



# 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

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## Summary

**Background** CAPItello-291 is an ongoing phase 3 trial in which capivasertib–fulvestrant significantly improved progression-free survival versus placebo–fulvestrant in patients with hormone receptor-positive, HER2-negative advanced breast cancer who had relapse or disease progression during or after aromatase inhibitor treatment, in both the overall population and in patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours. This study further explored patient-reported health-related quality of life (HRQOL), functioning, symptoms, and symptom tolerability in CAPItello-291.

**Methods** This phase 3, randomised, double-blind, placebo-controlled trial, which was conducted across 193 hospitals and cancer centres in 19 countries, enrolled women with any menopausal status or men, aged  $\geq 18$  years ( $\geq 20$  years in Japan), with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer who had relapse or disease progression during or after treatment with an aromatase inhibitor, with or without previous cyclin-dependent kinase (CDK) 4 or 6 inhibitor therapy. Patients had an Eastern Cooperative Oncology Group/WHO performance score of 0 or 1 and could have received up to two previous lines of endocrine therapy and up to one previous line of chemotherapy for advanced disease. Patients were randomly assigned (1:1) using block randomisation (stratified according to the presence or absence of liver metastases, previous use of a CDK4/6 inhibitor [yes vs no], and geographical region) to receive oral capivasertib 400 mg (twice daily for 4 days, followed by 3 days off) plus intramuscular fulvestrant 500 mg (every 14 days for the first three injections, then every 28 days) or placebo with matching fulvestrant dosing. The dual primary endpoint of the trial was investigator-assessed progression-free survival assessed both in the overall population and among patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours. The EORTC Quality of Life Questionnaire 30-item core module (QLQ-C30) and breast module (QLQ-BR23), Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), and Patient Global Impression of Treatment Tolerability (PGI-TT) questionnaires were used to assess patient-reported outcomes. Evaluation of EORTC QLQ-C30 and EORTC QLQ-BR23 were secondary endpoints and evaluation of PRO-CTCAE and PGI-TT were pre-defined exploratory endpoints, and these endpoints are the subject of analysis in this Article. Data were collected at baseline and prespecified timepoints. Patient-reported outcomes were analysed in all randomly assigned patients with an evaluable baseline assessment and at least one evaluable post-baseline assessment. Change from baseline was assessed using mixed model with repeated measures for EORTC QLQ-C30 and summarised for QLQ-BR23. Time to deterioration was described using the Kaplan–Meier method. PGI-TT and PRO-CTCAE responses were summarised at each treatment cycle. Patient-reported outcomes were not prospectively powered for statistical comparison. The trial is registered with ClinicalTrials.gov, NCT04305496.

**Findings** Between June 2, 2020, and Oct 13, 2021, 901 patients were enrolled, of whom 708 patients were randomly assigned to receive capivasertib–fulvestrant ( $n=355$ ) or placebo–fulvestrant ( $n=353$ ). The median age of the patients was 59 years (IQR 51–67) in the capivasertib–fulvestrant group and 58 years (IQR 49–66) in the placebo–fulvestrant group. At data cutoff (Aug 15, 2022), the median duration of follow-up for progression-free survival in censored patients was 13·0 months (IQR 9·1–16·7) for capivasertib–fulvestrant and 12·7 months (IQR 2·0–16·4) for placebo–fulvestrant in the overall population. EORTC QLQ-C30 global health status/quality of life (GHS/QOL) scores were maintained from baseline and were similar between treatment groups throughout the study period (difference in mean change from baseline of  $-2·5$  [95% CI  $-4·5$  to  $-0·6$ ] with capivasertib–fulvestrant vs  $-5·6$  [ $-7·9$  to  $-3·4$ ] with placebo–fulvestrant; treatment difference  $3·1$  [95% CI  $0·2$  to  $6·0$ ]). Median time to deterioration in EORTC QLQ-C30 GHS/QOL was 24·9 months (95% CI 13·8 to not reached) in the capivasertib–fulvestrant group and 12·0 months (10·2 to 15·7) in the placebo–fulvestrant group (hazard ratio [HR] 0·70, 95% CI 0·53 to 0·92). Time to deterioration HRs for all EORTC QLQ-C30 and QLQ-BR23 subscale scores showed little difference between the treatment groups,

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See Online for appendix

except for diarrhoea, which was worse in the capivasertib–fulvestrant group than in the placebo–fulvestrant group (HR 2.75, 95% CI 2.01–3.81). In PRO-CTCAE symptom assessment, the proportion of patients reporting loose and watery stools “frequently” or “almost constantly” was 29% higher at cycle 1, day 15 in the capivasertib–fulvestrant group than in the placebo–fulvestrant group, decreasing at subsequent cycles. Other PRO-CTCAE-reported symptoms (rash, mouth or throat sores, itchy skin, and numbness or tingling in hands or feet) were absent or mild in most patients in both groups throughout treatment. According to the PGI-TT, most patients in both groups reported “not at all” or “a little bit” of bother from treatment side-effects.

**Interpretation** Patient-reported outcomes from CAPItello-291 demonstrated that capivasertib–fulvestrant delayed time to deterioration of GHS/QOL and maintained other dimensions of HRQOL (except symptoms of diarrhoea) similarly to fulvestrant. With the clinical efficacy and manageable safety profile, these exploratory results further support the positive benefit–risk profile of capivasertib–fulvestrant in this population.

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## Introduction

Endocrine therapy plus a cyclin-dependent kinase 4 or 6 (CDK4/6) inhibitor is the preferred first-line treatment option for some patients with hormone receptor-positive, HER2-negative advanced breast cancer.<sup>1</sup> Although these regimens are efficacious, treatment resistance is inevitable in the majority of patients<sup>2</sup> and there is no clear standard of care for subsequent treatment. Later-line treatment options include the selective oestrogen receptor degrader fulvestrant, which can be used as monotherapy or in combination with other agents.<sup>1</sup> Progression on CDK4/6 inhibitors is associated with poorer outcomes with subsequent endocrine therapy,<sup>3</sup> underscoring the need for new subsequent therapies

in the current landscape. Since activation of phosphoinositide 3-kinase (PI3K)–AKT phosphatase and tensin homologue (PTEN) signalling is implicated in resistance to endocrine therapy and CDK4/6 inhibitors,<sup>4,5</sup> AKT, as the key central node of this pathway, is now a therapeutic target in this setting.

Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3).<sup>6</sup> The phase 3 CAPItello-291 trial<sup>7</sup> assessed the use of capivasertib in patients with hormone receptor-positive, HER2-negative advanced breast cancer and relapse or progression on or after an aromatase inhibitor, with or without previous CDK4/6 inhibitor treatment. The trial met its dual primary endpoints: capivasertib–fulvestrant significantly

## Research in context

### Evidence before this study

We searched PubMed and relevant congress abstracts for clinical trials evaluating treatments for patients with hormone receptor-positive, HER2-negative advanced breast cancer following recurrence or progression on or after treatment with an aromatase inhibitor, published before Feb 7, 2022. The search terms included “hormone-receptor”, “HER2-negative”, “breast cancer”, and “second line” or “pretreated” and was restricted to English language publications. Approved treatment options for use in this patient population at the time included fulvestrant monotherapy, alpelisib in combination with fulvestrant (based on the phase 3 SOLAR-1 trial), and everolimus in combination with exemestane (based on the phase 3 BOLERO-2 trial). The phase 2 FAKTION trial had also demonstrated that capivasertib in combination with fulvestrant significantly improved progression-free and overall survival compared with fulvestrant alone in this patient population.

### Added value of this study

This detailed exploratory analysis of patient-reported outcomes from CAPItello-291 evaluated whether health-related quality of

life (HRQOL) was affected by the addition of capivasertib to fulvestrant. Our findings show that HRQOL was maintained with capivasertib–fulvestrant, and was similar to that with placebo–fulvestrant. In the capivasertib–fulvestrant group, time to deterioration in global health status or quality of life (GHS/QOL) was two times longer than placebo–fulvestrant. Time to deterioration was similar between the two groups in all other assessed GHS/QOL areas (functional and symptom domains), except diarrhoea, for which time to deterioration was significantly longer in the placebo–fulvestrant group than in the capivasertib–fulvestrant group. However, diarrhoea appeared to be tolerable when taken in context with the largely favourable treatment tolerability responses and stability in other HRQOL dimensions.

### Implications of all the available evidence

Together with the clinical efficacy and manageable safety profile, this exploratory analysis of patient-reported outcomes further supports the positive benefit–risk profile of capivasertib–fulvestrant in patients with hormone receptor-positive, HER2-negative advanced breast cancer who relapsed or progressed on standard-of-care therapy.

improved progression-free survival versus placebo–fulvestrant, both in the overall population (median 7·2 months vs 3·6 months; hazard ratio [HR] 0·60, 95% CI 0·51–0·71;  $p < 0·001$ ) and in the subgroup of patients with *PIK3CA*, *AKT1*, or *PTEN* alterations (median 7·3 months vs 3·1 months; HR 0·50, 95% CI 0·38–0·65;  $p < 0·001$ ). Overall survival data were not yet mature at the time of analysis, but were encouraging (overall population HR 0·74, 95% CI 0·56–0·98; patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours HR 0·69, 95% CI 0·45–1·05).<sup>7</sup>

The most common adverse events with capivasertib–fulvestrant were diarrhoea (in 72·4% of patients) and nausea (34·6%) at any grade, and rash (12·1%), diarrhoea (9·3%), and hyperglycaemia (2·3%) at grade 3 or worse severity.<sup>7</sup> These data led to the first regulatory approval of capivasertib–fulvestrant in patients with hormone receptor-positive, HER2-negative advanced breast cancer and one or more tumour biomarker alterations (*PIK3CA*, *AKT1*, or *PTEN*)<sup>8</sup> and inclusion of this treatment option in the guidelines.<sup>1</sup>

The health-related quality of life (HRQOL) burden in patients with advanced breast cancer can be substantial, and might encompass disease-related symptoms such as chronic pain and fatigue, treatment side-effects, emotional distress, and impaired functioning.<sup>9,10</sup> Given that treatment is typically non-curative, it is important to evaluate the HRQOL effect of novel treatments,<sup>10</sup> especially for combination therapies that have the potential to worsen the adverse event burden. Patient-reported outcomes also complement clinician-reported adverse event data because patient data are provided without interpretation by clinicians or other health-care providers. Patient-reported outcomes are therefore increasingly incorporated into phase 3 trials to assess subjective HRQOL alongside clinical efficacy and safety, and to inform the overall benefit–risk profile of a treatment. Information on disease-related symptoms is also especially relevant for patients in studies where overall survival data are immature, as is the case for CAPItello-291, or where an overall survival benefit of treatment has not been demonstrated.

In CAPItello-291, we previously reported that the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30-item core module (EORTC QLQ-C30) global health status (GHS)/QOL was maintained from baseline in both treatment groups, and that time to deterioration in GHS/QOL was longer in the capivasertib–fulvestrant treatment group than in the placebo–fulvestrant group in the overall population.<sup>7</sup> Here, we report detailed patient-reported outcome results for both the overall population and for patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours, including assessments of disease-related symptoms, functional domains, and relevant adverse events, including global impression of tolerability.

## Methods

### Study design and participants

The CAPItello-291 study design and primary efficacy and safety results have been previously reported.<sup>7</sup> Briefly, CAPItello-291 is a phase 3, randomised, double-blind, placebo-controlled study that assessed the efficacy and safety of capivasertib–fulvestrant in women (with any menopausal status) or men with hormone receptor-positive, HER2-negative advanced breast cancer who had relapsed or progressed on or after an aromatase inhibitor, with or without previous CDK4/6 inhibitor treatment. The protocol did not specify how sex or gender and race or ethnicity should be defined. These data were collected during patient visits or from patient records. The trial took place in 193 hospitals and cancer centres across 19 countries (appendix pp 2–8).

Patients were aged 18 years and older ( $\geq 20$  years in Japan) with an Eastern Cooperative Oncology Group (ECOG) or WHO performance status of 0 or 1 with no deterioration in the 2 weeks before screening, a life expectancy of at least 12 weeks, and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, per the protocol. Patients were allowed to have received up to two previous lines of endocrine therapy and one previous line of chemotherapy in the context of advanced disease. Exclusionary medical conditions, laboratory values, and previous treatments are provided in the protocol (appendix). The protocol provided recommendations for the management of adverse events, which were used at the discretion of the investigators as clinically indicated.

The CAPItello-291 study was done 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 written informed consent before enrolment. The study protocol, amendments, and other relevant documents were reviewed by an Institutional Review Board and independent Ethics Committee at each site. This study used an external independent data monitoring committee. This study is registered with ClinicalTrials.gov, NCT04305496.

### Randomisation and masking

Patients were randomly assigned (1:1) to receive capivasertib–fulvestrant or placebo–fulvestrant using block randomisation. Randomisation was done using an interactive web-based system from a centrally produced randomisation scheme independent from the study and was stratified according to the presence or absence of liver metastases, previous use of a CDK4/6 inhibitor (yes or no), and geographical region (region 1: USA, Canada, western Europe, Australia, and Israel; region 2: Latin America, eastern Europe, and Russia; and region 3: Asia). Participants were assigned unique trial numbers and treatment groups, and a confirmatory

email was sent to the investigator with the treatment assignment. Patients and investigators remained masked to treatment assignment. Masking was achieved through the use of a placebo with an identical appearance to capivasertib. Patients were enrolled by investigators and their study teams at the centres.

### Procedures

Patients in the capivasertib–fulvestrant group received 400 mg oral capivasertib (twice daily for 4 days, followed by 3 days off) plus intramuscular fulvestrant 500 mg (every 14 days for the first three injections, then every 28 days). Patients in the placebo–fulvestrant group received matching placebo and fulvestrant. Premenopausal and perimenopausal women also received subcutaneous luteinising hormone-releasing hormone agonist every 28 days or per manufacturer's instructions for the duration of the study treatment. Study treatment continued until disease progression (assessed according to RECIST), the occurrence of unacceptable toxic effects, withdrawal of consent, or death. Tumour assessments (according to RECIST) were performed by CT or MRI scans at screening (within the 4 weeks before randomisation), every 8 weeks for the first 18 months, and then every 12 weeks until disease progression. Radiographical bone scans were performed at screening and repeated as clinically indicated. Patients who discontinued study treatments for reasons other than disease progression continued to have scans every 8 weeks until disease progression (according to RECIST version 1.1; see appendix p 1 and protocol [appendix]).

Patients were required to complete all patient-reported outcome questionnaires at home, using either their own or a provided mobile device, or at the clinic if the assessment timepoint coincided with a scheduled site visit. All patient-reported outcome questionnaires were completed electronically; proxy-reported patient outcomes were not allowed.

Patients completed the EORTC QLQ-C30 and EORTC Quality of Life Questionnaire breast module (QLQ-BR23) on day 1 of cycle 1, and every 4 weeks until second progression, and at discontinuation of trial treatment. Patients who discontinued for reasons other than progression completed the EORTC QLQ-C30 and EORTC QLQ-BR23 at the time of discontinuation of trial treatment and until the first progression event on subsequent therapy.

The EORTC QLQ-C30<sup>11</sup> is a 30-item questionnaire that comprises a two-item GHS/QOL scale with five functional domains (physical, role, cognitive, emotional, and social), three symptom domains (fatigue, pain, and nausea and vomiting), and five individual item symptom scores (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea). The EORTC QLQ-BR23<sup>12</sup> 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 were required to complete the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and Patient Global Impression of Treatment Tolerability (PGI-TT) on day 1 of cycle 1 and every 2 weeks up to and including week 12, and then every 4 weeks until discontinuation of study treatment, at discontinuation of study treatment, and at 4 weeks after discontinuation.

The PRO-CTCAE,<sup>13</sup> developed by the National Cancer Institute, is an item library of symptoms experienced by patients while undergoing cancer treatment. Items (mouth or throat sores, loose or watery stools [diarrhoea], rash, itchy skin, and numbness or tingling in hands or feet) were pre-selected based on a review of the treatment-related symptoms of capivasertib and fulvestrant alone or in combination and in consideration of symptoms that are already captured in the other patient-reported outcome instruments, with a view to minimise the respondent burden of questionnaire completion.

The PGI-TT is a single-item questionnaire that assesses how a patient perceives the overall tolerability of study treatment by asking them to rate the bother they associate with their treatment-related symptoms. Patients responded to the question, "In the last 7 days, how bothered were you by the side-effects of your cancer treatment?" by selecting an item from the provided response scale ("very much", "quite a bit", "somewhat", "a little bit", or "not at all").

### Outcomes

The dual primary endpoint of the trial was investigator-assessed progression-free survival (time from randomisation to disease progression or death) in the overall population and in patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours; key secondary endpoints included overall survival (time from randomisation to death from any cause) and investigator-assessed objective response rate (the proportion of patients with a complete or partial response according to RECIST). Evaluation of HRQOL and functioning using the EORTC QLQ-C30<sup>11</sup> and QLQ-BR23<sup>12</sup> questionnaires, including change from baseline and time to deterioration in each scale or item, was a pre-defined secondary endpoint and is the subject of analysis in this Article.

Treatment-related symptoms and tolerability were assessed using the Patient-Reported Outcomes version of the PRO-CTCAE<sup>13</sup> and PGI-TT questionnaires and were pre-defined exploratory endpoints.

Additional exploratory endpoints not reported in this paper include The European Quality of Life 5-Domain 5-Level Scale (known as EQ-5D-5L), the patient global impression of severity of cancer symptoms, which was assessed using the Patient Global Impression–Severity (known as PGIS), and the impression of change in health



status, which was assessed using the Patient Global Impression–Change (known as PGIC).

### Statistical analysis

This trial was powered to assess the effect of capivasertib therapy on the primary endpoint of progression-free survival and key secondary endpoints of overall survival and objective response rate (for which a total sample size of around 700 patients was planned; see appendix p 1 for further details of sample size determination and analyses); no other endpoints were prospectively powered for statistical comparison, and no formal claims of statistical significance can be made for other secondary or exploratory endpoints.

Patient-reported outcome analyses were performed in all patients with an evaluable baseline and at least one evaluable post-baseline assessment. Analyses in both the overall population and in patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours were protocol-defined. Completion rates were calculated as the number of patients with an evaluable patient-reported outcome form at each visit divided by the number of patients expected to complete that form (according to the statistical analysis plan; appendix); available data rates were calculated as the number of patients with an evaluable patient-reported outcome form at each visit divided by the number of patients in each treatment group. Overall completion rate was defined as the number of patients with an evaluable questionnaire at baseline and at least one post-baseline timepoint, divided by the number of patients still expected to complete questionnaires, all multiplied by 100; the overall available data rate was defined as the number of patients with an evaluable questionnaire at baseline and at least one post-baseline timepoint, divided by the number of patients in each treatment group. For calculations of completion rates and available data rates, both on-treatment and off-treatment assessments were included for each visit up to second progression in the overall population for the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires, and up to treatment discontinuation for the PGI-TT and PRO-CTCAE questionnaires. Selected patient demographics (age, sex, and race and ethnicity) were summarised descriptively in a post-hoc analysis of patients who had returned evaluable EORTC QLQ-C30 forms at cycles 2, 4, and 6.

Final scores for all items on the EORTC QLQ-C30 and EORTC QLQ-BR23 were converted to a 0–100 scale, per EORTC scoring guidelines. For GHS/QOL and functional domains, higher scores represent a better level of functioning and QOL; for symptom domains, higher scores represent worse symptoms.

Change from baseline in EORTC QLQ-C30 on-treatment scores was analysed using a mixed model with repeated measures analysis of all post-baseline scores for each visit. The mixed model with repeated measures consisted of treatment, visit, and

treatment-by-visit interaction as explanatory variables, and the baseline score and baseline score by visit as covariates. The patient was included as a random effect. An unstructured covariance matrix was used to model the within-patient error; the Kenward–Roger approximation estimated degrees of freedom. This approach assumes that missing data are missing at random, and so estimates the mean treatment effect as though those missing patients were still available, borrowing across patients with similar observed data.

Change from baseline in EORTC QLQ-C30 scores was summarised at timepoints where at least 20 patients in either treatment group had an assessment. Change from baseline in EORTC QLQ-BR23 scores were summarised at all timepoints where the number of observations was a minimum of 20 and at least a third of the patients had received a study treatment in either treatment group.

	Capivasertib- fulvestrant group	Placebo- fulvestrant group
EORTC QLQ-C30 QOL	313	308
GHS/QOL	66.8 (21.0)	67.7 (19.5)
EORTC QLQ-C30 functional domain	n=313	n=308
Physical	81.1 (17.9)	79.4 (19.2)
Role	79.6 (25.9)	79.8 (25.7)
Cognitive	84.9 (17.4)	85.0 (18.0)
Emotional	73.4 (21.6)	71.9 (21.1)
Social	83.2 (22.2)	81.6 (24.5)
EORTC QLQ-C30 symptom domain	313	308
Fatigue	31.4 (23.0)	33.8 (22.4)
Pain	28.6 (26.2)	26.9 (26.0)
Nausea and vomiting	5.4 (13.6)	7.3 (14.9)
Dyspnoea	17.7 (24.9)	16.8 (23.5)
Insomnia	31.8 (29.8)	30.5 (27.8)
Appetite loss	16.1 (24.8)	16.6 (23.8)
Constipation	15.3 (24.1)	14.3 (22.5)
Diarrhoea	5.5 (15.3)	6.6 (14.4)
EORTC QLQ-BR23 functional domain	305	301
Body image	78.1 (23.7)	75.8 (25.5)
Sexual functioning	87.8 (17.9)	87.9 (19.2)
Sexual enjoyment*	56.8 (24.3)	57.7 (29.7)
Future perspective	44.6 (31.7)	44.6 (31.1)
EORTC QLQ-BR23 symptom domain	305	301
Systemic therapy side-effects	16.0 (13.1)	16.2 (13.7)
Breast symptoms	13.4 (16.8)	13.1 (16.1)
Arm symptoms	17.0 (19.1)	17.9 (20.7)
Upset by hair loss†	39.4 (32.6)	30.7 (29.8)

Data are n or mean (SD). EORTC=European Organisation for Research and Treatment of Cancer. EORTC QLQ-BR23=EORTC Quality of Life Questionnaire breast module. EORTC QLQ-C30=EORTC Quality of Life Questionnaire 30-item core module. GHS=global health status. QOL=quality of life. \*n=88 for capivasertib-fulvestrant and n=85 for placebo-fulvestrant. †n=105 for capivasertib-fulvestrant and n=114 for placebo-fulvestrant.

**Table: Baseline scores of EORTC QLQ-C30 and EORTC QLQ-BR23 subscales by treatment group**

A clinically meaningful improvement or worsening from baseline in EORTC QLQ-C30 GHS/QOL and EORTC QLQ-C30 and EORTC QLQ-BR23 functional scores was pre-defined in the statistical analysis plan as an increase of 10 points or more or a decrease of 10 points or more, respectively, and a clinically meaningful improvement or worsening from baseline in EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scores was pre-defined in the study statistical analysis plan as a decrease of 10 points or more or an increase of 10 points or more, respectively.<sup>14,15</sup> Clinically meaningful improvement or worsening was defined for the purposes of within-group change in scores, and not for comparison of between-treatment differences.

Time to deterioration was defined as the time from the date of randomisation until the date of the first clinically meaningful deterioration in EORTC QLQ-C30 or EORTC QLQ-BR23 scores (definitive worsening from baseline of  $\geq 10$  points), described using the Kaplan–Meier method; progressive disease was not considered in these analyses. If a patient did not have a definitive deterioration event before analysis cutoff, the time to definitive deterioration was censored at the date of the last evaluation. Patients with a deterioration or death after two or more missed patient-reported outcome visits were censored at the date of the last evaluation. A stratified Cox proportional hazards model was used to calculate HRs and 95% CIs. For all items except the EORTC QLQ-BR23 sexual functioning, upset by hair loss, and breast symptoms items, HRs were stratified by liver metastases (yes vs no) and previous use of CDK4/6 inhibitors (yes vs no). For the EORTC QLQ-BR23 sexual

functioning and upset by hair loss items, HRs were unadjusted; for the EORTC QLQ-BR23 breast symptoms item, HRs were stratified by previous CDK4/6 inhibitor use (yes vs no). HRs for EORTC QLQ-BR23 sexual enjoyment were not calculated due to an insufficient number of events.

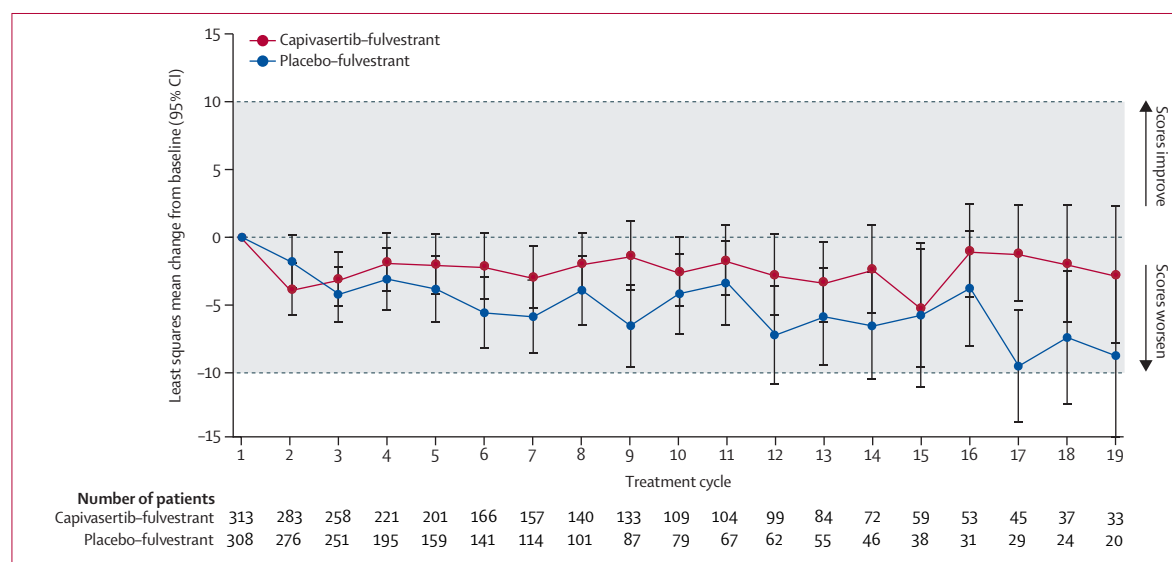
Responses for the PRO-CTCAE and PGI-TT were summarised descriptively at all timepoints at which at least 20 patients in either treatment group had an assessment, and, for the PGI-TT, when at least a third of the patients had also received a study treatment in either treatment group. Responses were summarised as the number of patients and corresponding percentage for each category in the questionnaire at each visit, by treatment group. Further details of the statistical analyses can be found in the statistical analysis plan (appendix). SAS (version 9.4) was used for all analyses.

### Role of the funding source

The funder of the study had a role in the study design, provision of study drugs, protocol development, regulatory and ethics approvals, safety monitoring, data collection, data analysis, data interpretation, and writing of the report, in collaboration with the study authors.

### Results

Between June 2, 2020, and Oct 13, 2021, a total of 901 patients were enrolled and 708 patients were randomly assigned to receive capivasertib–fulvestrant (n=355) or placebo–fulvestrant (n=353); 193 patients did not meet one or more of the study eligibility criteria. Baseline demographics and disease characteristics



**Figure 1: Least squares mean change from baseline in EORTC QLQ-C30 GHS/QOL score by treatment visit**

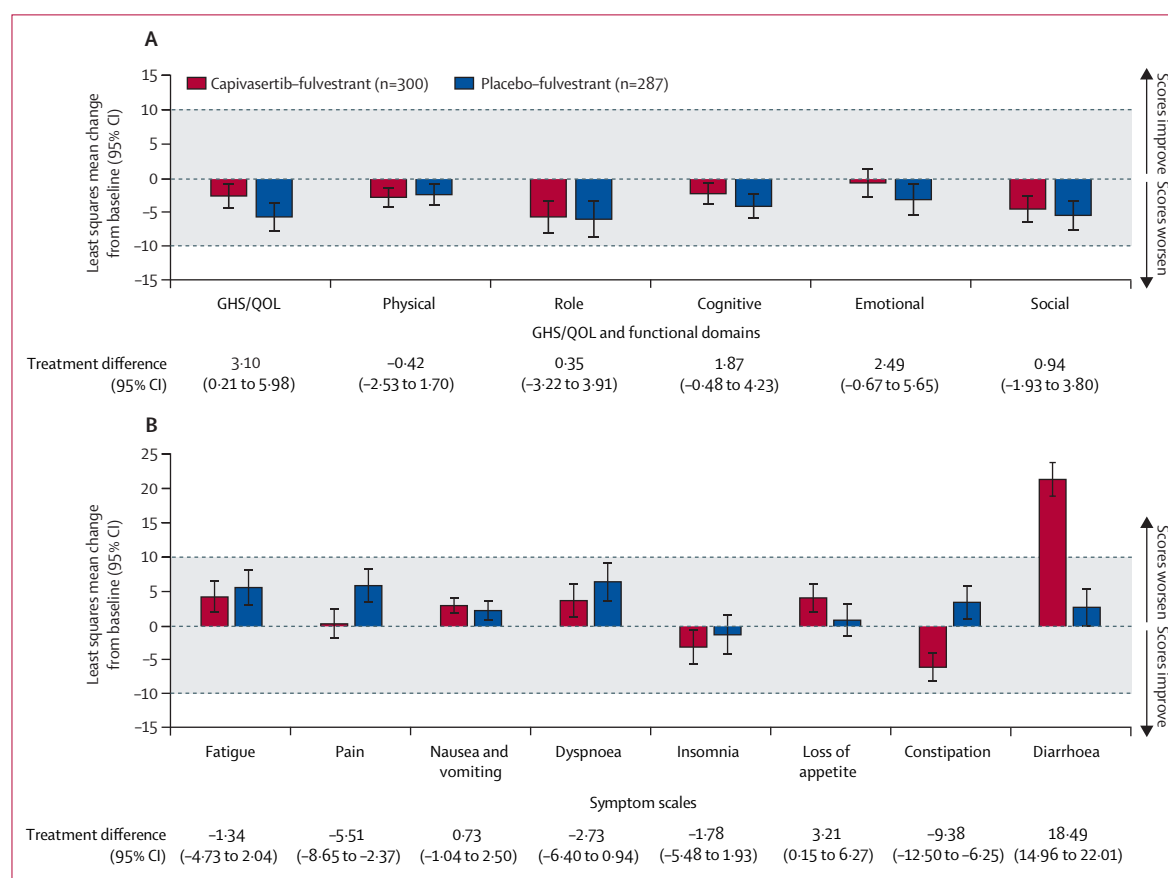
Baseline was defined as the first assessment collected on cycle 1, day 1, before the start of study treatment. Error bars represent 95% CIs. Includes all randomly assigned patients with an evaluable baseline assessment and at least one evaluable post-baseline assessment. Only on-treatment assessments were included. Data are presented for cycles where there were at least 20 events in each treatment group. Least squares mean change from baseline of  $\geq 10$  indicates a clinically meaningful change. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item core module. GHS=global health status. QOL=quality of life.

were broadly well balanced between the two treatment groups (appendix p 9) and have been previously reported.<sup>7</sup> Of the 708 patients, 478 (68%) had visceral metastases, 306 (43%) had liver metastases, 489 (69%) had received previous CDK4/6 inhibitor for advanced breast cancer, and 129 (18%) had previously received chemotherapy for advanced breast cancer.<sup>7</sup> The median age of the patients was 59 years (IQR 51–67) in the capivasertib–fulvestrant group and 58 years (49–66) in the placebo–fulvestrant group. Analyses reported here were conducted at the time of the primary analysis of progression-free survival (data cutoff date, Aug 15, 2022). Three patients in the placebo–fulvestrant group did not receive any treatment (appendix p 13). At this time, the median duration of follow-up for progression-free survival in censored patients was 13·0 months (IQR 9·1–16·7) for capivasertib–fulvestrant and 12·7 months (2·0–16·4) for placebo–fulvestrant in the overall population. As previously reported,<sup>7</sup> the majority of treated patients in both treatment groups (230 [65%] of 355 in the capivasertib–fulvestrant group and 275 [79%] of 350 in the placebo–fulvestrant

group) discontinued study treatment due to radiological progression (appendix p 13).

Mean baseline scores for all EORTC QLQ-C30 and EORTC QLQ-BR23 subscales were similar across all items between treatment groups (table).

The baseline completion rates for the EORTC QLQ-C30 were 88% (313 of 355 patients) for the capivasertib–fulvestrant group and 87% (308 of 353) for the placebo–fulvestrant group and were 86% (305 of 355) and 85% (301 of 353), respectively, for the EORTC QLQ-BR23 (appendix p 11). The overall completion rates for EORTC QLQ-C30 forms were 86% (300 of 349 patients) for the capivasertib–fulvestrant group and 84% (288 of 344) for the placebo–fulvestrant group and were 84% (293 of 349) and 82% (282 of 344), respectively, for the EORTC QLQ-BR23 (appendix p 11). The baseline completion rates for the PGI-TT were 83% (294 of 355 patients) for the capivasertib–fulvestrant group and 83% (291 of 350) for the placebo–fulvestrant group and were 83% (293 of 355) and 79% (276 of 350), respectively, for the PRO-CTCAE (appendix p 11). The overall completion rates for the PGI-TT were 81%



**Figure 2: Overall least squares mean change from baseline in EORTC QLQ-C30 GHS/QOL, functional domains, and symptom scales**

Error bars represent 95% CIs. Patients with a baseline score and at least one post-baseline score were included. A clinically meaningful improvement or worsening from baseline in EORTC QLQ-C30 GHS/QOL and functional domains (A) was defined as an increase of  $\geq 10$  or a decrease of  $\geq 10$ , respectively. A clinically meaningful improvement or worsening from baseline in EORTC QLQ-C30 symptom scales (B) was defined as a decrease of  $\geq 10$  or an increase of  $\geq 10$ , respectively. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item core module. GHS=global health status. QOL=quality of life.

(286 of 355 patients) for the capivasertib–fulvestrant group and 82% (286 of 350) for the placebo–fulvestrant group and were 80% (285 of 355) and 77% (270 of 350), respectively, for the PRO-CTCAE (appendix p 11). Completion rates for these patient-reported outcomes decreased throughout the trial period but remained similar between treatment group (appendix p 14). In a post-hoc analysis, demographic characteristics (age, sex, and race/ethnicity) of patients who completed the EORTC QLQ-C30 forms within the first year (at cycles 2, 4, and 6) were similar to those of the overall population (appendix p 12).

EORTC QLQ-C30 GHS/QOL scores were consistently maintained from baseline and were similar between treatment groups throughout the study period (overall least squares mean change from baseline of  $-2.5$ , 95% CI  $-4.5$  to  $-0.6$  with capivasertib–fulvestrant vs  $-5.6$ , 95% CI  $-7.9$  to  $-3.4$  with placebo–fulvestrant; treatment difference  $3.1$ , 95% CI  $0.2$  to  $6.0$ ; figures 1, 2).

Functional domain scores were also maintained from baseline throughout the study period and remained similar between treatment groups (figure 2A).

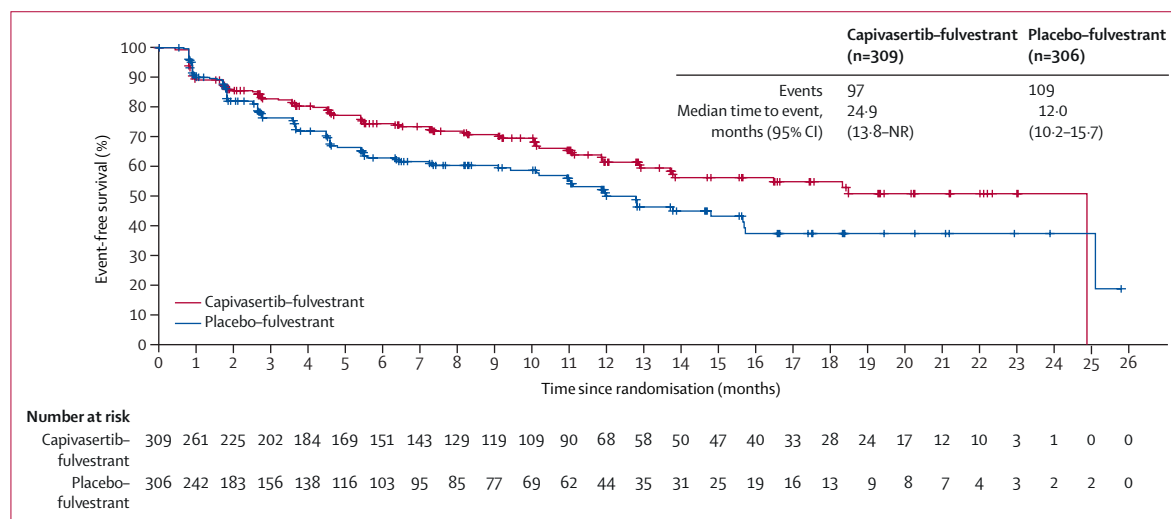
The least squares mean change from baseline for symptom domain scores were broadly similar (ie, had a difference of  $<10$  points) between treatment groups throughout the study period, except for diarrhoea, which worsened substantially from baseline in the capivasertib–fulvestrant group (figure 2B).

Mean change from baseline of EORTC QLQ-BR23 functional and symptom domain subscale scores were broadly maintained from baseline with capivasertib–fulvestrant and placebo–fulvestrant, and were similar between treatment groups (appendix p 15).

Capivasertib–fulvestrant reduced the risk of a clinically meaningful deterioration of GHS/QOL compared with placebo–fulvestrant (median time to deterioration 24.9 months [95% CI 13.8–not reached] with capivasertib–fulvestrant vs 12.0 months [95% CI 10.2–15.7] with placebo–fulvestrant; HR 0.70 [95% CI 0.53–0.92]; figure 3). HRs for risk of deterioration for all functional and symptom domains of the GHS/QOL are shown in figure 4A. Risk of deterioration in all EORTC QLQ-BR23 domains are shown in figure 4B.

At baseline, PRO-CTCAE-reported symptoms were similar between treatment groups, with the majority of patients reporting no symptoms or only mild or infrequent symptoms (figure 5). In PRO-CTCAE symptom assessment, the proportion of patients reporting loose and watery stools “frequently” or “almost constantly” was 29% higher at cycle 1, day 15 in the capivasertib–fulvestrant group versus the placebo–fulvestrant group and decreased throughout subsequent treatment cycles (figure 5A). The proportion of patients reporting loose or watery stools more than “occasionally” in the capivasertib–fulvestrant group was highest at cycle 1, day 15 (91 [31%] of 293), and decreased throughout subsequent treatment cycles (figure 5). Throughout treatment, most patients in both treatment groups reported an absence of rash (figure 5B), and “none” or a “mild” severity of itchy skin (figure 5C), mouth or throat sores (figure 5D), and numbness or tingling in hands or feet (figure 5E). Any between-group differences became less pronounced at later treatment cycles.

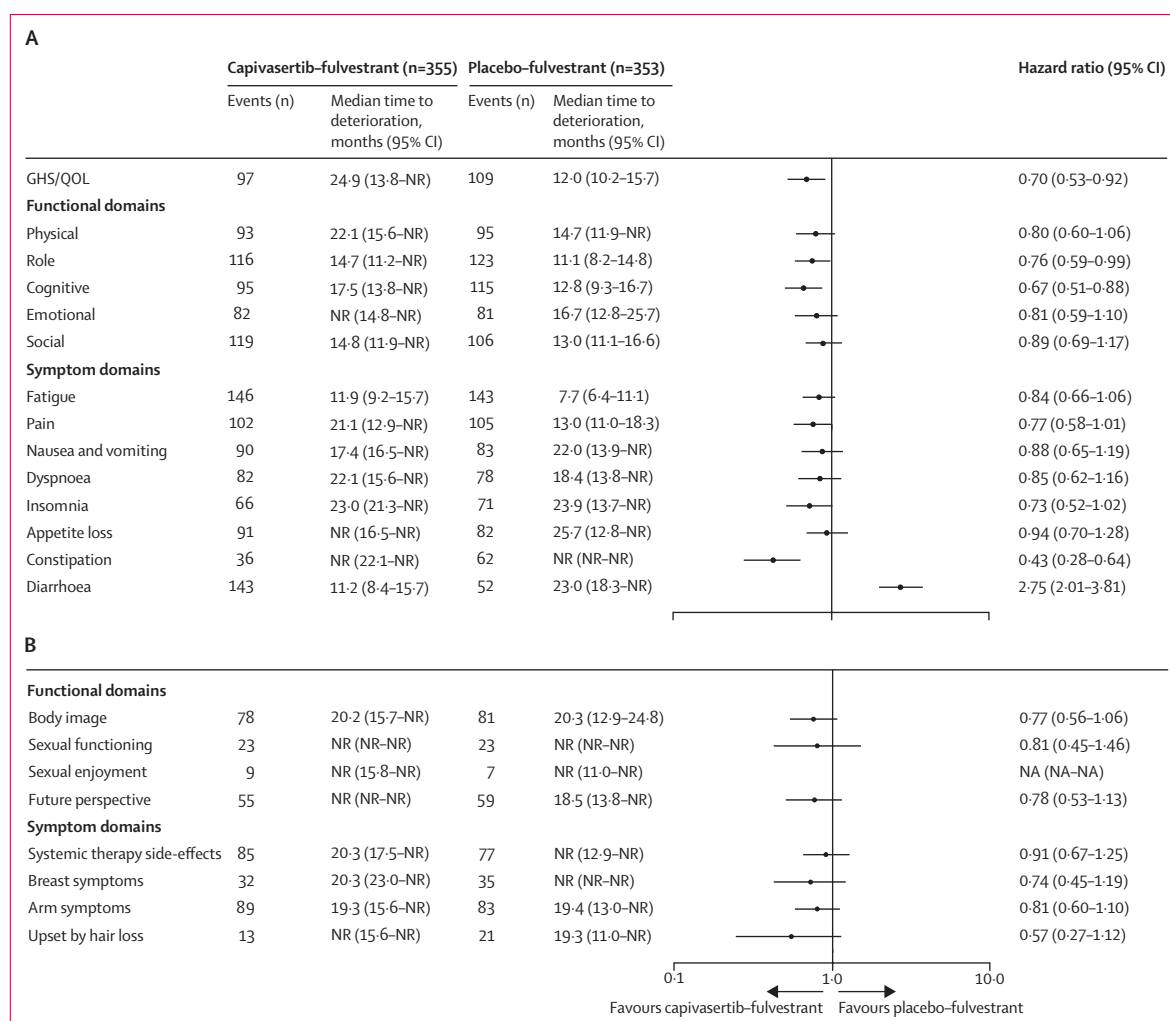
At baseline, PGI-TT ratings were similar between treatment groups, with the majority of patients reporting that they were “not at all” or “a little bit” bothered by



**Figure 3: Kaplan-Meier plot of time to definitive deterioration in EORTC QLQ-C30 GHS/QOL**

Crosses represent censored observations. Patients without a clinically meaningful deterioration at the time of the analysis were censored at the time of their last patient-reported outcome assessment, regardless of whether the patient was alive or had died. Patients without an evaluable baseline assessment, or with a baseline GHS/QOL score  $<10$  points, were excluded from this analysis. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item core module. GHS=global health status. NR=not reached. QOL=quality of life.





**Figure 4: Time to deterioration in EORTC QLQ-C30 GHS/QOL and functional and symptoms domains and EORTC QLQ-BR23 functional and symptoms domains** (A) EORTC QLQ-C30 GHS/QOL and functional and symptoms domains. (B) EORTC QLQ-BR23 functional and symptoms domains. If fewer than 20 events occurred between the two treatment groups for a subscale or item, hazard ratio and 95% CI were not calculated. EORTC=European Organisation for Research and Treatment of Cancer. EORTC QLQ-BR23=EORTC Quality of Life Questionnaire breast module. EORTC QLQ-C30=EORTC Quality of Life Questionnaire 30-item core module. GHS=global health status. NA=not available. NR=not reached. QOL=quality of life.

the side-effects of their cancer treatment (appendix p 17). In both treatment groups, 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 cycles (eg, 76% [139 of 184] of patients in the capivasertib–fulvestrant group compared with 75% [121 of 161] of patients in the placebo–fulvestrant group at cycle 6, day 1; appendix p 17). The proportion of patients responding as “somewhat”, “quite a bit”, or “very much” bothered by side-effects was consistently higher in the capivasertib–fulvestrant group than in the placebo–fulvestrant group. These between-group differences (capivasertib–fulvestrant minus placebo–fulvestrant) were greatest at cycle 1, day 15 (28%; 134/302–50/302) and at day 1 of cycle 2 (18%, 109/300–56/297) but decreased thereafter (13%, 93/273–55/266 at cycle 3; 8%, 71/237–47/215 at cycle 4;

7%, 65/220–41/180 at cycle 5; and –3%, 24/184–25/161 at cycle 6; appendix p 17).

Across all patient-reported outcomes, results were broadly similar in patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours to those in the overall population. EORTC QLQ-C30 GHS/QOL scores were maintained in both the capivasertib–fulvestrant group and the placebo–fulvestrant group (overall least squares mean change from baseline –0.60 points and –3.73 points, respectively; difference 3.12 points, 95% CI –0.97 to 7.21; appendix p 18). Results from other patient-reported outcomes in patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours are not shown.

In patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours, GHS/QOL was maintained for longer with capivasertib–fulvestrant than with placebo–fulvestrant. The median time to deterioration in GHS/QOL was

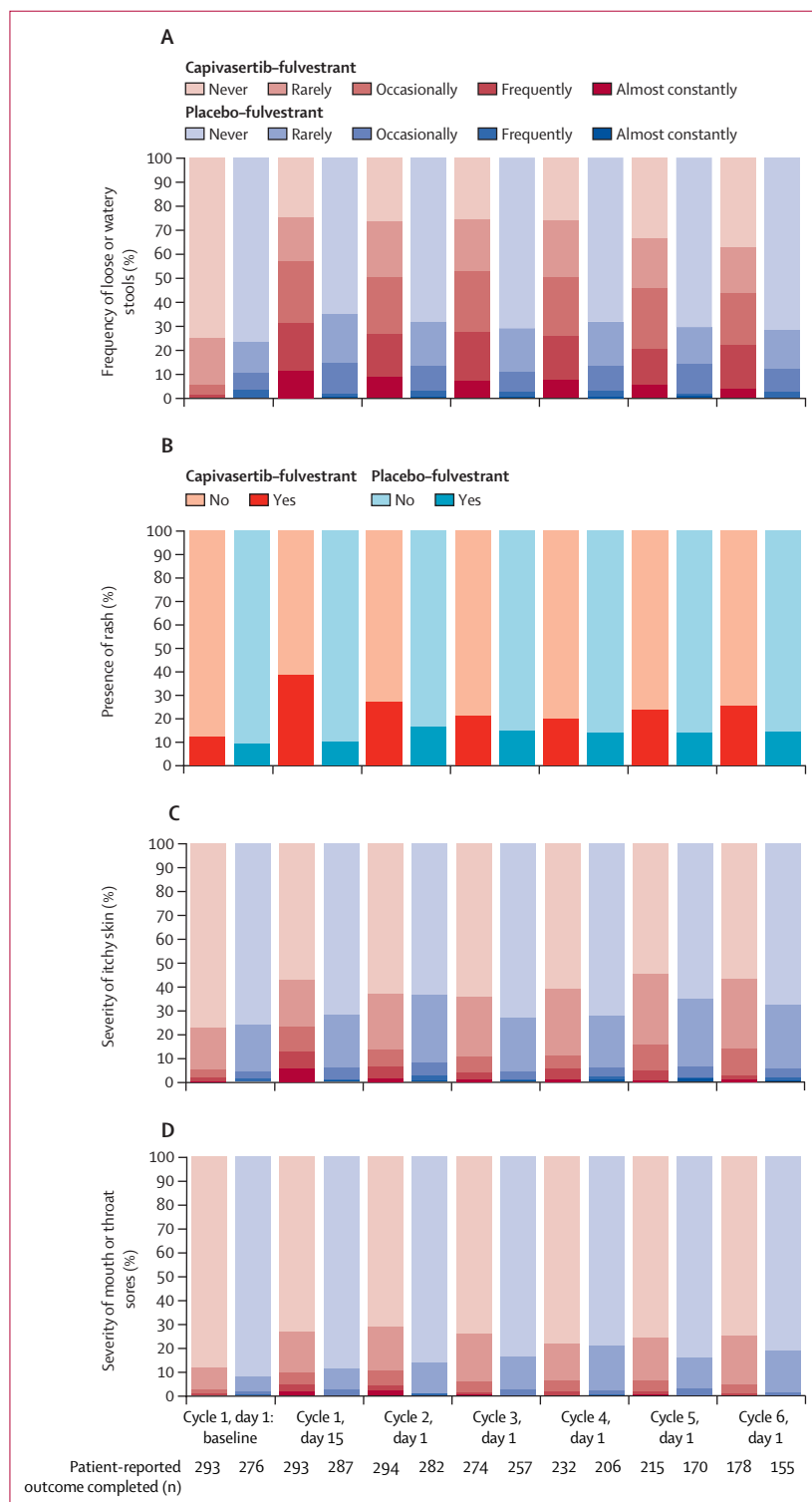
18.5 months (95% CI 12.9 to not reached) in the capivasertib–fulvestrant group compared with 13.8 months (95% CI 7.4 to not reached) in the

placebo–fulvestrant group (HR 0.62, 95% CI 0.39–0.98; appendix p 19).

## Discussion

Subjective HRQOL, including symptoms, patient functioning, and adverse events, is increasingly evaluated to support the benefit–risk profile of novel anticancer treatments. In this exploratory analysis of the randomised phase 3 CAPItello-291 trial, we demonstrate that the addition of capivasertib to fulvestrant maintained the EORTC QLQ-C30 GHS/QOL score and prolonged time to deterioration in patients with hormone receptor-positive, HER2-negative advanced breast cancer and previous progression on or after an aromatase inhibitor. Since disease progression can have a substantial detrimental impact on GHS/QOL, it is likely that the improved progression-free survival with capivasertib–fulvestrant compared with placebo–fulvestrant contributed to the delay in deterioration of GHS/QOL observed. Across all EORTC QLQ-C30 and EORTC QLQ-BR23 functional and symptom domain subscales, except diarrhoea, there were no clinically meaningful changes from baseline. In PRO-CTCAE symptom assessment, more patients in the capivasertib–fulvestrant group than in the placebo–fulvestrant group reported worse loose and watery stools, but other symptoms were absent or mild in most patients in both treatment groups. Most patients reported little or no bother from the side-effects of cancer treatment, as measured by the PGI-TT, and any differences between treatment groups in this outcome decreased over time. For the EORTC QLQ-C30, similar results were observed in patients with *PIK3CA*, *AKT1*, or *PTEN*-altered tumours.

Patient-reported outcomes complement clinician-reported adverse event data and provide additional insight into the tolerability of treatment from a patient perspective. Patient-reported outcomes related to adverse events can, however, differ from clinician-reported data, as findings from patients are provided without interpretation by clinicians or other health-care providers. As reported previously, diarrhoea (mostly grade 1 or 2 [63%], with some grade 3 events [9%]) was the most common adverse event with capivasertib–fulvestrant.<sup>7</sup> This was reflected in the subjective assessments reported herein, with EORTC QLQ-C30 responses showing clinically meaningful worsening and more rapid time to deterioration of diarrhoea with capivasertib–fulvestrant compared with placebo–fulvestrant. PRO-CTCAE assessments also indicated more frequent loose or watery stools in the capivasertib–fulvestrant group, especially during the first weeks of the study. Importantly, diarrhoea appeared to be tolerable, as supported by the largely favourable PGI-TT responses, stability in the other HRQOL dimensions (including physical functioning), and the delay in time to deterioration in GHS/QOL observed despite the symptom. Furthermore, as previously reported,

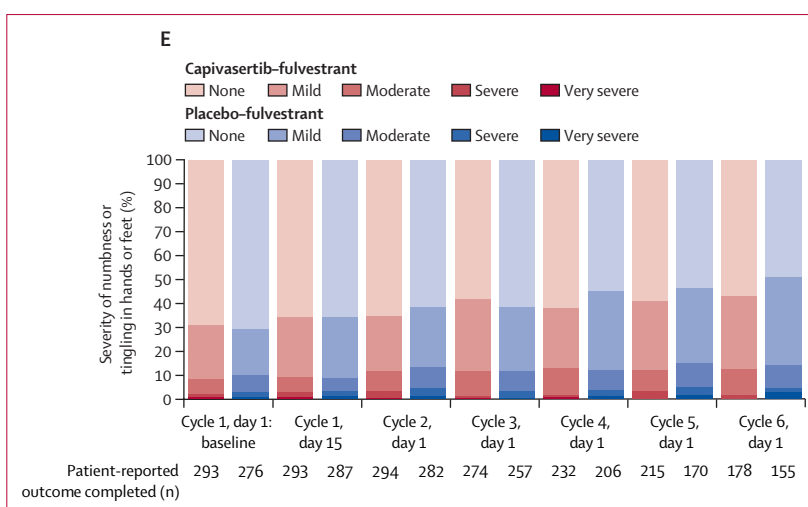


(Figure 5 continues on next page)

diarrhoea led to low rates of dose reduction (7·9%), interruption (9·9%), and discontinuation (2·0%).<sup>16</sup> These observations collectively underscore the tolerability of diarrhoea and indicate a small negative impact of this adverse event on overall HRQOL. Conservative management of diarrhoea, including lifestyle measures and anti-diarrhoeals such as loperamide, is warranted to support HRQOL during treatment.

Other than diarrhoea, most other EORTC QLQ-C30 and EORTC QLQ-BR23 symptom domains, subscales, and functional domains were maintained for longer in patients treated with capivasertib–fulvestrant compared with those treated with placebo–fulvestrant, although the statistical significance of these differences was not tested. Specific symptom subscales showing numerically longer time to deterioration with capivasertib–fulvestrant included pain, fatigue, and insomnia, which are the most common symptoms in patients with breast cancer, and rank among their most important concerns.<sup>17,18</sup> Since pain and fatigue are known to worsen upon disease progression, delays in time to deterioration in these symptoms could be directly attributable to the longer progression-free survival in the capivasertib–fulvestrant group. Furthermore, all functional domains showed longer time to deterioration with capivasertib–fulvestrant, consistent with the multi-dimensional deterioration in HRQOL associated with breast cancer progression.<sup>18</sup> The strongest trend was observed for EORTC QLQ-C30 cognitive function. Longer preservation of cognitive function might relate to the delayed time to deterioration in insomnia, which has been directly linked to cognitive performance in patients with breast cancer.<sup>19</sup>

To place our data into context, it is important to consider that this study was investigating the addition of capivasertib to fulvestrant, a well tolerated endocrine therapy. As such, an improvement in HRQOL during treatment was not necessarily expected, and maintenance or delay in deterioration in HRQOL, which was achieved with capivasertib treatment, should be considered an important finding that can complement the overall benefit–risk assessment. Although cross-trial comparisons should always be made with caution, to add further context to our findings, it should be noted that several recent phase 3 trials in hormone receptor-positive, HER2-negative advanced breast cancer have shown no meaningful difference in overall HRQOL time to deterioration with the addition of targeted agents to endocrine therapy,<sup>20–23</sup> although delays in time to deterioration were seen with palbociclib–fulvestrant in PALOMA-3.<sup>24</sup> The delay in GHS/QOL time to deterioration with capivasertib–fulvestrant compares favourably with data for other PI3K–AKT pathway-targeting agents used in combination with endocrine therapy after aromatase inhibitor therapy. Applying the same criterion for GHS/QOL time to deterioration as in the present analysis ( $\geq 10$ -point decrease), no difference between everolimus–exemestane and



**Figure 5: PRO-CTCAE incidence per visit for symptoms**

(A) Frequency of loose or watery stools (diarrhoea). (B) Presence of rash. (C) Severity of itchy skin. (D) Severity of mouth or throat sores. (E) Severity of numbness or tingling in hands or feet. Patients with an evaluable baseline assessment and at least one evaluable post-baseline assessment were included in this analysis.

PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.

placebo–exemestane was reported in the BOLERO-2 trial (HR 0·80, 95% CI 0·61–1·06;  $p=0\cdot1017$ ),<sup>22</sup> although a delay with everolimus–exemestane was observed at a less-stringent time to deterioration threshold ( $>5\%$  decrease; HR 0·74, 95% CI 0·58–0·95;  $p=0\cdot0084$ ). Furthermore, SOLAR-1<sup>23</sup> reported no meaningful difference (defined as a  $\geq 10\%$  decrease) in GHS/QOL time to deterioration with alpelisib–fulvestrant versus placebo–fulvestrant in patients with *PIK3CA*-mutated hormone receptor-positive, HER2-negative advanced breast cancer (HR 1·03, 95% CI 0·72–1·48). Median time to a 10-point or greater deterioration in GHS/QOL appeared longer with capivasertib–fulvestrant (24·9 months) in CAPitello-291 than with everolimus–exemestane (11·7 months) in BOLERO-2<sup>22</sup> or alpelisib–fulvestrant (14·8 months) in SOLAR-1.<sup>23</sup> However, extra caution is needed when comparing studies such as CAPitello-291, BOLERO-2, and SOLAR-1 due to the pronounced difference in the time interval between trials and differences in patient populations as a result of changes in the treatment landscape. Of note, incidence and grades of stomatitis and hyperglycaemia were low with capivasertib–fulvestrant compared with stomatitis with everolimus–exemestane and hyperglycaemia with alpelisib–fulvestrant, which could contribute to any HRQOL differences.<sup>25,26</sup>

The strengths of this study include the use of a range of patient-reported outcome measures, including a validated, multi-dimensional generic instrument (EORTC QLQ-C30)<sup>11</sup> and a breast cancer-specific module (EORTC QLQ-BR23),<sup>12</sup> alongside targeted assessments of relevant treatment-related symptoms (PRO-CTCAE) and global patient assessment of overall tolerability (PGI-TT), to provide a comprehensive picture of patient HRQOL

during treatment. The characteristics of patients in this study were also considered largely representative of patients with hormone receptor-positive, HER2-negative breast cancer.<sup>7</sup> Limitations include the reduction in questionnaire completion over time due to treatment discontinuation, which is common in studies in this setting.<sup>20–24,27–30</sup> Change from baseline in EORTC QLQ-C30 scores was analysed using a mixed model with repeated measures, which assumes that data are missing at random and does not account for non-random missing data. Although non-random missing data have the potential to influence results (eg, due to reduced questionnaire completion in patients with more severe symptoms), we believe that missing data are likely to be balanced between treatment groups based on our post-hoc analysis of demographic characteristics in those that completed questionnaires, and, as such, would not affect the estimate of mean treatment effect. Our analyses used a 10-point change in EORTC QLQ-C30 and EORTC QLQ-BR23 scores to identify a clinically meaningful improvement or worsening in symptoms scores; this was pre-defined in the protocol and is a commonly used threshold in breast cancer trials.<sup>20–24,29</sup> However, smaller changes of between 5 and 10 points have been considered of clinical relevance and, as such, our use of a stringent threshold might have reduced the sensitivity of our analyses.

In conclusion, the findings from this exploratory analysis of patient-reported outcomes from the CAPItello-291 study, together with the clinical efficacy and manageable safety profile previously demonstrated, further support the positive benefit–risk profile of caviplasertib–fulvestrant in women or men with hormone receptor-positive, HER2-negative advanced breast cancer who relapsed or progressed on standard-of-care therapy.

#### Contributors

HLG, HSR, JC, KJ, MOI, NCT, SJH, SL, and XH were involved in the design of the study. ET, FD, HLG, HSR, JC, JHS, LZ, MOI, MOK, NCT, MT, PK, SJH, SMM, SY, YHP, and ZN were involved in data collection. MF, HA, IW, and CD'C were involved in data analysis and all authors were involved in data interpretation. MOI, MF, HA, IW, and CD'C have accessed and verified the data from this study. All authors critically revised the manuscript for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had access to the underlying study data that were used in the present analysis. All authors had final responsibility for the decision to submit for publication.

#### Declaration of interests

MOI has received honoraria from Eisai, Gilead Sciences, Libbs, Eli Lilly, Novartis, Pfizer, Roche, Seagen, AstraZeneca Taiwan, and Merck Sharp & Dohme; has received research funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Roche, Seagen, Zenith Epigenetics, Gilead Sciences, Ayala Pharmaceuticals, and Genentech; has received travel grants from Eisai and Gilead Sciences; has served as a consultant for AstraZeneca, Daiichi Sankyo, Gilead Sciences, ITeos Therapeutics, Eli Lilly, Merck Sharp & Dohme, Relay Therapeutics, Roche, Seagen, and Pierre Fabre; and serves as the head on the board of directors for the SOLTI Breast Cancer Research Group. HSR has served as a consultant or advisor for Napo Pharmaceuticals, Puma Biotechnology, Mylan, Eisai, and Daiichi Sankyo, and has received research funding from OBI Pharma, Pfizer, Novartis, Eli Lilly, Merck Sharp & Dohme, Daiichi Sankyo,

AstraZeneca, Gilead Sciences, Astellas Pharma, Taiho Oncology, Veru, GlaxoSmithKline, Genentech/Roche, and Stemline Therapeutics. SJH has received institutional grants from Eli Lilly; has served as a consultant for Pfizer; has received payments to their institution per patient from AstraZeneca (study sponsor); has participated on a Data Safety Monitoring Board or Advisory Board for Eli Lilly; has received honoraria from Eli Lilly, Pfizer, Novartis, and AstraZeneca; and has received support for attending meetings and travel from Novartis. FD has received honoraria from Eli Lilly, Gilead Sciences, and AstraZeneca and has received travel grants from Daiichi Sankyo, Novartis, Gilead Sciences, and Pfizer. JC has served as a consultant or advisor for Celgene, Cellectia Biotech, AstraZeneca, Roche, Seagen, Daiichi Sankyo, ERYTECH Pharma, Polyphor, Athenex Oncology, Eli Lilly, SERVIER, Merck Sharp & Dohme, GlaxoSmithKline, Leuko, Clovis Oncology, Bioasis, Boehringer Ingelheim, Ellipses Pharma, HiberCell, Bioinvent, GEMoA Monoclonals, Gilead Sciences, Menarini, Zymeworks, Reveal Genomics, ExpresZion Biotechnologies, Jazz Pharmaceuticals, AbbVie, Bridgebio, and BioNTech; has received travel grants from Roche, Pfizer, Eisai, Novartis, Daiichi Sankyo, Gilead Sciences, AstraZeneca, Merck Sharp & Dohme, and Stemline Therapeutics; holds stock in Leuko and MAJ3 Capital; holds two patents, WO 2014/199294 A and US 2019/0338368 A1; has received honoraria from Novartis, Eisai, Celgene, Pfizer, Roche, Samsung, Eli Lilly, Merck Sharp & Dohme, Daiichi Sankyo, AstraZeneca, Gilead Sciences, and Stemline Therapeutics; and has received research funding from ARIAD Pharmaceuticals, AstraZeneca, Baxalta, Bayer, Eisai, Guardant Health, Merck Sharp & Dohme, Pfizer, Puma Biotechnology, Queen Mary University of London, Roche, and Piquor. HLG has served as a consultant or advisor for AstraZeneca; has received research funding from Merck Sharp & Dohme; and has served on speakers' bureaus for Roche, AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Technofarma, and Novartis. MT has served on advisory boards for Athenex Oncology, Bertis, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Kansai Medical Net, and Terumo; has received compensation as an invited speaker from AstraZeneca, Bertis, Bristol Myers Squibb, Chugai, Devicore Medical Japan, Eisai, Eli Lilly, Exact Science, Kyowa-Kirin, Merck Sharp & Dohme, Nippon-Kayaku, Novartis, Pfizer, Shimadzu, Sysmex, Taiho, Takeda, and Yakult; has received research funding from AFI Technology, Astellas, AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, GL Science, Kansai Medical Net, Luxonus, Pfizer, Sanwa Shurui, Shimadzu, Takeda, The Japan Breast Cancer Research Group association, The Kyoto Breast Cancer Research Network association, and Yakult; has served on steering committees for AstraZeneca, Chugai, and Daiichi Sankyo; and serves as a member of the board of directors for the Organisation for Oncology and Translational Research, The Japan Breast Cancer Research Group association, The Japanese Onco-Cardiology Society, The Kyoto Breast Cancer Research Network association, and The Japanese Breast Cancer Society. KJ has served on advisory boards for Novartis, Pfizer, AstraZeneca, Jounce Therapeutics, Synthron, Intellisphere, Bristol Myers Squibb, Genentech, AbbVie, Eli Lilly, Blueprint Medicines, Seagen, Daiichi Sankyo, Biotheranostics, Sun Pharma Advanced Research Company, Taiho Oncology, Sanofi, Gilead Sciences, and Scorpion Therapeutics; has received research funding from Novartis, Genentech, Debiopharm Group, ADC Therapeutics, Pfizer, Novita Pharmaceuticals, Clovis Oncology, Eli Lilly, Zymeworks, Immunomedics, Puma Biotechnology, VelosBio/Merck, AstraZeneca, Context Therapeutics, Scorpion Therapeutics, and Blueprint Medicines; and has received travel grants from Taiho Pharmaceutical, Jounce Therapeutics, Pfizer, AstraZeneca, Intellisphere, Eli Lilly, Gilead Sciences, and Genentech/Roche. SL has served as a consultant or on advisory boards for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, EirGenix, Gilead Sciences, GlaxoSmithKline, Eli Lilly, Merck, Novartis, Olema, Pfizer, Pierre Fabre, Relay Therapeutics, Roche, Sanofi, Seagen, and AGO (German Gynecological Oncology Group) Kommission Mamma; has served as an invited speaker at AstraZeneca, DSI, Gilead Sciences, Novartis, Pfizer, Roche, Seagen, Stemline-Menarini, and Medscape; is a full or part-time employee at BGB Forschungen GmbH; has received licensing or royalties from VMscope GmbH, and research funding from AbbVie, AstraZeneca, Celgene, Daiichi Sankyo, Greenwich Life Sciences, Immunomedics/Gilead Sciences, Molecular Health, Novartis, Pfizer, and Roche; and has served as a principal investigator at PI Aphinity. YHP has received research funding from MSD, Pfizer,



Roche, Novartis, AstraZeneca, Gencurix, and Genome Insight; has received honoraria from AstraZeneca, Pfizer, Eli Lilly, MSD, Roche, Daiichi Sankyo, Novartis, and Gilead Sciences; has received consulting fees from AstraZeneca, Pfizer, Eli Lilly, Gilead Sciences, MSD, Eisai, Roche, Daiichi Sankyo, Menarini, Everest, and Novartis; has received travel grants from Gilead Sciences, Pfizer, and AstraZeneca; has served on advisory boards for AstraZeneca, Pfizer, Roche, Menarini, Novartis, Daiichi Sankyo; and has received equipment, materials, drugs, medical writing, gifts, or other services from Dong-A ST, Sanofi, Roche, and Pfizer. JHS has received research funding from MSD, Roche, Novartis, Eli Lilly, Pfizer, Daiichi Sankyo, AstraZeneca, GlaxoSmithKline, Sanofi, Boehringer Ingelheim, Seagen, Quriient, Dragonfly Therapeutics, Eikon Therapeutics, Gilead Sciences, Celcuity, Bristol Myers Squibb, HLB Pharmaceutical, Sermonix Pharmaceuticals, Olema Oncology, Hanmi, Ildong Pharmaceutical, and Samyang Holdings. ET has received honoraria from Eli Lilly, Daiichi Sankyo, AstraZeneca, and Chugai. NCT has served on the advisory board for AstraZeneca, Eli Lilly, Novartis, Pfizer, Roche/Genentech, GlaxoSmithKline, Repare Therapeutics, Relay Therapeutics, Gilead Sciences, Inivata, Guardant Health, and Exact Sciences and received research funding from AstraZeneca, Pfizer, Roche/Genentech, MSD, Invitae, Inivata, Personalis, and Natera. CD'C, HA, MF, and IW are employees of AstraZeneca, and may hold AstraZeneca stocks or shares. All other authors declare no competing interests.

#### Data sharing

Data underlying the findings described in this manuscript can be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmam.com/ST/Submission/Disclosure>. Data for studies directly listed on Vivli can be requested through Vivli at [www.vivli.org](http://www.vivli.org). Data for studies not listed on Vivli can be requested through Vivli at <https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/>. The AstraZeneca Vivli member page is also available, outlining further details: <https://vivli.org/ourmember/astrazeneca/>.

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