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ORIGINAL ARTICLE

Patient-reported outcomes in the SERENA-6 trial of camizestrant plus CDK4/6 inhibitor in patients with advanced breast cancer and emergent *ESR1* mutations during first-line endocrine-based therapy☆

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Background: In SERENA-6, switching from aromatase inhibitor (AI) to camizestrant with continuation of CDK4/6 inhibitor (CDK4/6i) guided by emergence of *ESR1* mutations (*ESR1*-mut) during first-line AI-CDK4/6i in patients with hormone receptor (HR)-positive advanced breast cancer (ABC) resulted in statistically significant and clinically meaningful improvement in progression-free survival compared with AI-CDK4/6i and reduction in the risk of deterioration in global health status (GHS)/quality of life (QoL) (hazard ratio 0.54). Here we report additional data from patient-reported outcomes (PROs).

Patients and methods: Patients completed PRO questionnaires at pre-specified timepoints, including the European Organisation for Research and Treatment of Cancer (EORTC) oncology-specific EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and breast cancer-specific (QLQ-BR23) and Patient Global Impression of Treatment Tolerability (PGI-TT). All PRO endpoints and analyses were pre-defined, including secondary endpoints of time to deterioration (TTD) in pain, physical functioning, breast symptoms and arm symptoms.

Results: EORTC QLQ-C30 and EORTC QLQ-BR23 baseline scores were similar between treatment arms. Switching to camizestrant-CDK4/6i delayed TTD and reduced the risk of deterioration in patient-reported cancer symptoms [pain (hazard ratio 0.57, 95% confidence interval 0.37-0.86), fatigue (0.75, 0.46-1.24), shortness of breath/dyspnoea (0.52, 0.28-0.93), breast symptoms (0.59, 0.28-1.24) and arm symptoms (0.69, 0.34-1.39)] and functioning [physical (0.74, 0.44-1.24), role (0.73, 0.48-1.10) and emotional (0.51, 0.29-0.87)] compared with AI-CDK4/6i. Most patients reported they were 'not at all' or 'a little bit' bothered by the side effects of cancer therapy across timepoints (e.g. week 2: 86% camizestrant-CDK4/6i versus 82% AI-CDK4/6i).

Conclusions: Together with the clinical efficacy and manageable safety profile of camizestrant-CDK4/6i, and reduced risk of GHS/QoL deterioration, the PROs from the SERENA-6 trial support switching to this combination as a potential new treatment strategy to optimise and improve outcomes in patients with HR-positive/HER2-negative ABC and *ESR1*-mut emergence, ahead of disease progression, during first-line AI-CDK4/6i.

Key words: patient-reported outcomes, quality of life, camizestrant, hormone receptor-positive advanced breast cancer, emergent *ESR1* mutations

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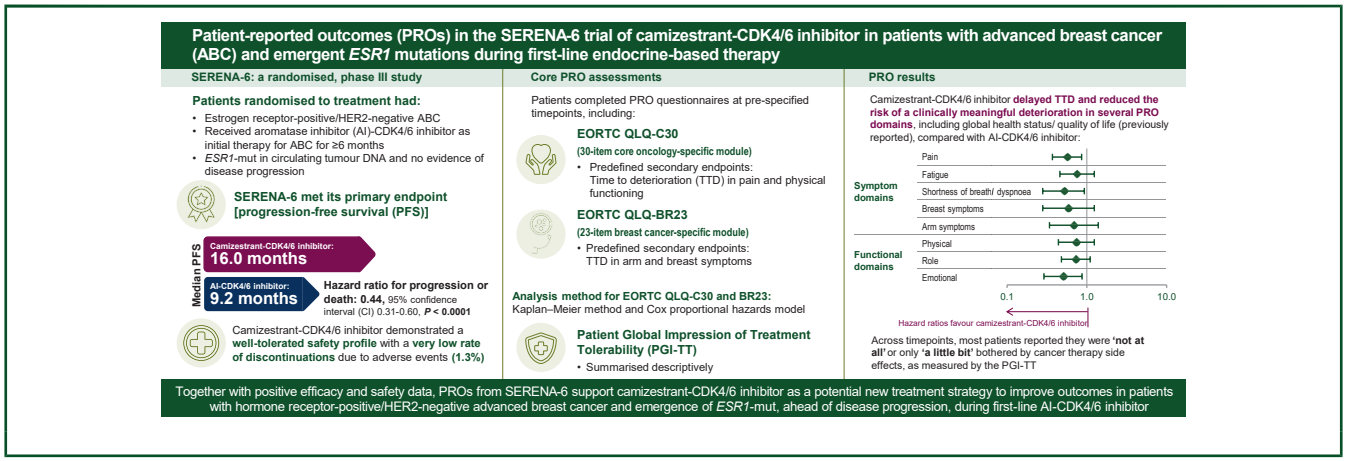
INTRODUCTION

The current first-line standard of care for patients with hormone receptor (HR)-positive/human epidermal growth factor receptor (HER2)-negative advanced breast cancer (ABC) is treatment with an aromatase inhibitor (AI)

GRAPHICAL ABSTRACT



combined with a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor.[1-3] *ESR1* mutations (*ESR1*-mut), which lead to constitutive (estrogen-independent) activation of estrogen receptor (ER) alpha,[4] are rare at initial diagnosis of ABC but are the most common mechanism of acquired resistance to AI treatment and are detectable in ∼40% of patients at disease progression following first-line treatment with an AI plus a CDK4/6 inhibitor.[5-7] *ESR1*-mut can be detected in circulating tumour DNA (ctDNA) from blood samples before clinical progression on first-line AI-CDK4/6 inhibitor,[8,9] providing an early indication that the tumour is acquiring resistance to the AI.

Camizestrant, the next-generation oral selective ER degrader (SERD) and complete ER antagonist, was designed to have activity against *ESR1*-mut as well as wild-type ER. The phase III randomised, double-blind SERENA-6 trial was the first global registrational study to use serial ctDNA monitoring in breast cancer to identify the emergence of an acquired resistance mutation, in this case *ESR1*-mut, before progression and direct a change in therapy.[10] SERENA-6 demonstrated that switching from an AI to camizestrant with continued CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib) in the first-line setting, guided by the emergence of *ESR1*-mut in ctDNA, and ahead of clinical or radiological progression, resulted in a statistically significant and clinically meaningful improvement in progression-free survival compared with continuation of AI-CDK4/6 inhibitor [median 16.0 months versus 9.2 months; hazard ratio 0.44, 95% confidence interval (CI) 0.31-0.60, stratified log-rank test $P < 0.0001$].[10] Camizestrant demonstrated a well-tolerated safety profile with a very low rate of discontinuations due to adverse events (1.3%).[10]

The importance of patient-reported outcomes (PROs) in clinical trials is widely recognised, especially in oncology, where treatments have the potential to have a major effect on patients' daily functioning and well-being. As such, the United States Food and Drug Administration (FDA) recommends that clinical trials in oncology collect the core PROs of disease-related symptoms, symptomatic adverse events, overall impact of side effects, and physical and role function.[11] PROs are also important to help clinicians understand patients' lived experiences and may be particularly relevant for patients, as well as clinicians, when making important decisions about switching treatments, as is the case in SERENA-6, where detection of an *ESR1*-mut was used to guide treatment. PROs also complement clinician-reported adverse event data as patient-reported data are provided without interpretation by clinicians or other health care providers.

As previously reported, patients who switched to camizestrant in SERENA-6 had a longer time until a deterioration in their global health status and quality of life (GHS/QoL), as measured by the European Organisation for Research and Treatment of Cancer (EORTC) oncology-specific EORTC Quality of Life Questionnaire Core 30 (QLQ-C30), than those who continued to receive an AI (21.0 months versus 6.4 months; hazard ratio 0.54, 95% CI 0.34-0.84).[10] Here, we report detailed PRO results from SERENA-6, including assessments of breast cancer symptoms, functional domains and the patients' global impression of treatment tolerability.

METHODS

Study design and patients

SERENA-6 is a phase III, randomised, double-blind, placebo-controlled study that assessed the safety and efficacy of switching from an AI to camizestrant with continuation of CDK4/6 inhibitor during first-line therapy at emergence of *ESR1*-mut but ahead of disease progression (NCT04964934). The SERENA-6 study design, primary efficacy and safety results have been previously reported.[10] Patients who had received at least 6 months of treatment with a first-line AI-CDK4/6 inhibitor for metastatic disease entered surveillance and were tested for *ESR1*-mut in ctDNA every 2 to 3 months (Guardant360 CDx, Guardant Health, Palo Alto, CA), coinciding with routine clinical assessment. Patients with *ESR1*-mut and no evidence of radiologic or clinical disease

progression according to investigator assessment, and who met other eligibility criteria, were randomised in a 1 : 1 ratio to continue to receive AI-CDK4/6 inhibitor with matching camizestrant placebo or to switch to camizestrant (75 mg once daily)-CDK4/6 inhibitor (same type and dose) with matching AI placebo. The study was conducted in accordance with the Declaration of Helsinki and the applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice guidelines. All patients gave informed consent before enrolment. The study protocol, amendments, and other relevant documents were reviewed by an Institutional Review Board and an independent Ethics Committee.

PRO measures and assessment

Patients who were randomised to treatment were required to complete all PRO questionnaires at home or in the clinic if the time of assessment coincided with a scheduled visit. All questionnaires were completed on an electronic device only by the patient; proxy-reported patient outcomes were not allowed. A summary of PRO assessments reported here is provided in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.006 (data cut-off: 28 November 2024).

Patient-reported symptoms, functioning, and health related QoL were assessed using the EORTC QLQ-C30[12] and EORTC Quality of Life Questionnaire breast cancer module (QLQ-BR23)[13] questionnaires. The EORTC QLQ-C30[12] is a 30-item questionnaire that comprises a two-item GHS/QoL scale as well as five functional domains (physical, role, cognitive, emotional and social), three symptom domains (fatigue, pain and nausea and vomiting), and five individual item symptom scores (shortness of breath/dyspnoea, insomnia, appetite loss, constipation and diarrhoea). The EORTC QLQ-BR23[13] is a validated 23-item breast cancer-specific module of the EORTC QLQ-C30 and comprises four functional domains (body image, sexual functioning, sexual enjoyment and future perspective) and four symptom domains (systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss). Patients completed the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires at baseline (on day 1 of cycle 1), every 4 weeks for the first 12 weeks, and every 8 weeks thereafter until second progression. Assessment of PROs was more frequent than tumour assessments, which were carried out every 8 weeks for the first 18 months, and then every 12 weeks until disease progression. Patients who discontinued treatment due to reasons other than progression completed the EORTC QLQ-C30 and EORTC QLQ-BR23 at the time of treatment discontinuation until the first progression event on subsequent therapy.

Treatment-related symptoms and tolerability were assessed using the Patient Global Impression of Treatment Tolerability (PGI-TT) questionnaire. The PGI-TT is a single-item questionnaire that assesses how a patient perceives the overall tolerability of study treatment by responding to the question, 'In the last 7 days, how bothered were you by the side effects of your cancer treatment?' with provided response options 'not at all', 'a little bit', 'somewhat', 'quite a bit', or 'very much'. Patients completed the PGI-TT at baseline, weekly for the first 12 weeks, and every 8 weeks thereafter until treatment discontinuation, and at treatment discontinuation.

Other PRO measures collected in this study but not reported here included the Patient Global Impression of Change[14] and the Patient Global Impression of Severity,[14] used for determination of meaningful change thresholds, and the European Quality of Life 5 Dimensions 5-Level Version,[15] Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events,[16] the Visual Symptom Assessment Questionnaire and the National Eye Institute 25-Item Visual Function Questionnaire.

PRO endpoints

Time to deterioration (TTD) in pain and physical functioning, evaluated using the EORTC QLQ-C30 questionnaire, and breast and arm symptoms, evaluated using the EORTC QLQ-BR23 questionnaire, were pre-defined secondary endpoints. Evaluation of TTD in the remaining EORTC QLQ-C30 and EORTC QLQ-BR23 domains was a pre-defined exploratory endpoint, as was the change from baseline in all EORTC QLQ-C30 and EORTC QLQ-BR23 domains and the PGI-TT.

Statistical analysis

Patient-reported endpoints were not part of the multiple testing procedure for the SERENA-6 study and were not powered or type I error-controlled for statistical comparison. As such, no formal claims of statistical significance can be made for these endpoints and no formal hypotheses were tested.

PRO adherence was calculated for each timepoint and was defined as the number of patients who received a questionnaire divided by the total number of patients expected to complete the questionnaire at that timepoint.

EORTC QLQ-C30 and EORTC QLQ-BR23 final scores for all domains were converted to a 0-100 scale, per EORTC scoring guidelines. For GHS/QoL and functional domains, higher scores correspond to a better level of functioning and QoL, whereas for symptom domains, higher scores correspond to worse symptoms.

TTD was analysed in all randomised patients who had a baseline score that would allow deterioration and at least one assessable assessment after baseline assessment. TTD was defined as the time from randomisation until the first clinically meaningful deterioration in EORTC QLQ-C30 or EORTC QLQ-BR23 scores that was confirmed at a subsequent timepoint after the initial deterioration, regardless of whether the patient discontinues study treatment or receives another anticancer therapy before the deterioration. Patients with a single deterioration and no further assessments were treated as deteriorated in the analysis. If a patient did not have a deterioration event by data cut-off, the TTD was censored at the date of the last evaluation.

Patients whose EORTC QLQ-C30 or EORTC QLQ-BR23 scores had not shown a deterioration at the time of the analysis, including patients who had died without deterioration, were censored at the time of their last PRO assessment. Meaningful change thresholds for EORTC QLQ-C30 GHS/QoL, functional (physical, role, emotional, cognitive, social) and symptom (pain and fatigue) scores, as well as EORTC QLQ-BR23 arm and breast symptom scores, were determined based on pre-specified analyses and have been described previously.[17] Patient Global Impression of Change, Patient Global Impression of Severity, and the EORTC QLQ-C30 item 29 (overall health) were used as anchors in the calculation of meaningful change thresholds. The within-participant threshold for deterioration was estimated as −16.6 points for GHS/QoL, role, emotional, cognitive and social functioning, +16.6 points for pain and breast symptoms, +22.2 points for fatigue and arm symptoms, and −13.3 points for physical functioning.[17] TTD for each domain was described using the Kaplan—Meier method and analysed using a Cox proportional hazards model to calculate hazard ratios and 95% CIs, which was adjusted by stratification factors at randomisation that had been subject to a pre-specified pooling strategy and included baseline value as a covariate. In addition to the pre-specified analysis of TTD in EORTC QLQ-C30 and EORTC QLQ-BR23 scores using study-specific meaningful change thresholds, a *post hoc* sensitivity analysis was also conducted using a 10-point meaningful change threshold.[18,19]

Change from baseline in EORTC QLQ-C30 and EORTC QLQ-BR23 on-treatment scores was analysed using a mixed model for repeated measures (MMRM) for all timepoints after baseline up to week 28, where at least 20 subjects in a treatment arm had a score. The MMRM model included treatment, timepoint and treatment by timepoint interaction as categorical variables, and the baseline score and baseline score by timepoints interaction as covariates. An unstructured covariance matrix was used to model the within-patient error, and the Kenward—Roger approximation was used to estimate the degrees of freedom.

PGI-TT was analysed in patients who had received at least one dose of any trial treatment. As an exploratory endpoint, PGI-TT responses were summarised descriptively, and data are presented for all timepoints at which at least 20 patients in either treatment arm had an assessment.

RESULTS

Patient characteristics

The SERENA-6 study enrolled patients between June 2021 and June 2024 and randomised 315 patients with emergent *ESR1*-mut during first-line therapy and no evidence of disease progression to switch to camizestrant-CDK4/6 inhibitor (157 patients) or to continue receiving AI-CDK4/6 inhibitor (158 patients); 155 patients in each group received study treatment. Baseline and disease characteristics of the overall study population have been previously published and showed that patient characteristics were well balanced between treatment arms at baseline.[10] Patient characteristics of those who completed at least one item on the EORTC QLQ-C30 at baseline, as well as patients included in the TTD analyses of EORTC QLQ-C30 GHS/QoL, were comparable with those in the overall population (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.006). Mean baseline scores on the EORTC QLQ-C30 and EORTC QLQ-BR23 were similar between treatment arms across all domains (Table 1).

Adherence to questionnaire completion

Overall, 211 patients (n = 111 camizestrant-CDK4/6 inhibitor; n = 100 AI-CDK4/6 inhibitor) completed at least one EORTC QLQ-C30 domain at baseline (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.10.006). Adherence to questionnaire completion for all three questionnaires were broadly consistent and similar between treatment arms over the first year of the study (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.10.006). The study centres did not provide reasons for missing questionnaires at baseline for

Table 1. Mean baseline scores of EORTC QLQ-C30 and EORTC QLQ-BR23 domains

Mean (standard deviation)	Camizestrant-CDK4/6 inhibitor	AI-CDK4/6 inhibitor
EORTC QLQ-C30 QoL	n = 110	n = 100
GHS/QoL	70.5 (17.3)	72.8 (20.8)
EORTC QLQ-C30 functional domain	n = 111	n = 100
Physical	80.5 (18.3)	79.7 (18.7)
Role	84.1 (20.3)	80.7 (22.7)
Cognitive	84.1 (18.5)[a]	87.2 (16.0)
Emotional	76.7 (19.5)[a]	80.6 (19.7)
Social	84.2 (21.4)[a]	84.8 (20.3)
EORTC QLQ-C30 symptom domain	n = 111	n = 100
Fatigue	30.0 (21.1)	30.3 (23.8)
Pain	24.2 (22.7)	22.0 (23.0)
Nausea and vomiting	6.6 (17.2)	4.2 (12.2)
Shortness of breath/ dyspnoea	16.5 (22.9)	11.7 (20.3)
Insomnia	25.2 (25.9)	25.0 (30.5)
Appetite loss	11.4 (20.3)	10.7 (19.5)
Constipation	12.6 (27.4)	13.7 (23.3)
Diarrhoea	9.4 (20.8)[a]	8.0 (17.8)
EORTC QLQ-BR23 functional domain	n = 107	n = 96
Body image	76.1 (27.3)	78.4 (25.0)
Sexual functioning	89.9 (15.5)	87.5 (19.6)
Sexual enjoyment[b]	57.1 (23.8)	45.7 (30.9)
Future perspective	54.5 (31.5)	58.0 (30.7)
EORTC QLQ-BR23 symptom domain	n = 107	n = 96
Systemic therapy side effects	18.1 (15.0)	16.6 (14.4)
Breast symptoms	10.1 (13.1)[c]	8.3 (13.2)
Arm symptoms	17.7 (19.7)[c]	14.0 (20.4)
Upset by hair loss[d]	35.7 (28.1)	37.3 (30.5)

EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23, EORTC Quality of Life Questionnaire breast cancer module; EORTC QLQ-C30, EORTC Quality of Life Questionnaire 30-item core module; GHS, global health status; QoL, quality of life.
[a] n = 110.
[b] n = 28 for camizestrant-CDK4/6 inhibitor and n = 27 for AI-CDK4/6 inhibitor.
[c] n = 106.
[d] n = 57 for camizestrant-CDK4/6 inhibitor and n = 42 for AI-CDK4/6 inhibitor.

the EORTC QLQ-C30 and EORTC QLQ-BR23; however, across time, where data were available, the most common reasons for missing questionnaires were due to technical problems with the device or the patient forgetting to complete the questionnaire.

Time to deterioration in GHS/QoL

Of the 211 patients who completed at least one EORTC QLQ-C30 domain at baseline, 202 patients ($n = 107$ camizestrant-CDK4/6 inhibitor; $n = 95$ AI-CDK4/6 inhibitor) were analysed for TTD in EORTC QLQ-C30 GHS/QoL. Camizestrant-CDK4/6 inhibitor substantially reduced the risk of deterioration of GHS/QoL compared with AI-CDK4/6 inhibitor (median TTD 21.0 months, 95% CI 13.8 months-not calculated) versus 6.4 months (95% CI 2.8-14.0 months, hazard ratio 0.54, 95% CI 0.34-0.84) (Figure 1). The Kaplan–Meier curve shows early separation between treatment arms, with more patients in the AI-CDK4/6 inhibitor arm experiencing an early deterioration in GHS/QoL.

Time to deterioration in functioning and symptoms

TTD in pain and physical functioning (EORTC QLQ-C30) and breast and arm symptoms (EORTC QLQ-BR23) (pre-specified secondary endpoints) are shown in Figure 1, alongside role functioning, emotional functioning, and fatigue and shortness of breath/dyspnoea as evaluated by the EORTC QLQ-C30. Camizestrant-CDK4/6 inhibitor delayed TTD and reduced risk of deterioration in patient-reported physical (hazard ratio 0.74, 95% CI 0.44-1.24), role (hazard ratio 0.73, 95% CI 0.48-1.10) and emotional (hazard ratio 0.51, 95% CI 0.29-0.87) functioning compared with AI-CDK4/6 inhibitor (Figure 1A). Camizestrant-CDK4/6 inhibitor also delayed TTD and reduced risk of deterioration in patient-reported cancer symptoms of pain (hazard ratio 0.57, 95% CI 0.37-0.86), fatigue (hazard ratio 0.75, 95% CI 0.46-1.24), shortness of breath/dyspnoea (hazard ratio 0.52, 95% CI 0.28-0.93), breast symptoms (hazard ratio 0.59, 95% CI 0.28-1.24) and arm symptoms (hazard ratio 0.69, 95% CI 0.34-1.39) compared with AI-CDK4/6 inhibitor (Figure 1A). Hazard ratios for risk of deterioration in all EORTC QLQ-C30 domains are shown in Figure 2, and for EORTC QLQ-BR23 domains in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.10.006. Results from the *post hoc* sensitivity analysis of TTD using a 10-point meaningful change threshold were consistent with findings from the pre-specified analysis (Figure 2 and Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2025.10.006).

Mean change from baseline in EORTC QLQ-BR23 and EORTC QLQ-C30

EORTC QLQ-C30 GHS/QoL scores did not undergo a meaningful worsening from baseline in either treatment arm when using a custom −16.6 point meaningful change threshold or in a sensitivity analysis using a previously validated 10-point meaningful change threshold. EORTC QLQ-C30 GHS/QoL scores were numerically better in the camizestrant-CDK4/6 inhibitor arm compared with the AI-CDK4/6 inhibitor arm (overall least squares mean change from baseline to week 28 treatment difference: 4.33, 95% CI 0.31-8.35) (Figure 3). Mean change from baseline in pain and physical functioning showed numerical improvement in the camizestrant-CDK4/6 inhibitor arm compared with worsening in the AI-CDK4/6 inhibitor arm. All other EORTC QLQ-C30 and EORTC QLQ-BR23 domain scores did not undergo a meaningful worsening from baseline in either treatment arm when using a custom meaningful change threshold or in a sensitivity analysis using a previously validated 10-point meaningful change threshold. All other EORTC QLQ-C30 functional and symptom domains numerically favoured camizestrant-CDK4/6 inhibitor compared with AI-CDK4/6 inhibitor for all domains, except for diarrhoea, where there was minimal (−0.02) mean change from baseline in the camizestrant-CDK4/6 inhibitor arm compared with numerical improvement (−1.61) in AI-CDK4/6 inhibitor arm (Figure 3). Mean change from baseline in EORTC QLQ-BR23 domains was also comparable between treatment arms (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2025.10.006).

Patient assessment of overall tolerability

In both treatment arms, most patients who completed the PGI-TT reported that they were 'not at all' or 'a little bit' bothered by the side effects of their cancer treatment across all timepoints; >76% across all timepoints for camizestrant-CDK4/6 inhibitor and >72% across all timepoints for AI-CDK4/6 inhibitor and 86% and 82%, respectively, at week 2 (Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2025.10.006).

DISCUSSION

In this analysis of the randomised phase III SERENA-6 trial in patients with HR-positive/HER2-negative ABC switching to camizestrant while continuing CDK4/6 inhibitor at emergence of *ESR1*-mut during first-line AI-CDK4/6 inhibitor ahead of disease progression demonstrated consistent benefit in delaying TTD and reducing the risk of deterioration in patient-reported cancer symptoms (e.g. pain, fatigue, shortness of breath/dyspnoea) and functioning (e.g. physical, role, emotional), in addition to the delayed TTD and a reduced risk of deterioration in GHS/QoL reported previously.[10] Importantly, and consistent with the well-tolerated safety profile, most patients reported little or no bother from the side effects of either treatment, as measured by the PGI-TT. These PRO results complement the main clinical findings of SERENA-6 that showed a statistically significant and clinically meaningful increase in progression-free survival when switching from AI to camizestrant and a well-tolerated safety profile.[10]

Camizestrant-CDK4/6 inhibitor was associated with a substantial delay in TTD in pain, a pre-defined secondary endpoint, compared with AI-CDK4/6 inhibitor, as well as shortness of breath/dyspnoea, a symptom commonly reported at disease progression. Kaplan–Meier curves for TTD in pain mirrored those of TTD in GHS/QoL, with both

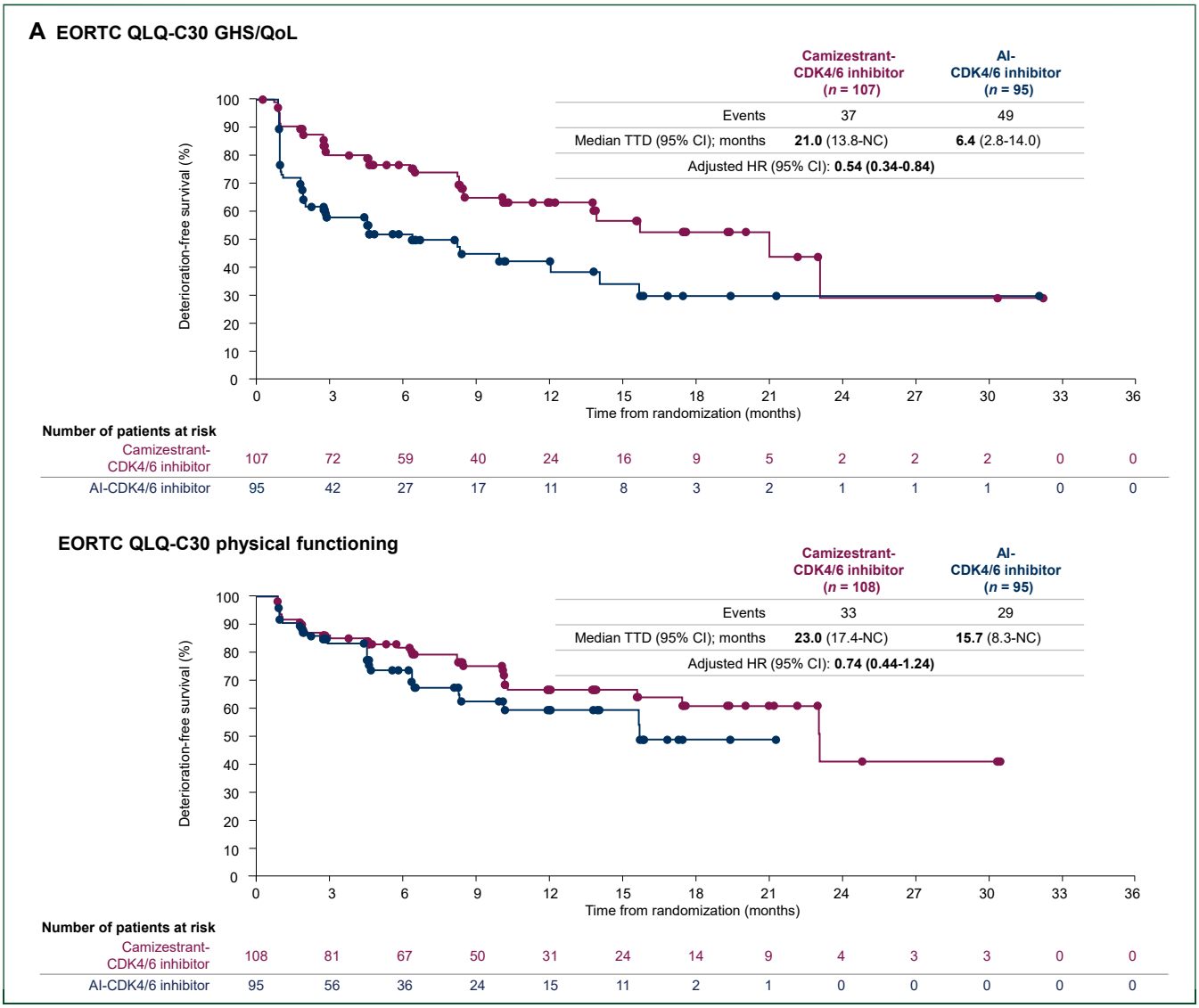


Figure 1. Time to deterioration in (A) GHS/QoL, physical, role, and emotional functioning and (B) selected symptom domains. The hazard ratio and the 95% confidence interval were estimated using a Cox proportional hazards model with stratification according to timing of the detection of an *ESR1* mutation (first test or subsequent test) and the time from the initiation of an aromatase inhibitor plus a CDK4/6 inhibitor until randomisation (<18 months or ≥18 months).
CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23, EORTC Quality of Life Questionnaire breast cancer module; EORTC QLQ-C30, EORTC Quality of Life Questionnaire 30-item core module; GHS, global health status; HR, hazard ratio; NC, not calculable; QoL, quality of life; TTD, time to deterioration.
(A) The EORTC QLQ-C30 figure is from *New Engl J Med*, Bidard FC, et al., 'First-Line Camizestrant for Emerging *ESR1*-Mutated Advanced Breast Cancer', Volume 393, Page No. 578, Copyright © 2025 Massachusetts Medical Society. Reprinted with permission.

endpoints showing a clear and early separation. TTD findings for pain and GHS/QoL are consistent with the progression-free survival analysis with early and continued separation of the treatment arms,[10] further supporting the benefit of switching endocrine therapy at emergence of *ESR1*-mut and ahead of clinical disease progression. Pain, a frequently reported symptom in patients with ABC that increases in frequency as disease progresses, requires special attention in ABC management.[20,21] Delaying deterioration in pain may be especially important in patients with *ESR1*-mut ABC, as these patients often present with bone metastases,[22,23] which can be associated with moderate to severe pain.[24]

In addition to delays in pain deterioration, another notable finding was that camizestrant-CDK4/6 inhibitor was also associated with a substantial delay in deterioration of emotional functioning, an exploratory endpoint, compared with AI-CDK4/6 inhibitor, which is not surprising given the association between emotional functioning and pain perception.[20,25] Delays in deterioration of physical functioning (a secondary endpoint) as well as other exploratory endpoints (fatigue, shortness of breath/dyspnoea and role functioning), with camizestrant-CDK4/6 inhibitor is also notable given previous research has shown that these areas should be prioritised when treating patients with metastatic breast cancer.[26]

Disease progression is known to be associated with patient distress and a worsening of patient-reported QoL in patients with ABC.[27-29] Although studies that have investigated the benefit of adding a CDK4/6 inhibitor to AI treatment in the first-line setting generally have not shown

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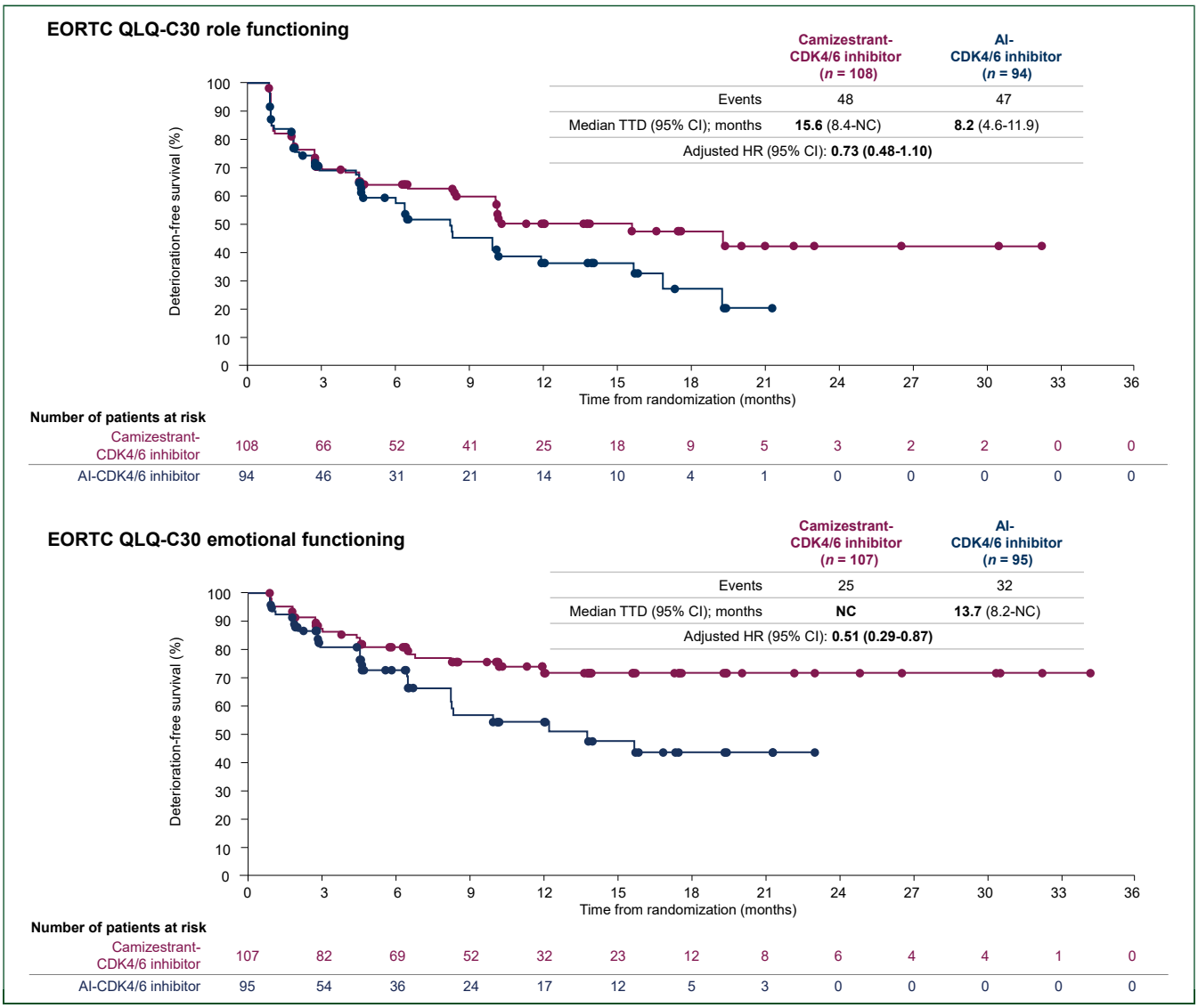

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a difference in QoL between treatment arms,[29-31] exploratory analyses have demonstrated the relationship between progression and overall QoL; deterioration in overall QoL was significantly delayed in patients without progression versus those with progression.[29,31] Our findings support the importance of delaying progression from the patient perspective. The switch to camizestrant with continuation of CDK4/6 inhibitor, before a patient experiences disease progression on AI-CDK4/6 inhibitor, significantly improved progression-free survival,[10] and meaningfully delayed TTD in patient-reported cancer symptoms, functioning, and overall GHS/QoL in the camizestrant-CDK4/6 inhibitor arm. As the patient-reported outcome assessment in SERENA-6 was ahead of the first radiological assessment after randomisation, the early and persistent separation of the Kaplan—Meier curves provides important insights from the patient perspective on the importance of switching to an effective treatment early. It is important to consider that although some patients may receive an oral SERD after progression on first-line AI-CDK4/6 inhibitor, others may no longer be candidates for subsequent endocrine therapy and may require treatment escalation to chemotherapy. As such, *ESR1*-mut monitoring during first-line therapy increases the ability of patients whose cancers develop an *ESR1*-mut to benefit from oral SERD therapy. Delaying the initiation of agents targeting *ESR1*-mut until clinical disease progression risks unnecessary worsening in QoL and pain, increased tumour burden and molecular heterogeneity, and an increasing likelihood that the patient will not be suitable for oral SERD therapy.

Consistent with the low treatment discontinuation rate due to adverse events with camizestrant-CDK4/6 inhibitor observed in primary analysis (1.3%),[10] most patients reported little or no bother from the side effects of camizestrant-CDK4/6 inhibitor, with comparable reports in patients receiving AI-CDK4/6 inhibitor. Taken together, PGI-TT responses, favourable results in patient-reported functioning and GHS/QoL collectively underscore the tolerability of camizestrant-CDK4/6 inhibitor. Indeed, the well-tolerated

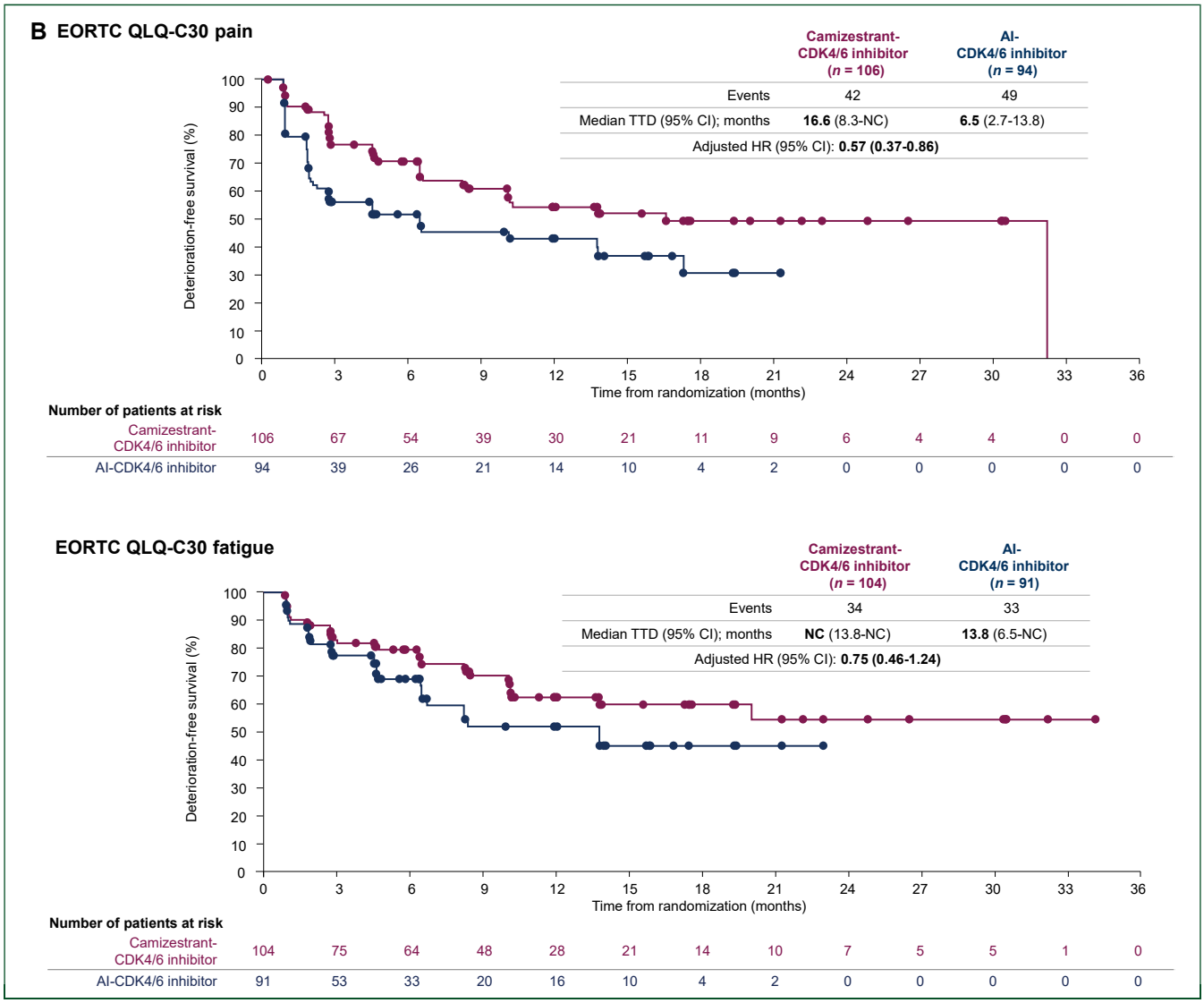

Figure 1. **Continued.**

safety profile may have contributed to the delayed TTD in GHS/QoL and other symptom/functional domains.

To our knowledge, SERENA-6 is the first randomised phase III trial in the first-line setting to compare a novel SERD-CDK4/6 inhibitor with an AI-CDK4/6 inhibitor and demonstrate a clinically meaningful delay in TTD in GHS/QoL. The concept of a molecularly-driven switch in endocrine therapy during first-line therapy to improve progression-free survival was initially demonstrated in the PADA-1 trial,[8] which did not include assessment of PROs as part of its design. The findings from SERENA-6 fill this evidence gap and show the benefits of switching extend to patient-reported GHS/QoL, symptoms and functioning.

A key strength of SERENA-6 is the double-blind placebo-controlled study design, which minimises the possibility of bias in patient-reported data from patients' expectations of possible benefits and harms after knowingly receiving a new treatment; the relatively balanced reporting of adverse events between treatment arms also reduces the chance of a patient guessing their treatment assignment. PRO measures included validated, multi-dimensional generic assessments (EORTC QLQ-C30) as well as a breast cancer-specific module (EORTC QLQ-BR23), alongside global patient assessment of overall tolerability (PGI-TT) to provide a comprehensive picture of patient-reported symptoms, functioning and health related QoL, with assessments completed early and at regular intervals in line with FDA guidance. Our pre-specified analyses of TTD used a robust, trial-specific meaningful change threshold for deterioration estimated from blinded study data and provides context-specific thresholds that may better reflect a meaningful change in the targeted patient population.[32] Consistent findings were also demonstrated in a *post hoc* sensitivity analysis where the meaningful change threshold was set to $\geq$10-points, a previously validated threshold[18,19] that has been used in many ABC trials,[29,33-39] adding further confidence in our findings. Exploratory analysis of mean change from baseline scores supports the findings from TTD

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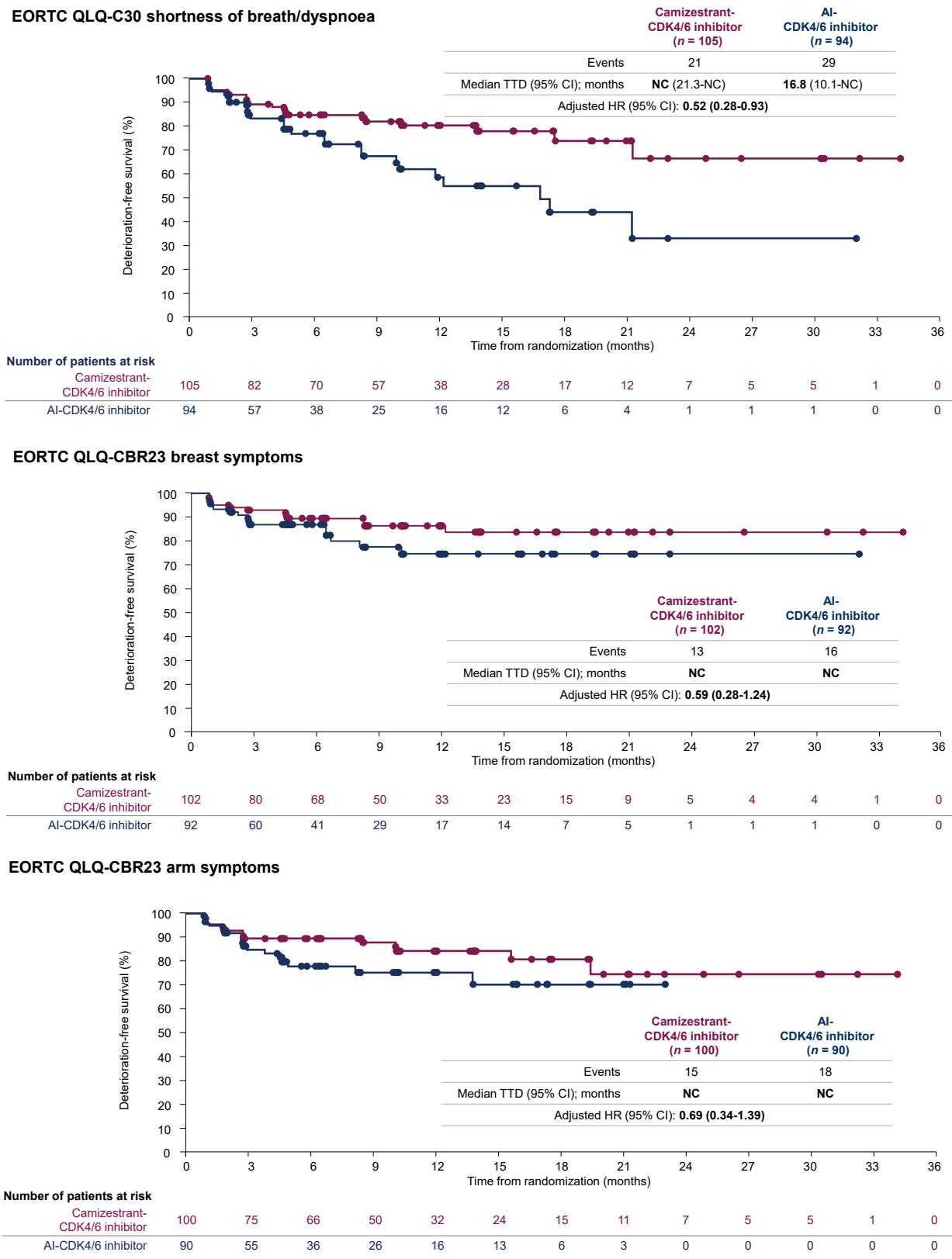

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analyses; mean change from baseline scores favoured camizestrant-CDK4/6 inhibitor over AI-CDK4/6 inhibitor in the majority of scales, although did not cross the threshold for meaningful worsening or improvement in either arm when using our study-specific thresholds, validated 10-point thresholds[18,19] or breast cancer-specific thresholds.[40] It should also be noted that we collected data from EORTC QLQ-C30 and QLQ-BR23 questionnaires until second progression to enable the

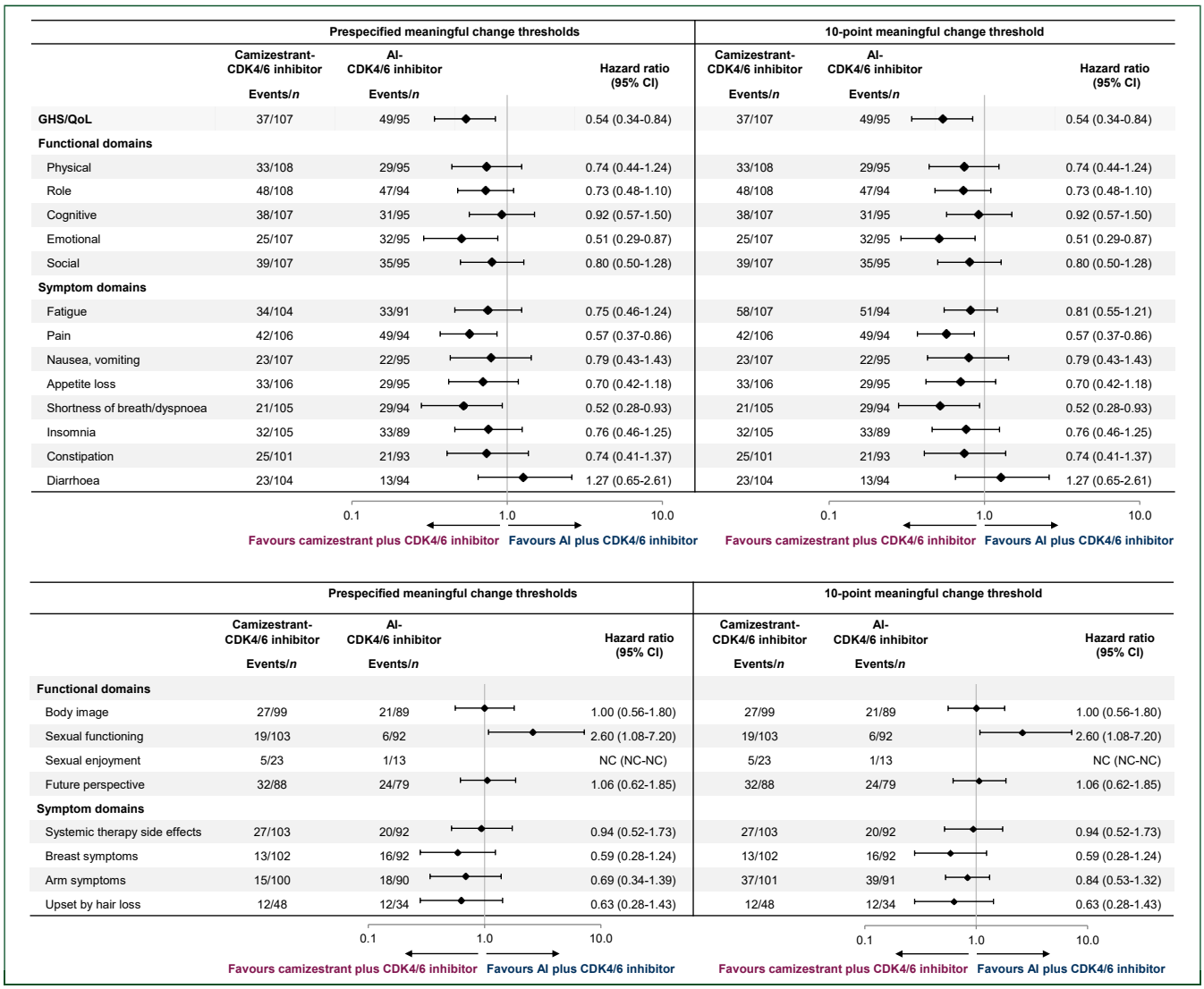

Figure 2. Time to deterioration in EORTC QLQ-C30 GHS/QoL, functional and symptoms domains.
AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30, EORTC Quality of Life Questionnaire 30-item core module; GHS, global health status; QoL, quality of life.

assessment of long-term effects of treatment on QoL. Mean baseline EORTC QLQ-C30 and EORTC QLQ-BR-23 scores in patients enrolled in SERENA-6 were generally representative of patients with metastatic breast cancer[41] and consistent with those published in other first-line trials of ET-CDK4/6 inhibitor.[29,42]

Rates of questionnaire adherence were ∼70%, which could be considered a limitation; however, they were broadly similar between treatment arms, remained relatively constant throughout treatment and were consistent with rates reported in other studies using electronic questionnaires.[43] *Post hoc* analysis of the baseline characteristics of patients who completed at least one item on the EORTC QLQ-C30 suggests that these patients were representative of the overall study population, providing confidence that missing PRO data is unlikely to have impacted study results. Available data demonstrate that technical difficulties and patient forgetfulness were the most common reasons for missing data and further support that missing data is unlikely to bias findings. Results reported here are from the first analysis of data from this study at an interim analysis; additional follow-up will provide further insight into the benefits of this treatment approach for patients.

In SERENA-6, switching from AI to camizestrant with continuation of CDK4/6 inhibitor guided by emergence of *ESR1*-mut during first-line AI-CDK4/6 inhibitor resulted in consistent benefit in delaying TTD and reducing the risk of deterioration in patient-reported cancer symptoms, functioning and GHS/QoL, in addition to statistically significant and clinically meaningful improvement in progression-free survival. Our findings further support this combination as a potential new treatment strategy to optimise and improve outcomes in patients with HR-positive/HER2-negative ABC and emergence of *ESR1*-mut, ahead of clinical disease progression, during first-line AI-CDK4/6 inhibitor treatment.

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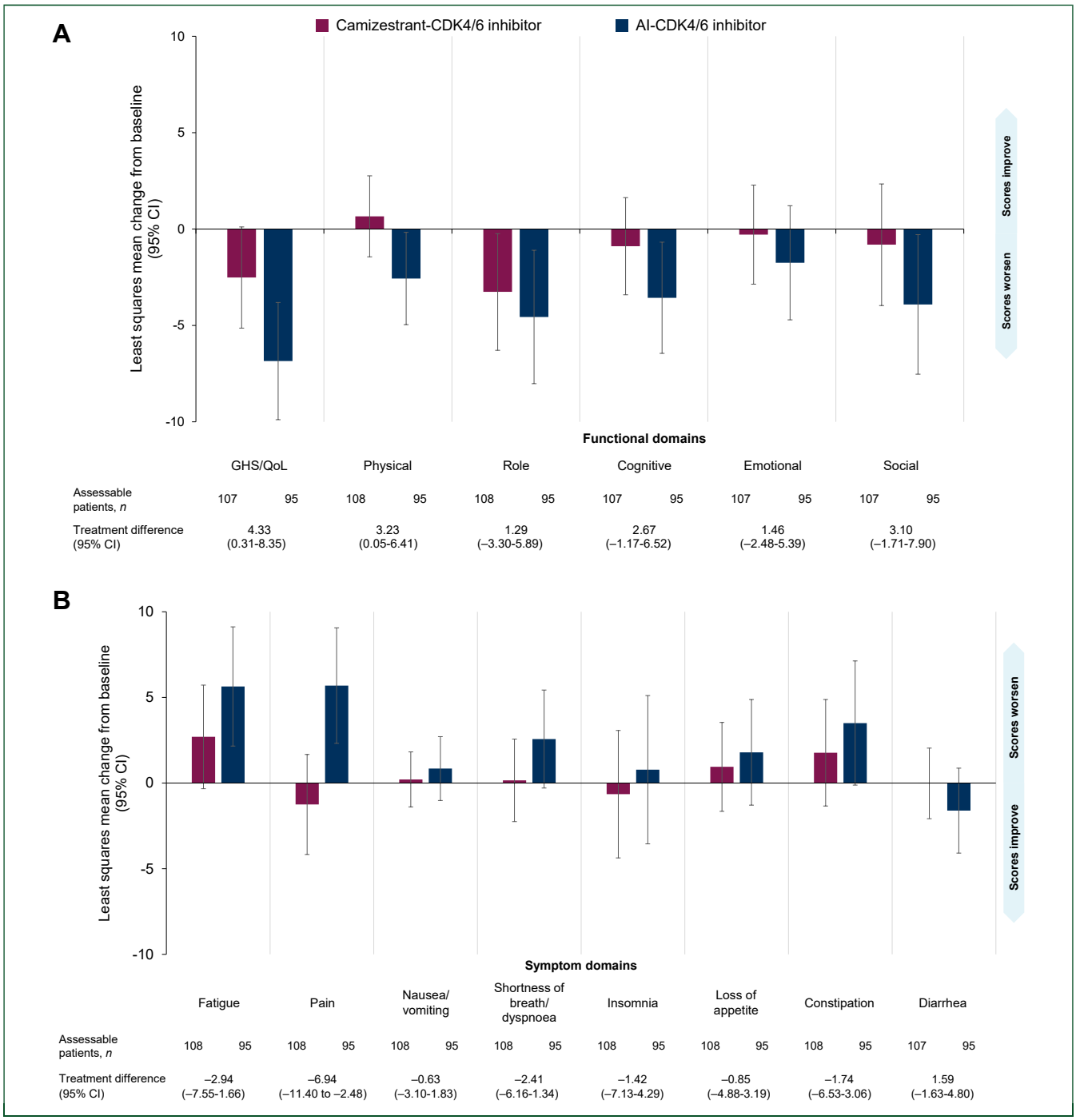

Figure 3. Overall least squares mean change from baseline in EORTC QLQ-C30 GHS/QoL, functional domains, (A) and symptom domains (B).
AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30, EORTC Quality of Life Questionnaire 30-item core module; GHS, global health status; QoL, quality of life.

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/.

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REFERENCES

1. Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, et al. 6th and 7th International consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *Breast*. 2024;76:103756.
2. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J Clin Oncol*. 2021;39(35):3959-3977.
3. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32(12):1475-1495.
4. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res*. 2021;23(1):85.
5. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246-3256.
6. Bhave MA, Quintanilha JCF, Tukachinsky H, et al. Comprehensive genomic profiling of ESR1, PIK3CA, AKT1, and PTEN in HR(+)HER2(−) metastatic breast cancer: prevalence along treatment course and predictive value for endocrine therapy resistance in real-world practice. *Breast Cancer Res Treat*. 2024;207(3):599-609.
7. Chaudhary N, Chibly AM, Collier A, et al. CDK4/6i-treated HR+/HER2- breast cancer tumors show higher ESR1 mutation prevalence and more altered genomic landscape. *NPJ Breast Cancer*. 2024;10(1):15.
8. Bidard FC, Hardy-Bessard AC, Dalenc F, et al. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2022;23(11):1367-1377.
9. Fribbens C, Garcia Murillas I, Beaney M, et al. Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. *Ann Oncol*. 2018;29(1):145-153.
10. Bidard FC, Mayer EL, Park YH, et al. First-line camizestrant for emerging *ESR1*-mutated advanced breast cancer. *N Engl J Med*. 2025;393(6):569-580.
11. U.S. Department of Health and Human Services Food and Drug Administration OCoEO. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Core patient-reported outcomes in cancer clinical trials: guidance for industry (10/17/2024). 2024. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials. Accessed July 18, 2025.
12. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
13. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol*. 1996;14(10):2756-2768.
14. Guy W. The ECDEU Assessment Manual for Psychopharmacology. *Revised edition. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration*. National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
15. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*. 2001;33(5):337-343.
16. Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and reliability of the US National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol*. 2015;1(8):1051-1059.
17. Arizmendi C, Daskalopoulou C, Ivanescu C, et al. Estimating meaningful change thresholds (MCTs) for selected scales from the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires in the phase 3 SERENA-6 trial in patients with hormone receptor-positive/human epidermal growth factor receptor 2—negative advanced breast cancer (ABC). *J Clin Oncol*. 2025;21(10 Suppl.):409.
18. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-144.
19. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer*. 2012;48(11):1713-1721.
20. Costa WA, Monteiro MN, Queiroz JF, Gonçalves AK. Pain and quality of life in breast cancer patients. *Clinics (Sao Paulo)*. 2017;72(12):758-763.
21. Doan LV, Yoon J, Chun J, Perez R, Wang J. Pain associated with breast cancer: etiologies and therapies. *Front Pain Res (Lausanne)*. 2023;4:1182488.
22. Cabel L, Bachelot T, Hardy-Bessard A-C, et al. Abstract 1O: Kinetics and determinants of blood ESR1 mutation under AI and palbociclib in HR+/HER2- metastatic breast cancer patients in the PADA-1 trial. *ESMO Open*. 2025;10:104556.
23. Schiavon G, Hrebien S, Garcia-Murillas I, et al. Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. *Sci Transl Med*. 2015;7(313):313ra182.
24. Li BT, Wong MH, Pavlakis N. Treatment and prevention of bone metastases from breast cancer: a comprehensive review of evidence for clinical practice. *J Clin Med*. 2014;3(1):1-24.
25. Zaza C, Baine N. Cancer pain and psychosocial factors: a critical review of the literature. *J Pain Symptom Manage*. 2002;24(5):526-542.
26. Kawahara T, Iwamoto T, Takashima I, et al. Association of change in health-related quality of life and treatment discontinuation in metastatic breast cancer: a post hoc, exploratory analysis of two randomized clinical trials. *Support Care Cancer*. 2022;30(10):8367-8375.
27. Marschner N, Zacharias S, Lordick F, et al. Association of disease progression with health-related quality of life among adults with breast, lung, pancreatic, and colorectal cancer. *JAMA Network Open*. 2020;3(3):e200643.

28. Muller V, Nabieva N, Häberle L, et al. Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry. *Breast*. 2018;37:154-160.
29. Verma S, O'Shaughnessy J, Burris HA, et al. 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. *Breast Cancer Res Treat*. 2018;170(3):535-545.
30. Harbeck N, Franke F, Villanueva-Vazquez R, et al. 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). *Ther Adv Med Oncol*. 2020;12:1758835920943065.
31. Rugo HS, Diéras V, Gelmon KA, et al. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial. *Ann Oncol*. 2018;29(4):888-894.
32. Ousmen A, Touraine C, Deliu N, et al. Distribution- and anchor-based methods to determine the minimally important difference on patient-reported outcome questionnaires in oncology: a structured review. *Health Qual Life Outcomes*. 2018;16(1):228.
33. Curigliano G, O'Shaughnessy J, Bidard FC, et al. Patient-reported outcomes (PROs) in patients with ER+, HER2- advanced breast cancer (ABC) treated with imlunestrant, investigator's choice standard endocrine therapy, or imlunestrant + abemaciclib: results from the phase III EMBER-3 trial. *J Clin Oncol*. 2025;43(suppl 16):1001. 1001.
34. Kaufman PA, Toi M, Neven P, et al. Health-related quality of life in MONARCH 2: abemaciclib plus fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. *Oncologist*. 2020;25(2):e243-e251.
35. Fasching PA, Beck JT, Chan A, et al. Ribociclib plus fulvestrant for advanced breast cancer: health-related quality-of-life analyses from the MONALEESA-3 study. *Breast*. 2020;54:148-154.
36. Burris HA 3rd, Lebrun F, Rugo HS, et al. Health-related quality of life of patients with advanced breast cancer treated with everolimus plus exemestane versus placebo plus exemestane in the phase 3, randomized, controlled, BOLERO-2 trial. *Cancer*. 2013;119(10):1908-1915.
37. Ciruelos EM, Rugo HS, Mayer IA, et al. Patient-reported outcomes in patients with *PIK3CA*-mutated hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer from SOLAR-1. *J Clin Oncol*. 2021;39(18):2005-2015.
38. Harbeck N, Iyer S, Turner N, et al. 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. *Ann Oncol*. 2016;27(6):1047-1054.
39. Oliveira M, Rugo HS, Howell SJ, et al. Capivasertib and fulvestrant for patients with hormone receptor-positive, HER2-negative advanced breast cancer (CAPItello-291): patient-reported outcomes from a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2024;25(9):1231-1244.
40. Musoro JZ, Coens C, Sprangers MAG, et al. Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: a synthesis across 21 clinical trials involving nine different cancer types. *Eur J Cancer*. 2023;188:171-182.
41. Mierzynska J, Taye M, Pe M, et al. Reference values for the EORTC QLQ-C30 in early and metastatic breast cancer. *Eur J Cancer*. 2020;125:69-82.
42. Goetz MP, Martin M, Tokunaga E, et al. Health-related quality of life in MONARCH 3: abemaciclib plus an aromatase inhibitor as initial therapy in HR+, HER2- advanced breast cancer. *Oncologist*. 2020;25(9):e1346-e1354.
43. Hu X, Curigliano G, Yonemori K, et al. Patient-reported outcomes with trastuzumab deruxtecan in hormone receptor-positive, HER2-low or HER2-ultralow metastatic breast cancer: results from the randomized DESTINY-Breast06 trial. *ESMO Open*. 2025;10(5):105082.