF/MEK inhibitors are often given to patients with more-advanced symptoms and lower HRQoL than patients who are started on immunotherapy. Apart from a patient’s clinical characteristics, the therapy choice often depends on the clinician’s experience, financial considerations, and the patient’s preferences, which include, for example, the route of drug administration or side effect profile.

The association between treatment-related side effects and the patient’s perception of global health status is logical and is supported by earlier clinical observations (Mazzotti et al., 2012). The
differences in study design across recent trials preclude the determination of a correlation between the rate of treatment-related side effects and patients’ perceived HRQoL. For example, the most common AEs in the nivolumab + ipilimumab therapy groups of the CheckMate 069 and 067 trials were diarrhea and fatigue, which are addressed in the QLQ-C30 questionnaire. Despite this observation, an increased rate of treatment-related side effects in the combination therapy group was not associated with significant deterioration of the global health subscale compared with patients in the respective monotherapy arms. The interpretation of results from these trials is complicated by the fact that patients who discontinued treatment due to side effects were not included in the reported interim QoL analysis (Boughton, 2015). This was not the case in another recent double-blinded trial of adjuvant ipilimumab in high-risk stage III melanoma, where all patients were included in the QoL analysis regardless of disease recurrence or treatment discontinuation (Coens et al., 2017). In this study, 52% of patients in the ipilimumab arm discontinued treatment due to adverse events. This discontinuation rate was associated with a statistically significant reduction in the global health subscale score by QLQ-C30 in patients in the ipilimumab arm, although this difference did not reach the predetermined MID cutoff of 10 points.

The opportunity for cross-trial comparison is very interesting, but interpretation of results from an HRQoL perspective is challenging and should be done cautiously. For example, Daud, Gill, Kamra, Chen, and Ahuja (2017) performed a comparison of efficacy and safety results between the COMBI-v and coBRIM trials that showed a better safety profile for dabrafenib plus trametinib compared with vemurafenib plus cobimetinib, an observation that does not necessarily translate into a difference in HRQoL outcomes. The blinded or unblinded nature of a trial’s design can also greatly impact the perception of benefit and thus comparisons between trials with open-label and double-blind designs should be interpreted cautiously. Additionally, the difference in kinetics of clinical effect and AE development in different drug classes and incomplete collecting or reporting of data (i.e., low questionnaire completion rate by the patients, missing baseline values or raw data in the publication) can limit the interpretation of cross-trial comparisons of HRQoL.

To date, most studies of HRQoL in patients with advanced or metastatic melanoma have used generic instruments, such as the QLQ-C30 and EQ-5D questionnaires. One validation study revealed potential biases of the questionnaires (Groenvold et al., 1997). Examples of these possible biases include selective reporting bias, when patients would not report pain if they believed it did not originate from cancer, and demand characteristics, which posits that cues in the research setting can affect patient responses. The latter phenomenon could be more problematic and pronounced in open-label trials (Orne, 1969).

Although these generic questionnaires provide a useful overall assessment despite aforementioned caveats, they may not address some specific symptoms associated with new melanoma treatments, such as rash and pruritus, which can substantially impact patients’ HRQoL. Use of the FACT-M instrument may help clinicians focus on HRQoL issues specific to this patient population and overcome some of the limitations of generic assessments. Acknowledging the differences in the two most commonly used HRQoL assessment tools, QLQ-C30 and FACT-M, Luckett et al. (2011) have proposed a useful algorithm for choosing between them, depending upon what aspects of QoL (specific symptoms or emotional state and social support system) a given study focuses on.

Apart from measurement tools, patients’ cultural backgrounds can also influence their perception of QoL. For example, Schwarz and Hinz (2001) reported that the QLQ-C30 global health perception score (where a higher score means perception of better health) was slightly higher in randomly selected Norwegian adults compared with Germans, but the scores for constipation and diarrhea were three times higher (where a higher score means more bothersome symptoms) in Norwegians compared with Germans (Hjermstad, Fayers, Bjordal, & Kaasa, 1998). Such discrepancies might complicate interpretation and clinical application of results from multicenter trials.

6 | CONCLUSION

Despite the limiting factors discussed herein, we see more widespread inclusion of HRQoL as an outcome measure in melanoma clinical trials and a shift in the paradigm toward an increasing role for patient-reported wellness perception. The results of the reviewed trials showed that the observed survival improvement with anti-PD-1 immune checkpoint inhibitor monotherapy, as well as with BRAF and MEK inhibitors over chemotherapy, is associated with patient HRQoL benefit. Multiple trials showed consistent HRQoL advantages of combination BRAF and MEK inhibitors over BRAF inhibitor monotherapy in patients with BRAF V600 mutations. Although in some studies, we observed an association between patients’ global health perception and the burden of treatment-related adverse events, as a subjective matter, the HRQoL outcomes remain hard to measure. Researchers will need to focus on finding a unified pattern for reporting clinically meaningful HRQoL data. Providing raw scores from questionnaires and including patients in HRQoL analysis who discontinued therapy due to toxicity would be important steps in this endeavor.

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Weber, J. S., Flaherty, K. T., Infante, J. R., Falchook, G. S., Keeford, R. F., Daud, A., ... Sosman, J. A. (2012). Updated safety and efficacy results from a phase I/II study of the oral BRAF inhibitor dabrafenib (GSK2118436) combined with the oral MEK 1/2 inhibitor trametinib (GSK1120212) in patients with BRAFi-naive metastatic melanoma. *Journal of Clinical Oncology*, 30, 8510.

Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management*, 13, 63–74.

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