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Quality-of-life methodology in hormone receptor–positive advanced breast cancer: Current tools and perspectives for the future

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ABSTRACT

Health-related quality of life (HRQOL) is increasingly recognized as important when evaluating cancer treatments. The use, reporting, and analysis of patient-reported outcome measures (PROMs), however, are not standardized in clinical trials and are often poorly implemented in clinical practice. We report the results of a systematic literature review (PubMed search: January 1, 2000 to August 15, 2020) of PROM use, reporting, and analysis in phase 3 clinical trials of hormone receptor–positive (HR+) advanced breast cancer (ABC). Further inspection of cyclin-dependent kinase 4/6 (CDK4/6) inhibitor publications was performed to examine PROMs in the HR+/human epidermal growth factor receptor 2–negative setting. A total of 88 results were identified in the initial search; 32 were included in the final analysis. Among included studies, most (66%) had been published in the last 5 years (2015 to 2020). CDK4/6 inhibitors (38%) were the most common agents reported. No clear standard for PROM use, reporting, or analysis was found. The most common PROMs were European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; 59%) and the Functional Assessment of Cancer Therapy–Breast (FACT-B; 34%). Important differences, among studies that reported them, ranged from 5 to 10 points for the EORTC QLQ-C30 and 8 points for the FACT-B total score. This review showed that a lack of clear consistency remains for PROM use, reporting, and analysis in phase 3 clinical trials of HR+ ABC. However, HRQOL is of high interest in the literature, including for CDK4/6 inhibitors.

Introduction

There is currently no cure for advanced breast cancer [1–3]. The primary goals of patient care are to prolong survival, minimize disease symptoms, and maximize health-related quality of life (HRQOL) [2]. Given the severity of the disease and potential toxicity associated with treatment, assessment of patient-reported HRQOL is gaining importance as a treatment goal in clinical trials of cancer drugs and is accepted by the US Food and Drug Administration and European Medicines Agency as an outcome to be considered in addition to efficacy endpoints during the drug evaluation process [4–7]. In addition, the Centers for Medicare & Medicaid Services and the National Quality Forum have developed initiatives to advocate for the implementation of quality measurements and patient-centered, value-based care in an effort to facilitate the improvement of patient care and provider accountability [8,9].

In a clinical trial setting, HRQOL is typically measured via the use of patient-reported outcome measures (PROMs) and directly reflects the patients' own perception, with no interpretation of patient response from any outside party (e.g., treating physician) [6,10]. While several established PROMs are available for evaluating HRQOL in clinical trials, many challenges persist. Attrition due to death, treatment discontinuation, or study discontinuation (because of disease progression or poor

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treatment response) commonly halts the collection of HRQOL data and affects the ability to detect changes in HRQOL over time [10,11]. This poses challenges of how to best address missing data as well as determining the most appropriate statistical methods required for suitable analysis. Inappropriate use of PROMs for a specific patient population, disease status, or treatment and inconsistent reporting of methods across studies also make it challenging to produce robust stand-alone data [11]. Specific tools to evaluate HRQOL in the advanced/metastatic setting, which inevitably should include assessment of the impact of having an incurable disease that requires ongoing treatment, do not currently exist. It is often desirable to devote particular attention to certain symptoms and/or side effects that have a great impact on the overall HRQOL in specific treatment contexts. For example, one might wish to focus on symptoms found to be important to patients with advanced breast cancer (e.g., diarrhea, fatigue) instead of focusing on the overall HRQOL score on questionnaires such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status (GHS) score or Functional Assessment of Cancer Therapy–Breast (FACT-B) total score [12].

Timing of HRQOL reporting should also be considered in clinical trials. Some adverse events may occur at specific times during treatment, which may affect HRQOL in a time-dependent manner. Effective treatments may also have a positive psychological impact associated with favorable disease control; however, some metrics may not account for the prolonged time period during which patients maintain HRQOL during treatment [13,14]. Additionally, the impact of treatment on endpoints that are important to patients, including time to subsequent treatment (particularly chemotherapy), are not captured in many HRQOL analyses.

Most breast cancers are hormone receptor positive (HR+; ≈75%); of these, ≈85% are human epidermal growth factor receptor 2–negative (HER2−), making HR+/HER2− the most prevalent subtype of breast cancer in both the early and the metastatic setting [15–17]. Patients with HR+/HER2− breast cancer have a number of treatment options and a relatively long survival after diagnosis of advanced disease [3,17,18]. Therefore, the impact of the disease and treatment on patients' symptoms and functioning is vital. Three cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (ribociclib, palbociclib, and abemaciclib) have been approved for the treatment of advanced HR+/HER2− breast cancer based on progression-free survival (PFS) efficacy results and have been recommended by multiple guidelines as standard of care for the first- or second-line treatment of patients with HR+/HER2− advanced breast cancer [1,3,19–21]. These drugs exhibit a consistent PFS benefit; however, overall survival and pre-clinical activity results are variable [22–27]. It will be important to understand the differences in PROM use, reporting, and analysis and outcomes for this class of agents in order to ensure the accuracy of health technology assessments; recent advancements (i.e., European Society of Medical Oncology–Magnitude of Clinical Benefit Scale [ESMO-MCBS]) are incorporating HRQOL data into the assessment of approved and investigational therapies [3,28].

To address these issues, a systematic review of literature on HRQOL methodology including usage, reporting, and analysis in patients with advanced HR+ breast cancer from phase 3 randomized controlled trials published in the last 2 decades was conducted. An analysis was then performed on CDK4/6 inhibitor studies (the most common class in the review) to examine usage, reporting, analysis, and outcomes in HR+/HER2− advanced breast cancer.

Methods

PubMed was searched using key words between January 1, 2000 and August 15, 2020. Studies were included in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Search terms were designed to include clinical trials with specific populations (patients with HR+ advanced breast cancer), interventions (phase 3 randomized controlled trials), and outcomes (HRQOL) (**Supplemental Table 1**). If a study included both patients with HR+ and HR− disease, it was included in the analysis only if > 50% of the population had the HR+ disease. Studies published in languages other than English were excluded.

All studies were screened for eligibility, and relevant data were extracted for qualitative synthesis. Data on population characteristics (e.g., location, demographic characteristics, sample size), interventions (e.g., treatment regimens), and outcomes (e.g., PROM data) from the included studies were extracted into a database. Relevant primary reports and clinicaltrials.gov were also searched for any missing data. Collection of data included items listed in the CONSORT-PRO extension (P1b, P2b, P6a, P12a, P20/P21) [29]. Two independent reviewers scored each study for risk of bias using the Cochrane ROB 2.0 tool (**Supplemental Table 2**) [30]. Any discrepancies were adjudicated by a third reviewer.

Results

Study selection and data extraction

In total, 88 records were identified based on the pre-specified search dates and search terms (Fig. 1). Of these, 56 did not meet the eligibility criteria. The most common reasons for exclusion were studies not reporting a phase 3 clinical trial (24/88 [27%]) and not including HRQOL data (16/88 [18%]). Overall, 32 studies were included in the final qualitative synthesis (Table 1).

Study and population characteristics

The most common class of drugs in this analysis was CDK4/6 inhibitors (12/32 [38%]) followed by endocrine therapy (6/32 [19%]) and chemotherapy (6/32 [19%]). Although the search period was from the years 2000 to 2020 within the PubMed database, 21 of 32 (66%) of the studies were published from 2015 to 2020 (Table 2). All 12 CDK4/6 inhibitor studies were published during this period (Table 3). Among the studies in the overall analysis, 15 of 32 (47%) published HRQOL data within the primary publication of the study; the remaining 17 of 32 (53%) were secondary publications. Among CDK4/6 inhibitor studies, 1 of 12 (8%) published HRQOL results within the primary publication.

The most common molecular subtype was HR+/HER2− (15/32 [47%]). Most studies focused on post-menopausal patients (15/32 [47%]) or included both pre- and post-menopausal patients (8/32 [25%]). One (3%) study focused exclusively on pre-menopausal patients. This trend was also observed in the CDK4/6 inhibitor studies: 6 of 12 (50%) post-menopausal, 5 of 12 (42%) pre- and post-menopausal, and 1 of 12 (8%) pre-menopausal patients (MONALEESA-7) [31,32].

PROM methodology and usage

Most studies did not define a PROM analysis population (19/32 [59%] overall, 7/12 [58%] for CDK4/6 inhibitor studies). For those that did, the most common was patients with baseline and ≥ 1 post-baseline PROM assessment (7/32 [22%] overall, 4/12 [33%] for CDK4/6 inhibitor studies). No study reported all items of the CONSORT-PRO extension. Most studies did not identify PROs in the abstract as a primary or secondary outcome (21/32 [66%]; P1b), did not state a PRO hypothesis (26/32 [81%]; P2b), did not discuss the validity and reliability of the PRO used (25/32 [78%]; P6a), did not report the use of any methods for dealing with missing data (28/32 [88%]; P12a), did not discuss PRO-specific limitations (24/32 [75%]; P20), and did not discuss clinical relevance for practice (23/32 [72%]; P21). Four studies (4/32 [13%]) analyzed the association of treatment efficacy with HRQOL by reporting PROM scores for patients who progressed vs those who did not or for responders vs non-responders [32–35]. Risk of bias assessment suggested a low risk of bias in 3 of 32 (9%), some concerns in 9 of 32 (28%), and a high risk of bias in 20 of 32 (63%) studies.

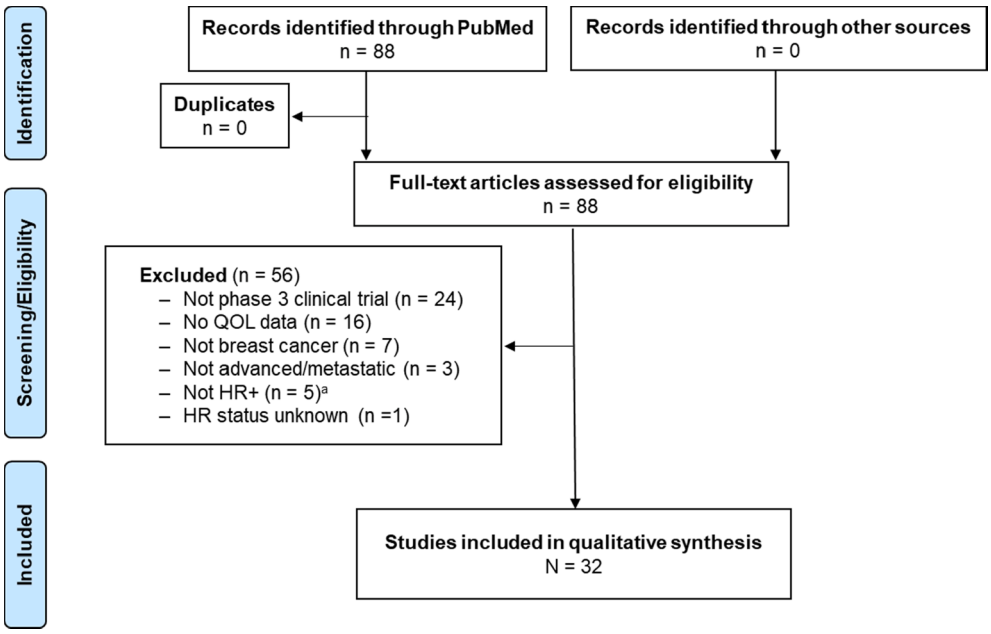

Fig. 1. PRISMA flow diagram. [a] Studies were excluded if the percentage of patients with the HR+ subtype was < 50%. HR, hormone receptor; QOL, quality of life.

The most common PROM used was the EORTC QLQ-C30 (19/32 [59%]) (Fig. 2). A breast cancer–specific PROM was used in 17 studies: FACT-B in 11 of 32 (34%) and the 23-item EORTC Quality of Life Questionnaire–Breast Cancer (QLQ-BR23) in 6 of 32 (19%). The use of multiple PROMs in the same study was common (11/32 [45%]), and the most common combination was the EORTC QLQ-C30 and EORTC QLQ-BR23 (6/32 [19%]). Similar trends were observed among CDK4/6 inhibitor studies: 9 of 12 (75%) used the EORTC QLQ-C30, and breast cancer–specific PROMs were used in 8 of 12 (67%) studies (FACT-B: 4/12 [33%]; EORTC QLQ-BR23: 4/12 [33%]; Fig. 3).

Important difference in PROM scores

Overall, 10 of 32 (31%) studies reported using an important difference (ID; i.e., smallest change in the PROM figure that patients perceive as important or that may prompt a change in clinical management). Among those studies that used the EORTC QLQ-C30, the IDs used were 10 points (3 studies), 5 points (1 study), and 5 to 10 points (1 study). Among these, 2 of 5 studies specified that the ID applied to all EORTC QLQ-C30 scales, and 3 of 5 studies did not specify which scales the ID applied to. Among studies that used the FACT-B, the IDs were 8 points (2 studies), 3 points (1 study), and 7 to 8 points (1 study). Among these, 2 studies stated that the ID specifically applied to the FACT-B total score (both 8 points), and 2 did not specify which FACT-B (e.g., total, subscale) scores the ID applied to. Among the CDK4/6 inhibitor studies that used the EORTC QLQ-C30, the most common ID was 10 points (2 studies)—both specified that the ID applied to all scales.

PROM reporting, analysis, and outcomes

Most studies that used the EORTC QLQ-C30 or FACT-B reported the GHS (18/19 [95%]) or the FACT-B total score (9/11 [82%]) (**Supplemental Table 3**). Studies that used the FACT-B but did not report the FACT-B total score reported the Trial Output Index (TOI; 2 studies; none specified the ID for the TOI score). There was no common consensus on other reported scale/subscale scores. Methods of reporting PROM scores also varied—change from baseline, mean score through time, and time to deterioration were all reported.

CDK4/6 inhibitor PROM results

All CDK4/6 inhibitor studies reported either the GHS or FACT-B total score (9 studies reported the GHS, and 4 reported the FACT-B total score [1 study reported the GHS and FACT-B, each used in a different trial]). Almost all CDK4/6 inhibitor studies reported that the GHS or FACT-B total score was similar to (no significant difference) or was significantly improved vs placebo. This trend was also observed in scale/subscale scores as well. One study reported a GHS score (difference in change from baseline) that significantly favored the placebo arm over the treatment arm (abemaciclib, MONARCH 3 trial); however, the difference did not meet the pre-defined ID (10 points) [36]. This was also observed for several EORTC QLQ-C30 scores (differences in change from baseline), which significantly favored the placebo arm over the treatment arm (abemaciclib, MONARCH 3 trial: fatigue, nausea/vomiting, diarrhea, appetite loss, and role functioning; abemaciclib, MONARCH 2 trial: nausea/vomiting, diarrhea, appetite loss), and for several EORTC QLQ-BR23 scores (abemaciclib, MONARCH 3 trial: body image, systemic therapy side effects; abemaciclib, MONARCH 2 trial: systemic therapy side effects) [25,36]. None of these differences vs placebo exceeded the pre-defined ID (10 points) except for diarrhea, which exceed it in both studies (MONARCH 2, MONARCH 3). Three CDK4/6 inhibitor studies analyzed the association of treatment efficacy with HRQOL; 1 reported that responders to palbociclib had a delayed time to deterioration of $\geq$ 7 points in FACT-B total score compared with non-responders [34]. Two studies reported that patients treated with ribociclib who did not have a PFS event had a delayed time to deterioration $\geq$ 10% in EORTC QLQ-C30 GHS compared with those who did [32,33].

Discussion

This systematic review of PROMs in phase 3 clinical trials of HR+ advanced breast cancer surveyed publications in PubMed from the years 2000 to 2020. A relative increase in publications reporting HRQOL in recent years was found. Most studies reported HRQOL outcomes in secondary rather than primary publications. Consistent with previous reviews that have analyzed PROM methodology, most studies did not report the PROM analysis population, and most did not report methods for handling missing data [37,38]. Additionally, no study included all of the items of the CONSORT-PRO extension, and many were assessed to

Table 1
Summary of included studies.

Study	Sample size, randomized (N)	Pre-/post-menopausal	PROMs used	Disease-specific PROM (Yes/No)	ID	Risk of bias assessment
Outcomes in Clinically Relevant Patient Subgroups From the EMBRACA Study: Talazoparib vs Physician's Choice Standard-of-Care Chemotherapy Rugo HS, 2020 [54]	432	Not specified	EORTC QLQ-C30, EORTC QLQ-BR23	Yes	Not specified	Some
Health-Related Quality of Life in MONARCH 3: Abemaciclib Plus an Aromatase Inhibitor as Initial Therapy in HR+, HER2− Advanced Breast Cancer Goetz MP, 2020 [36]	493	Post-menopausal	EORTC QLQ-C30, EORTC QLQ-BR23	Yes	EORTC QLQ-C30, EORTC QLQ-BR23: 10 points	Some
Health-Related Quality of Life in MONARCH 2: Abemaciclib Plus Fulvestrant in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer After Endocrine Therapy Kaufman PA, 2020 [25]	669	Pre- and post-menopausal	EORTC QLQ-C30, EORTC QLQ-BR23, BPI-SF	Yes	EORTC QLQ-C30, EORTC QLQ-BR23: 10 points	Some
Health-Related Quality of Life in Premenopausal Women With Hormone-Receptor-Positive, HER2-Negative Advanced Breast Cancer Treated With Ribociclib Plus Endocrine Therapy: Results From a Phase III Randomized Clinical Trial (MONALEESA-7) Harbeck N, 2020 [32]	672	Pre-menopausal	EORTC QLQ-C30	No	Not specified	High
Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial Saura C, 2020 [55]	621	Not specified	EORTC QLQ-C30	No	EORTC QLQ-C30: 10 points	High
Palbociclib Plus Letrozole as First-Line Therapy in Postmenopausal Asian Women With Metastatic Breast Cancer: Results From the Phase III, Randomized PALOMA-2 Study Im SA, 2019 [23]	95	Post-menopausal	FACT-B, FACT-G, EQ-5D	Yes	Not specified	Some
Randomized Open Label Phase III Trial of Irinotecan Plus Capecitabine Versus Capecitabine Monotherapy in Patients With Metastatic Breast Cancer Previously Treated With Anthracycline and Taxane: PROCEED Trial (KCSG BR 11–01) Park IH, 2019 [56]	221	Pre- and post-menopausal	EORTC QLQ-C30	No	Not specified	High
Palbociclib Plus Letrozole as First-Line Therapy in Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer With Extended Follow-Up Rugo HS, 2019 [57]	666	Post-menopausal	FACT-B, FACT-G, TOI	Yes	Not specified	Some
Efficacy and Safety of Everolimus Plus Exemestane in Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Locally Advanced or Metastatic Breast Cancer: Results of the Single-Arm, Phase IIIB 4EVER Trial Tesch H, 2019 [58]	299	Post-menopausal	EORTC QLQ-C30	No	Not specified	High
First-Line Ribociclib Plus Letrozole in Postmenopausal Women With HR+, HER2− Advanced Breast Cancer: Tumor Response and Pain Reduction in the Phase 3 MONALEESA-2 Trial Janni W, 2018 [59]	668	Post-menopausal	EORTC QLQ-C30	No	EORTC QLQ-C30: 5 points	Low
Health-Related Quality of Life of Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer Treated With Ribociclib + Letrozole: Results From MONALEESA-2 Verma S, 2018 [33]	668	Post-menopausal	EORTC QLQ-C30, EORTC QLQ-BR23	Yes	EORTC QLQ-C30: 5–10 points	Low
Health-Related Quality of Life From the FALCON Phase III Randomised Trial of Fulvestrant 500 mg Versus Anastrozole for Hormone Receptor-Positive Advanced Breast Cancer Robertson JFR, 2018 [60]	462	Post-menopausal	FACT-B, TOI	Yes	FACT-B total score: 8 points; FACT-B TOI: 6 points	Some
Impact of Palbociclib Plus Letrozole on Patient-Reported Health-Related Quality of Life: Results From the PALOMA-2 Trial Rugo HS, 2018 [34]	666	Post-menopausal	FACT-B, FACT-G, TOI, EQ-5D	Yes	FACT-B: 7–8 points; FACT-G: 5–6 points	Some
Clinical Considerations of the Role of Palbociclib in the Management of Advanced Breast Cancer Patients With and Without Visceral Metastases Turner NC, 2018 [24]	1187	Pre- and post-menopausal	PALOMA-2: FACT-B; PALOMA-3:	Yes	Not specified	High

(continued on next page)

Table 1 (*continued*)

Study	Sample size, randomized (N)	Pre-/post-menopausal	PROMs used	Disease-specific PROM (Yes/No)	ID	Risk of bias assessment
	PALOMA-2: 666, PALOMA-3: 521		EORTC QLQ-C30			
Do All Patients With Advanced HER2 Positive Breast Cancer Need Upfront-Chemo When Receiving Trastuzumab? Randomized Phase III Trial SAKK 22/99 Pagani O, 2017 [61]	173	Not specified	GLQ-8	Yes	Not specified	High
PALOMA-3: Phase III Trial of Fulvestrant With or Without Palbociclib in Premenopausal and Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That Progressed on Prior Endocrine Therapy—Safety and Efficacy in Asian Patients Iwata H, 2017 [62]	105	Pre- and post-menopausal	EORTC QLQ-C30	No	Not specified	Low
Efficacy and Safety of Low-Dose Capecitabine Plus Docetaxel Versus Single-Agent Docetaxel in Patients With Anthracycline-Pretreated HER2-Negative Metastatic Breast Cancer: Results From the Randomized Phase III JO21095 Trial Yamamoto D, 2017 [63]	163	Not specified	EORTC QLQ-C30	No	Not specified	High
Quality of Life With Palbociclib Plus Fulvestrant in Previously Treated Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer: Patient-Reported Outcomes From the PALOMA-3 Trial Harbeck N, 2016 [64]	521	Pre- and post-menopausal	EORTC QLQ-C30, EORTC QLQ-BR23	Yes	Not specified	Some
Final Results of the TANIA Randomised Phase III Trial of Bevacizumab After Progression on First-Line Bevacizumab Therapy for HER2-Negative Locally Recurrent/Metastatic Breast Cancer Vrdoljak E, 2016 [65]	494	Not specified	FACT-B, FACT-G, TOI	Yes	FACT-B, FACT-G, TOI: 3 points	High
Phase III Open-Label Randomized Study of Eribulin Mesylate Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated With an Anthracycline and a Taxane Kaufman PA, 2015 [66]	1102	Not specified	EORTC QLQ-C30	No	Not specified	Some
Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer Turner NC, 2015 [67]	521	Pre- and post-menopausal	EORTC QLQ-C30	No	Not specified	High
Efficacy of Everolimus With Exemestane Versus Exemestane Alone in Asian Patients With HER2-Negative, Hormone-Receptor-Positive Breast Cancer in BOLERO-2 Noguchi S, 2014 [68]	724	Post-menopausal	EORTC QLQ-C30	No	Not specified	High
AVEREL: a Randomized Phase III Trial Evaluating Bevacizumab in Combination With Docetaxel and Trastuzumab as First-Line Therapy for HER2-Positive Locally Recurrent/ Metastatic Breast Cancer Gianni L, 2013 [69]	424	Not specified	FACT-B	Yes	Not specified	High
Capecitabine Plus Paclitaxel Versus Epirubicin Plus Paclitaxel as First-Line Treatment for Metastatic Breast Cancer: Efficacy and Safety Results of a Randomized, Phase III Trial by the AGO Breast Cancer Study Group Lück HJ, 2013 [70]	340	Not specified	EORTC QLQ-C30, EORTC QLQ-BR23	Yes	Not specified	High
Bone-Related Complications and Quality of Life in Advanced Breast Cancer: Results From a Randomized Phase III Trial of Denosumab Versus Zoledronic Acid Martin M, 2012 [71]	2046	Pre- and post-menopausal	FACT-G, BPI-SF	No	FACT-G: 5 points	High
Quality of Life in Hormone Receptor–Positive HER-2+ Metastatic Breast Cancer Patients During Treatment With Letrozole Alone or in Combination With Lapatinib Sherrill B, 2010 [35]	219	Post-menopausal	FACT-B, FACT-G, TOI	Yes	FACT-B total score: 8 points; FACT-G, TOI: 6 points	High
Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer Di Leo A, 2010 [72]	736	Post-menopausal	FACT-B, TOI	Yes	Not specified	High
Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFECT Chia S, 2008 [73]	693	Post-menopausal	FACT-ES, TOI	No	Not specified	High
Randomized Phase III Study of Docetaxel Compared With Paclitaxel in Metastatic Breast Cancer Jones SE, 2005 [74]	449	Pre- and post-menopausal	FACT-B	Yes	Not specified	High
	451		FACT-B, TOI	Yes	Not specified	High

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size, randomized (N)	Pre-/post-menopausal	PROMs used	Disease-specific PROM (Yes/No)	ID	Risk of bias assessment
Fulvestrant, Formerly ICI 182780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment Howell A, 2002 [75]		Post-menopausal				
Phase III, Multicenter, Double-Blind, Randomized Study of Letrozole, an Aromatase Inhibitor, for Advanced Breast Cancer Versus Megestrol Acetate Buzdar A, 2001 [76]	602	Post-menopausal	EORTC QLQ-C30	No	Not specified	High
Exemestane Improves Survival in Metastatic Breast Cancer: Results of a Phase III Randomized Study Kaufmann M, 2000 [77]	769	Post-menopausal	EORTC QLQ-C30	No	Not specified	High

BPI-SF, Brief Pain Inventory–Short Form; EORTC QLQ-BR23, 23-item EORTC Quality of Life Questionnaire–Breast Cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, European Quality of Life 5 Dimensions; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-ES, Functional Assessment of Cancer Therapy–Endocrine Symptoms; FACT-G, Functional Assessment of Cancer Therapy–General; GLQ, Global Life Quality; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ID, important difference; PROM, patient-reported outcome measure; TOI, Trial Output Index.

Table 2
Study trends.

	Number of studies, n (%)
Primary publication	
Yes	15 (47)
No	17 (53)
PROM/QOL as endpoint	
Secondary	29 (91)
Exploratory	2 (6)
Unknown	1 (3)
Pre-/post-menopausal	
Post	15 (47)
Pre and post	8 (25)
Pre/peri	1 (3)
Not specified	8 (25)
HR+/HER2−	
All HR+/HER2−	15 (47)
HR+: 100%; HER2 status not reported	2 (6)
HR+: > 50% to < 100%; HER2−: 100%	3 (9)
HR+: > 50% to < 100%; HER2−: < 100%	3 (9)
HR+: > 50% to < 100%; HER2 status not reported	5 (16)
All HR+/HER2+	1 (3)
HR+: > 50% to < 100%; HER2+: 100%	3 (9)
Disease-specific PROMs	
Yes	17 (53)
No	15 (47)
Publication year	
2020	5 (16)
2019	4 (13)
2018	5 (16)
2017	3 (9)
2016	2 (6)
2015	2 (6)
2014	1 (3)
2013	2 (6)
2012	1 (3)
2011	0
2010	2 (6)
2009	0
2008	1 (3)
2007	0
2006	0
2005	1 (3)
2004	0
2003	0
2002	1 (3)
2001	1 (3)
2000	1 (3)

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PROM, patient-reported outcome measure; QOL, quality of life.

Table 3
QOL reporting in CDK4/6 inhibitor studies.

CDK4/6 inhibitor	Study	Publication	PROMs used
Palbociclib	PALOMA-2	Rugo HS (2019)	FACT-B, FACT-G, TOI
Palbociclib	PALOMA-2 (Asian patients)	Im SA (2019)	FACT-B, FACT-G, EQ-5D
Palbociclib	PALOMA-2	Rugo HS (2018)	FACT-B, FACT-G, TOI, EQ-5D
Palbociclib	PALOMA-2 and PALOMA-3	Turner NC (2018)	PALMOA-2: FACT-B PALOMA-3: EORTC QLQ-C30
Palbociclib	PALOMA-3 (Asian patients)	Iwata H (2017)	EORTC QLQ-C30
Palbociclib	PALOMA-3	Harbeck N (2016)	EORTC QLQ-C30, EORTC QLQ-BR23
Palbociclib	PALOMA-3	Turner NC (2015)	EORTC QLQ-C30
Ribociclib	MONALEESA-7	Harbeck (2020)	EORTC QLQ-C30
Ribociclib	MONALEESA-2	Janni W (2018)	EORTC QLQ-C30
Ribociclib	MONALEESA-2	Verma S (2018)	EORTC QLQ-C30, EORTC QLQ-BR23
Abemaciclib	MONARCH 3	Goetz MP (2020)	EORTC QLQ-C30, EORTC QLQ-BR23, BPI-SF
Abemaciclib	MONARCH 2	Kaufman PA (2020)	EORTC QLQ-C30, EORTC QLQ-BR23, BPI-SF

BPI-SF, Brief Pain Inventory–Short Form; CDK4/6, cyclin-dependent kinase 4/6; EORTC QLQ-BR23, 23-item EORTC Quality of Life Questionnaire–Breast Cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, European Quality of Life 5 Dimensions; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; PROM, patient-reported outcome measure; TOI, Trial Output Index.

have a high risk of bias via the Cochrane ROB 2.0 tool.

IDs are important for defining changes in PROM scores that patients perceive as important. In this analysis, there was no clear consensus on ID use; this lack of ID consensus has also been observed in a prior review of the literature [39]. For studies that used the EORTC QLQ-C30, the IDs were defined as 5, 10, and 5 to 10 points. Typically, this was based on

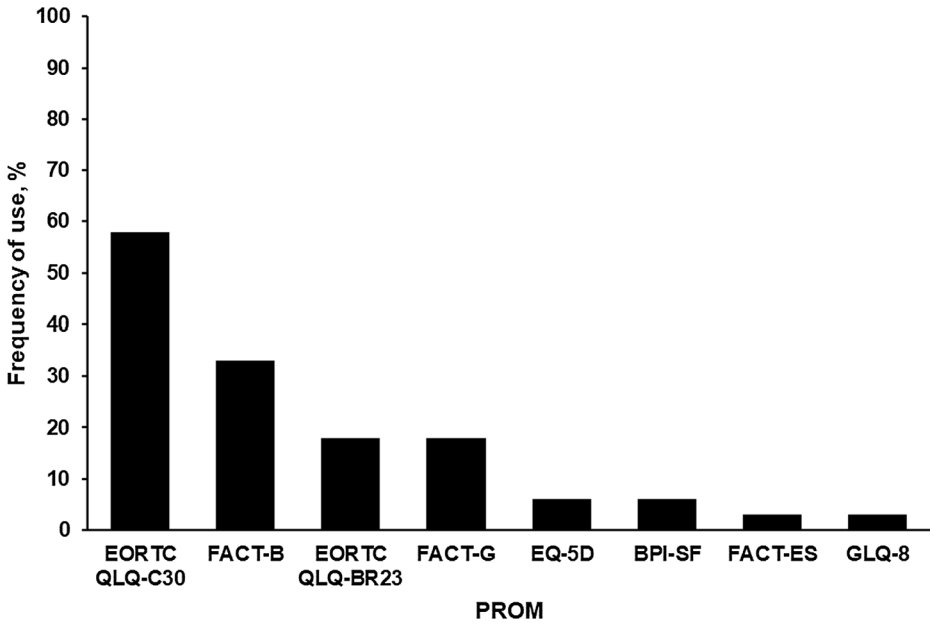

Fig. 2. PROM frequency of use. BPI-SF, Brief Pain Inventory–Short Form; EORTC QLQ-BR23, 23-item EORTC Quality of Life Questionnaire–Breast Cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, European Quality of Life 5 Dimensions; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-ES, Functional Assessment of Cancer Therapy–Endocrine Symptoms; FACT-G, Functional Assessment of Cancer Therapy–General; GLQ, Global Life Quality; PROM, patient-reported outcome measures.

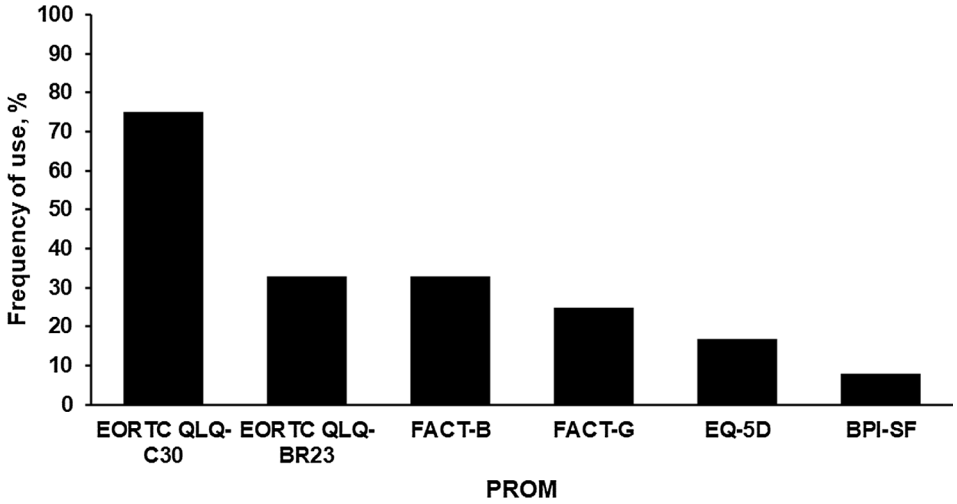

Fig. 3. PROM frequency of use in CDK4/6 inhibitor trials. BPI-SF, Brief Pain Inventory–Short Form; EORTC QLQ-BR23, 23-item EORTC Quality of Life Questionnaire–Breast Cancer; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, European Quality of Life 5 Dimensions; FACT-B, Functional Assessment of Cancer Therapy–Breast; FACT-G, Functional Assessment of Cancer Therapy–General; PROM, patient-reported outcome measure.

data from Osoba et al. (1998), which determined 5 to 10 points as the lowest for a perceived change in the EORTC QLQ-C30 among patients with breast cancer or small cell lung cancer [40]. This threshold has subsequently been used in many clinical trials [39,41]. However, estimates that utilize anchor and distribution methods have been developed to determine IDs, with some demonstrating that IDs can vary depending on scale and direction (improvement/deterioration) [41–43]. Future publications may take these more recent estimates into account when analyzing clinical trial outcomes.

Understanding the association of treatment efficacy and HRQOL remains an unmet need, as only 4 studies considered treatment efficacy (response, PFS) in the HRQOL analysis. It is expected that progression of disease may be associated with deterioration of HRQOL, at least because of its negative psychological impact. If that would be the case, then a relationship between higher therapeutic efficacy (including tumor response and length of progression-free and overall survival) and HRQOL improvement (including the length of maintained or improved HRQOL) should be seen. However, this is not proven, especially for a disease such as advanced breast cancer, in which progression of the disease is not always associated with worsening of symptoms [44,45]. Further research in this area is crucial, and the physical and psychological consequences of disease progression should be captured in newly developed HRQOL tools.

Additionally, other aspects of treatment outcomes that are valuable to the patient, including occurrence of first subsequent treatment (particularly if that treatment is chemotherapy), were not incorporated in the analyses reviewed. No studies used the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which has the potential to give insight into patient-reported assessments of adverse events reported in clinical trials [46]. Furthermore, in clinical trial reporting, all adverse events are “treated alike” but the impact of each adverse event on HRQOL and the ability to perform daily and professional activities are substantially different (i.e., diarrhea vs alopecia) and are also variable among individuals.

Consistent with prior reports, there was no clear consensus for PROM use, reporting, or analysis [37,38]. The most common PROMs used were the EORTC QLQ-C30 and FACT-B. There are multiple differences between these PROMs, and selection may ultimately depend on several factors including desired outcomes of interest [47]. The EORTC QLQ and FACT-B have been used to evaluate HRQOL in patients with advanced

breast cancer; however, while the development of these PROMs included patients with advanced disease, they were not developed specifically for *advanced* breast cancer. To address this, the FACT-B has been shortened and modified to address concerns specific to advanced breast cancer, referred to as the NCCN-FACT-Breast Symptom Index-16 (NFBSI-16) [12,48]. However, we found no examples of the use of this 16-item instrument in our review. Future studies may benefit from customization based on issues faced in advanced breast cancer, HR status, specific drug classes and their expected toxicity profile (e.g., endocrine therapy, targeted therapy, chemotherapy), patient characteristics (e.g., pre- vs post-menopausal, age, tolerability profile, HRQOL status at baseline), and the development of flexible approaches (e.g., using a combination of global scores from a PROM with functional, disease, and treatment-specific symptoms from item libraries). Uniformity in data collection and analysis can also be improved [11,49]. Indeed, there have been efforts to characterize PROM use, reporting, and analysis and establish recommended standards for cancer clinical trials [26,37,49,50].

CDK4/6 inhibitors were the most common agent class in this review; therefore, HRQOL methodology and outcomes for these specific studies were analyzed. Many of the trends observed for the overall analysis were also observed for CDK4/6 inhibitors. Although all of the CDK4/6 inhibitor studies reported an "overall" score, whether it was the EORTC QLQ-C30 GHS or the FACT-B total score, no clear consistency was found with the PROMs used, scales/subscales reported, or analyses. Among the scores reported, CDK4/6 inhibitor treatment arms were either similar (no significant difference) or were significantly improved compared with their respective placebo arms. In addition, some data indicated that patients who responded to palbociclib or maintained PFS on ribociclib had a better HRQOL compared with those who did not [32–34]. These data provided reassuring suggestions that the use of CDK4/6 inhibitors does not worsen HRQOL when compared with placebo (endocrine therapy) alone. Some exceptions were noted; the GHS (difference in change from baseline) from MONARCH 3 and several scores from MONARCH 2/MONARCH 3 (fatigue, nausea/vomiting, diarrhea, appetite loss, role functioning, body image, systemic therapy side effects) significantly favored placebo over abemaciclib. Importantly, these did not exceed the pre-defined ID—except for diarrhea [25,36].

The ESMO-MCBS v1.1 is a validated and reproducible tool that uses a rational, structured, and consistent approach to assess the magnitude of clinical benefit and rank cancer therapies [28]. ESMO-MCBS assessments include the use of HRQOL data to rank treatments. Recently, updates to ESMO-MCBS rankings for advanced breast cancer treatments were published, including those for CDK4/6 inhibitors [3]. The assessment determined that 2 CDK4/6 inhibitors improve HRQOL in patients with advanced breast cancer: ribociclib + endocrine therapy in the first-line setting (pre-menopausal; score 5/5) and palbociclib + fulvestrant in the second-line setting (score 4/5) [3]. HRQOL data are being continually published and updated for CDK4/6 inhibitors, and more guidance for incorporating HRQOL into assessments will be addressed in future versions of the ESMO-MCBS [28,51].

This systematic review has some limitations. First, this study focused specifically on phase 3 clinical trial studies and did not include phase 1 or 2 studies, real-world evidence registries, or studies that have been published in other sources (including conference abstracts). Only HR+ breast cancer was included, thereby excluding studies reporting on HR− breast cancer, most notably the triple-negative subtype. However, the results were generally consistent with those of other systematic reviews that included HR− studies [37,38]. Finally, this review focused only on advanced breast cancer and may not be applicable to all stages of breast cancer—symptoms, treatments, expectations, and goals for patients with advanced breast cancer are usually not the same as those for patients with earlier stages of breast cancer.

This systematic review showed that patterns of use, reporting, and analysis of PROMs remain inconsistent in phase 3 clinical trials in patients with HR+ advanced breast cancer. It also showed that HRQOL is a strong area of focus, including among CDK4/6 inhibitors. Improved standards for PROM reporting in clinical trials and improved means (including digital tools) for assessing HRQOL are being developed and trialed in phase 1 [49,52,53]. Notably, with the support of the Advanced Breast Cancer Global Alliance, the EORTC Breast and Quality for Life Groups are developing a specific HRQOL assessment tool for metastatic/advanced breast cancer. Similar to prior efforts with the NFBSI-16 and item libraries such as those available from the EORTC, FACIT, and PRO-CTCAE, these improvements may equip patients and physicians with sharper tools with which to work collaboratively and make optimal treatment decisions.

Declaration of Competing Interest

FC reports payment to the institution for the clinical trials and personal fees for advisory roles for Amgen, AstraZeneca, Astellas/Medivation, Celgene, Daiichi Sankyo, Eisai, GE Oncology, Genentech, GSK, Macrogenics, Medscape, MSD, Merus, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, Prime Oncology, Roche, Sanofi, Samsung Bioepis, Teva, and Seagen outside of the submitted work. DC reports personal fees from AbbVie, Astellas, BMS, Dompe, Merck, Novartis, Pfizer, Mei Pharma, and FACIT.org, outside the submitted work, and research funding to his institution from AbbVie, Astellas, BMS, Merck, Novartis, Pfizer, and the US National Institutes of Health, outside the submitted work. GV reports personal fees from Roche, Eisai, and Novartis and grants from Breast Cancer Now, EORTC, Yorkshire Cancer Research, and Pfizer outside of the submitted work. VH has nothing to report. ES-W has nothing to report. JR has nothing to report. AC has nothing to report. NH reports receiving investigator fees from Novartis for MONALEESA-7 to institution and receiving personal fees for honoraria for consulting and lectures from AstraZeneca, Novartis, Lilly, and Pfizer.

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Appendix A. Supplementary data

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