Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial

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Summary

Background Patients with HER2-positive breast cancer who have received two or more previous therapies for advanced disease have few effective treatment options. The monarcHER trial aimed to compare the efficacy of abemaciclib plus trastuzumab with or without fulvestrant with standard-of-care chemotherapy of physician's choice plus trastuzumab in women with advanced breast cancer.

Methods This phase 2, three-group, open-label trial was done across 75 hospitals, clinics, and medical centres in 14 countries. Eligible patients were women aged 18 years or older, who had hormone receptor-positive, HER2-positive advanced breast cancer with unresectable, locally advanced, recurrent or metastatic disease, Eastern Cooperative Oncology Group performance status of 0 or 1, and who had previously received at least two HER2-targeted therapies for advanced disease. Patients were randomly assigned 1:1:1 to the abemaciclib, trastuzumab, and fulvestrant (group A), abemaciclib and trastuzumab (group B), or standard-of-care chemotherapy and trastuzumab (group C). Oral abemaciclib 150 mg 12 hourly was administered on days 1–21 of a 21-day cycle, intravenous trastuzumab 8 mg/kg on cycle 1 day 1, followed by 6 mg/kg on day 1 of each subsequent 21-day cycle, and intramuscular fulvestrant 500 mg on days 1, 15, and 29 and once every 4 weeks thereafter. Standard-of-care chemotherapy was administered as specified by the product label. Randomisation was by a computer-generated random sequence by means of an interactive web-response system and stratified by number of previous systemic therapies for advanced breast cancer and measurable versus non-measurable disease. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population, first testing group A versus group C and, if this result was significant, then group B versus group C. Safety was assessed in all patients who had received at least one dose of study treatment. This trial is registered at ClinicalTrials.gov (NCT02675231) and is ongoing for long-term survival follow-up.

Findings Between May 31, 2016, and Feb 28, 2018, 325 patients were screened, of whom 237 eligible patients were enrolled and randomly assigned to groups A (n=79), B (n=79), and C (n=79). Median follow-up was 19·0 months (IQR 14·7–25·1). The study met its primary endpoint, showing a significant difference at the prespecified two-sided α of 0·2 in median progression-free survival between group A (8·3 months, 95% CI 5·9–12·6) and group C (5·7 months, 5·4–7·0; HR 0·67 [95% CI 0·45–1·00]; p=0·051). No difference was observed between median progression-free survival in group B (5·7 months, 95% CI 4·2–7·2) and group C (HR 0·94 [0·64–1·38]; p=0·77). The most common grade 3–4 treatment-emergent adverse event in groups A, B, and C was neutropenia (21 [27%] of 78 patients, 17 [22%] of 77, and 19 [26%] of 72). The most common serious adverse events were: in group A, pyrexia (three [4%]), diarrhoea (two [3%]), urinary tract infection (two [3%]), and acute kidney injury (two [3%]); in group B, diarrhoea (two [3%]) and pneumonitis (two [3%]); and in group C, neutropenia (four [6%]) and pleural effusion (two [3%]). Two deaths were attributed to treatment: one due to pulmonary fibrosis in group B and one due to febrile neutropenia in group C.

Interpretation The combination of abemaciclib, fulvestrant, and trastuzumab significantly improved progression-free survival versus standard-of-care chemotherapy plus trastuzumab while showing a tolerable safety profile. Our results suggest that a chemotherapy-free regimen might potentially be an alternative treatment option for patients with hormone receptor-positive, HER2-positive advanced breast cancer.

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Research in context

Evidence before this study

We searched PubMed on Nov 24, 2019, for clinical trials published between 2014 and 2019 with the terms "trastuzumab" AND "breast" AND "HER2-positive" AND "phase 2" OR "phase 3" with no restriction on language. 22 publications were identified, 11 of which focused on patients with metastatic or advanced disease. One of these studies (TH3RESA) reported a significantly longer overall survival in patients treated with trastuzumab emtansine than in patients treated with physician's choice. None of these publications reported cyclin-dependent kinase 4 (CDK4) and 6 (CDK6) inhibitor use alone, or in combination with HER2-targeted agents or tyrosine kinase inhibitors for the treatment of hormone receptor-positive, HER2-positive advanced breast cancer..

The CDK4 and CDK6 inhibitor abemaciclib has shown activity, both as a single agent and in combination with endocrine therapy, in patients with hormone receptor-positive, HER2-negative advanced breast cancer (MONARCH 1, 2, 3), and has shown preliminary efficacy as monotherapy or in combination with endocrine therapy in a small number of patients with hormone receptor-positive, HER2-positive advanced breast cancer. At the time of the monarcHER study design (2015–16), there were few approved treatment options for patients with hormone receptor-positive, HER2-positive advanced breast cancer who had progressed on standard therapies. There was an urgent need to identify new and potentially more tolerable treatment options.

Added value of this study

To our knowledge, this trial is the first randomised study to report positive results for a CDK4 and CDK6 inhibitor in combination with fulvestrant and trastuzumab versus standard-of-care chemotherapy and trastuzumab. The endocrine combination of abemaciclib plus fulvestrant and trastuzumab showed significant improvements in both progression-free survival and overall response compared with chemotherapy plus transtuzumab and was generally well tolerated.

The current study is noteworthy as it directly compared an endocrine-based regimen with standard-of-care chemotherapy in combination with trastuzumab, potentially offering a chemotherapy sparing treatment option.

Implications of all the available evidence

This study provides clinical validation of the preclinical hypothesis suggesting that treatment with a CDK4 and CDK6 inhibitor might overcome acquired resistance to trastuzumab. Furthermore, together with previously published data, abemaciclib has now shown activity in both hormone receptor-positive, HER2-negative and hormone receptor-positive, HER2-positive advanced breast cancer.

Introduction

Breast cancer is the most commonly diagnosed cancer in females globally,[1] with hormone receptor-positive, HER2 (also known as ERBB2)-positive breast cancer representing an estimated 10% of all breast cancer subtypes in the USA.[2] The addition of HER2-targeted therapies to standard chemotherapy has improved outcomes for patients with HER2-positive breast cancer.[3,4] Effective anti-HER2 agents include the monoclonal antibody trastuzumab and the small molecule inhibitor lapatinib. More recent advances include the dimerisation inhibitor pertuzumab and the antibody drug conjugate trastuzumab emtansine.[5] Unfortunately, multiple mechanisms of resistance are known to emerge against HER2-targeted therapies, notably those mediated by effectors downstream of the HER2 receptor.[6] International guidelines recommend that patients whose tumours progress on an anti-HER2 therapy in combination with a cytotoxic or endocrine agent should be offered additional anti-HER2 agents to achieve ongoing suppression of HER2 pathway signalling.[7] Patients with heavily pretreated HER2-positive breast cancer who have received two or more previous therapies for advanced disease have few effective treatment options. In this setting, HER2-targeted therapy combined with cytotoxic chemotherapy agents offer modest clinical benefit with associated toxicities.[8,9]

Abemaciclib, a potent oral cyclin-dependent kinase 4 (CDK4) and 6 (CDK6) inhibitor, has shown activity in hormone receptor-positive, HER2-negative advanced breast cancer as a monotherapy[10] and in combination with endocrine therapy.[11,12] However, activity of abemaciclib is not restricted to hormone receptor-positive, HER2-negative disease. In a phase 1 study of abemaciclib, four patients among a subset of 11 with hormone receptor-positive, HER2-positive advanced breast cancer (three of whom were receiving concomitant endocrine therapy) achieved a partial response (36%, 95% CI 10·9–69·2).[13] The median progression-free survival for this subpopulation was 7·2 months (95% CI 2·8–12·0). These results provide a clinical rationale to further investigate the role of abemaciclib in HER2-positive disease.

Preclinical studies have provided a biological rationale supporting the study of abemaciclib in HER2-positive advanced breast cancer. Using genetically engineered mouse models, cell lines, and patient-derived xenografts of HER2-therapy resistant breast cancer, Goel and colleagues[14] showed that the CDK4 and CDK6 pathway can mediate resistance to HER2-targeted therapies and that this can be overcome by abemaciclib. O'Brien and colleagues[15] subsequently confirmed this observation and showed that the addition of endocrine therapy further enhanced the efficacy of abemaciclib plus trastuzumab in models of hormone receptor-positive, HER2-positive breast cancer.

Here, we report the results of the monarcHER trial comparing the efficacy of abemaciclib plus trastuzumab with or without fulvestrant versus standard-of-care, single-agent chemotherapy of physician's choice plus trastuzumab in women with hormone receptor-positive, HER2-positive advanced breast cancer.

Methods

Study design and participants

This phase 2, randomised, three-group, open-label trial was done across 75 hospitals, clinics, and medical centres in 14 countries (Argentina, Australia, Belgium, Brazil, Canada, France, Germany, Greece, Italy, Mexico, Spain, South Korea, the UK, and the USA ; appendix pp 16–24). Women aged 18 years or older of any menopausal status (premenopausal or perimenopausal patients received a gonadotropin-releasing hormone agonist initiated at least 28 days before day 1, cycle 1), with a confirmed diagnosis of hormone receptor-positive, HER2-positive breast cancer and unresectable, locally advanced, recurrent or metastatic disease were eligible for this trial. Patients with either measurable or non-measurable disease, by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function (absolute neutrophil count ≥1·5×10⁹ cells per L, platelets ≥100×10⁹ per L, haemoglobin ≥8g/dL, total bilirubin ≤1·5×the upper limit of normal [ULN], alanine aminotransferase and aspartate aminotransferase ≤3×ULN, serum creatinine ≤1·5×ULN) were included. Patients must have received at least two HER2-targeted previous therapies for advanced breast cancer either in combination with chemotherapy or endocrine therapy, or as a single agent; exposure to dual HER2 blockade was considered as one previous HER2-targeted therapy. Previous trastuzumab emtansine and a taxane in any setting was required. Previous pertuzumab was permitted. Patients were allowed to have received any previous endocrine therapy except fulvestrant.

Key exclusion criteria included visceral crisis defined as severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease; known CNS metastases that were untreated, symptomatic, or required steroids; and previous treatment with any CDK4 and CDK6 inhibitor.

Protocol amendment (a) on Dec 22, 2015, included the safety lead-in portion for group A. Protocol amendment (b) on May 23, 2016, added an additional stratification factor (measurable *vs* non-measurable disease), and provided further clarification for exclusion criteria 24 (pre-existing conditions), 29 (live virus vaccines), and 31 (hypersensitivity; appendix pp 52–54).

This study was done in accordance with consensus ethics principles derived from international ethics guidelines including the Declaration of Helsinki and International Conference on Harmonisation and Good Clinical Practices guidelines. This study was approved by ethical and institutional review boards and applicable laws and regulations at all participating centres were adhered to. Written informed consent was obtained from all patients before enrolment.

Randomisation and masking

This was an open-label study in which patients were randomly assigned 1:1:1 between three groups by a computer-generated random sequence by means of an interactive web-response system: abemaciclib, trastuzumab, and fulvestrant (group A), abemaciclib plus trastuzumab (group B), or chemotherapy plus trastuzumab (group C). The randomisation was stratified by the number of previous systemic regimens excluding single-agent endocrine therapy (2–3 *vs* >3) and disease status (measurable *vs* non-measurable).

Procedures

Abemaciclib was administered orally at 150 mg every 12 h on a 21-day cycle. A safety lead-in cohort of 12 patients in group A did not show any safety issues with this dose in the triplet combination. As per standard of care at the time of study design, trastuzumab was administered intravenously at 8 mg/kg over 90 min on day 1 of cycle 1, then maintained at 6 mg/kg on day 1 of all subsequent 21-day cycles. Patients received fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1, and on day 8 of cycle 2 if no dose suspension for trastuzumab occurred; then once every 4 weeks. Standard-of-care, single-agent chemotherapy was chosen from an approved chemotherapy used in breast cancer and administered according to the product label. Patients received study treatment in their assigned treatment group until disease progression as per RECIST 1.1 or unacceptable toxicity. Both patient and physician could withdraw from the study at any time, the sponsor could discontinue the patient, the sponsor could stop the study, or the patient could be discontinued if enrolled in another clinical trial or substantially non-compliant with procedures and treatment. According to physician discretion, growth factors could be administered in accordance with American Society of Clinical Oncology Guidelines[16] and bone-modifying agents were allowed as needed to maximise quality of life.

Treatment was interrupted or delayed in case of adverse event occurrence and resumed if protocol-defined criteria were met. Dose reduction and delays were permitted for abemaciclib for toxicities prespecified in the protocol. Dose adjustments for trastuzumab, fulvestrant, or chemotherapy were determined by the investigator in accordance with the product label.

Tumour assessments were done by CT or MRI at baseline and every 6 weeks for 36 weeks from the first dose of study therapy, then every 9 weeks and within 14 days of clinical progression. All patients had bone scans at baseline and when disease progression in bone was suspected. Patients with identified bone lesions at baseline had repeated bone scans every 24 weeks.

See Online for appendix

Central haematology, chemistry, and cystatin C were done before day 1 of each cycle. Adverse events were monitored at each patient visit and graded according to the National Cancer Institute Common Terminology Criteria version 4.03. The modified Brief Pain Inventory short form (mBPI-sf) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)[18] were collected at baseline, at the beginning of each treatment cycle, and at the post-therapy follow-up visit.

The mBPI-sf included four pain items (worst, least, average, and current) and a pain interference composite score, and was scored on a 0–10-point response scale.[17] The EORTC QLQ-C30 assessed three dimensions from 30 total items: global health status or health-related quality of life (one scale); functioning (five scales: physical, role, emotional, cognitive, and social); and symptoms (nine scales: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC QLQ-C30 symptom and functioning items are scored on a four-point response scale, whereas the Global Health and quality-of-life items are scored on a seven-point response scale. These item-level scores were used to calculate domain-level scales that ranged from 0 to 100 according to the EORTC QLQ-C30 Scoring Manual. Higher scores for EORTC QLQ-C30 functional and health status quality-of-life scales reflect better or improved outcomes, whereas higher scores on EORTC QLQ-C30 symptom scales and mBPI-sf indicate poor or worsened outcomes.

Plasma pharmacokinetic samples were taken as follows: trastuzumab pharmacokinetic samples (groups A and B) were taken immediately before and just after each trastuzumab infusion for the first five cycles (total of ten samples); fulvestrant pharmacokinetic samples (group A only) were taken before dosing on cycle 1 day 1, cycle 1 day 15, cycle 2 day 8, cycle 3 day 15, and cycle 5 day 1; and abemaciclib pharmacokinetic samples were taken every time a pharmacokinetic sample was drawn as aforementioned for trastuzumab and fulvestrant, resulting in a total of 13 (group A) and ten (group B) pharmacokinetic samples for abemaciclib and its metabolites. Plasma pharmacokinetic samples were analysed using validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) methods for abemaciclib and its metabolites M2 and M20 (Q2 Solutions; Ithaca, NY, USA), or fulvestrant (Charles River Laboratories Montreal ULC; Senneville, QC, Canada), or trastuzumab (PPD; Richmond, VA, USA).

Outcomes

The primary endpoint—investigator-assessed progression-free survival—was measured from the date of randomisation to the date of objective cancer progression as defined by RECIST 1.1 or death from any cause. Secondary endpoints included overall survival, overall response (complete or partial response), duration of response (duration of complete or partial response), proportion of patients achieving disease control (complete response or stable disease), proportion of patients achieving clinical benefit (complete response, partial response, or stable disease for at least 6 months), safety, patient-reported outcomes, relationship between abemaciclib, trastuzumab, and fulvestrant exposure and response for safety and efficacy endpoints, and pharmacokinetics. As there were no differences in abemaciclib or trastuzumab pharmacokinetics exposures observed between study groups, exposure–response relationships were not investigated. Overall survival was measured from the date of randomisation to the date of death from any cause. Overall response is a summary measure of best overall response as defined by RECIST 1.1. Best overall response is derived from timepoint responses observed while on study treatment and during the short-term follow-up period (but before the initiation of post-discontinuation therapy), with the exception of patients who received surgery, radiotherapy, or both for advanced breast cancer. Duration of response was measured from the date of first evidence of complete response or partial response to the date of objective progression or the date of death due to any cause, whichever was earlier. Patient-reported outcome scales included the mBPI-sf, EORTC QLQ-C30, and the health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L). The EQ-5D 5L scores are incorporated into health economic models and are not reported here.

Statistical analysis

The study planned to enrol approximately 225 patients in 1:1:1 randomisation with 75 patients in each group. The primary analysis of progression-free survival was to be done after approximately 165 progression-free survival events had occurred in the intention-to-treat population, which would yield at least 80% power assuming a hazard ratio (HR) of 0·667 at an experiment-wise two-sided α level of 0·2. This corresponded to an approximately 2-month improvement in median progression-free survival if the true median progression-free survival was 4 months in the control group (group C). The two-sided α of 0·2 (equivalently, one-sided α of 0·1) is a commonly used α level for phase 2 clinical trials. Use of a two-sided α level of 0·05, as is done in phase 3 trials, would require a larger number of events and sample size.

Efficacy analyses and patient characteristics were based on the intention-to-treat population. Pharmacokinetic analyses were done on all patients who received at least one dose of abemaciclib and had at least one evaluable pharmacokinetic sample. The study was designed to test the superiority of abemaciclib, trastuzumab, and fulvestrant (group A) or abemaciclib and trastuzumab (group B) to standard-of-care single-agent chemotherapy and trastuzumab (group C) in improving progression-free survival in the intention-to-treat population. The analysis used the log-rank test stratified by the randomisation

strata. The two abemaciclib groups were tested sequentially against the control group to preserve the α level: only if there was a significant benefit for group A versus C would group B versus C be tested (as the triplet should have no less efficacy than the doublet). The safety population for safety analyses and exposure summaries was comprised of all enrolled patients receiving at least one dose of any drug. The key secondary endpoint of overall survival was tested inferentially for significance only if progression-free survival was significantly improved in both abemaciclib groups (A and B). Final overall survival analysis will be done after approximately 158 deaths have occurred in the intention-to-treat population.

An independent panel of radiologists did a post-hoc, exploratory blinded independent central review (BICR) of imaging scans by means of RECIST 1.1. Progression-free survival and censoring times were derived by means of the same rules as the primary progression-free survival analysis. The BICR HR was estimated by means of a Cox proportional hazard model stratified by the randomisation strata. A point estimate of the median BICR progression-free survival time was provided for each group. An additional post-hoc analysis of overall response was done in a subset of patients in the intention-to-treat population with measurable disease. Finally, a post-hoc analysis was done in the intention-to-treat population evaluating patients with brain metastases at study entry or progressive disease due to brain metastases.

Unless otherwise indicated, all hypothesis tests were done by means of a two-sided α level of 0·2, and all CIs were 95%. Significance of progression-free survival was defined as two-sided p<0·2. Kaplan-Meier methods were used to estimate the progression-free survival curves. HRs and 95% CIs with Wald's test p value were estimated by means of the Cox proportional hazard model. The assumption of proportional hazards was met for the test of progression-free survival, which was verified visually through the graph of log(–log[$S(t)$]) versus log(t), as well as a proportionality test of the interaction between treatment group and log(time) in the proportional hazards model, which was not significant (Wald's test p=0·85 for group A *vs* C, p=0·99 for group B *vs* C). The effects of prognostic variables (stratification factors, intrinsic, and extrinsic factors) on treatment response were established by means of an unstratified Cox regression model in a prespecified subgroup analysis. Comparisons of overall response between treatment groups were done using a stratified exact Cochran-Mantel-Haenszel test.

Compliance with questionnaires was calculated per cycle as the percentage of patients completing each instrument at that cycle. Because significance can sometimes be achieved for small changes in patient-reported outcome measures that might not represent a clinically meaningful benefit to the patient, it is important to also consider the magnitude of change.[19] For patient-reported outcome measurements, a clinically meaningful change was defined a priori as at least a 10-point score change from baseline for EORTC QLQ-C30 (0–100 scale) and a 2-point score change from baseline for mBPI-sf, on the basis of previous minimally important difference definitions for each instrument.[20,21] Significance was defined as p<0·05. Comparative change from baseline (all post-baseline visits) by study group was assessed for the EORTC QLQ-C30 and mBPI-sf worst pain score by means of longitudinal mixed regression when at least 25% of patients had an assessment in each study group. In patient-reported health-related quality of life, group B was not compared with group C because the predefined efficacy threshold for group B versus C was not met.

Time to sustained deterioration by subscale was assessed with Cox proportional hazards. Deterioration was defined as the time from randomisation to the time at which the patient reported a clinically meaningful worsening (defined by means of the minimally important difference threshold) compared with a patient's baseline score and followed by all subsequent scores meeting minimally important difference criteria compared with baseline, or death, whichever was earlier.

There is no external independent data monitoring committee established for this trial. SAS version 9.4 was used for all statistical analyses. This trial is registered at ClinicalTrials.gov, NCT02675231.

Role of the funding source

The funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report. The report was prepared by the corresponding author, SMT, with input and approval from all coauthors. SMT and FA had full access to all data in the study and SMT had final responsibility for the decision to submit for publication.

Results

Between May 31, 2016, and Feb 28, 2018, 325 patients were screened, of whom 237 (intention-to-treat population) were randomly assigned, with 79 patients assigned to each study group (figure 1). Baseline demographics and disease characteristics are given in table 1. Across all groups, 207 (87%) had measurable disease. 119 (50%) patients had received two to three previous systemic therapies for advanced breast cancer, and 118 (50%) patients had received more than three. Overall, patients in the intention-to-treat population received a median of four previous lines (IQR 3–5) of systemic therapy for ABC. 183 (77%) patients had received previous endocrine therapy in any setting. Previous pertuzumab had been received by 119 (50%) patients and 232 (98%) had received previous trastuzumab emtansine. The five patients who had not received previous trastuzumab emtansine therapy were found ineligible but were included in the intention-to-treat population.

At data cutoff on April 8, 2019, 16 (20%) of 79 patients in group A, nine (11%) of 79 patients in group B, and ten (13%)

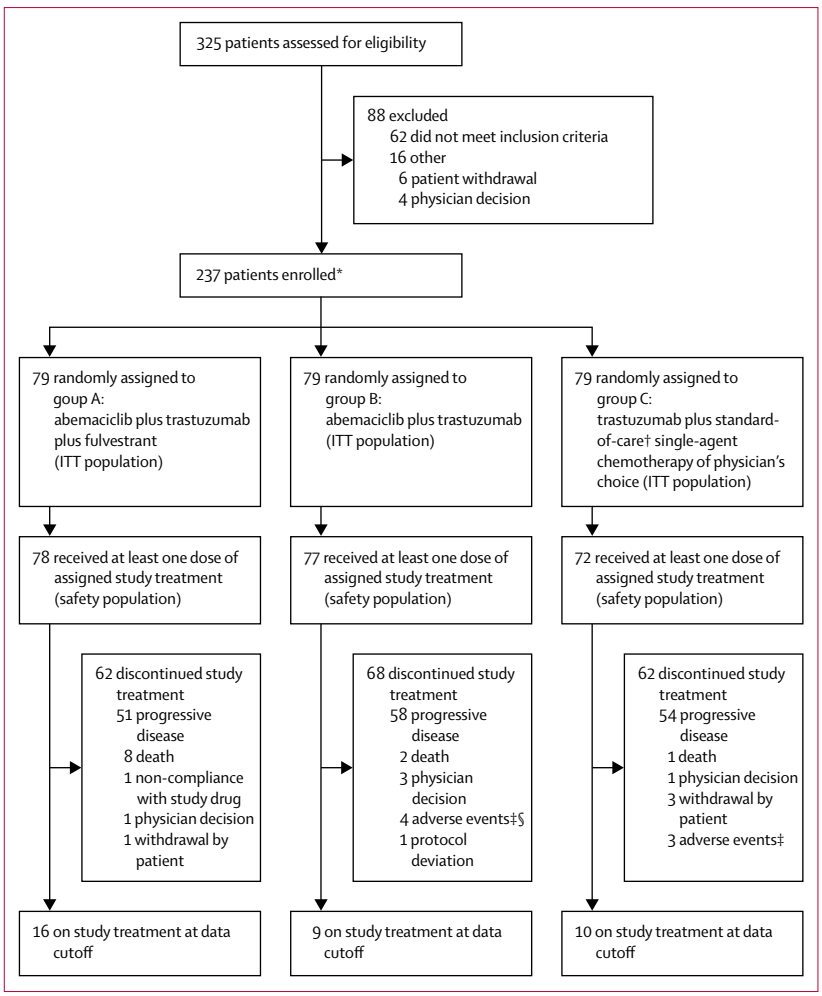

Figure 1: **Trial profile**
ITT=intention to treat. *Five patients were found ineligible having not received previous trastuzumab emstansine but were included in the ITT population.†Standard-of-care, single-agent chemotherapy should be an approved drug in breast cancer. ‡Patients who discontinued at least one study treatment owing to adverse events: group A (n=6), group B (n=11), group C (n=6). §Patients who discontinued abemaciclib only owing to adverse events: group A (n=6), group B (n=5).

of 79 patients in group C were still on treatment (figure 1); 59 (75%) patients in group A, 60 (76%) patients in group B, and 55 (70%) patients in group C had disease progression or had died. The most common chemotherapy agents administered in group C were vinorelbine (27 [38%] of 72 patients), capecitabine (19 [26%] patients), eribulin (12 [17%] patients), and gemcitabine (eight [11%] patients; appendix p 13). Dose reductions occurred in 39 (50%) of 78 patients in group A, 32 (42%) of 77 in group B, and 20 (28%) of 72 patients in group C (table 2). 36 (46%) of 78 patients in group A and 32 (42%) of 77 in group B had dose reductions due to abemaciclib.

Regarding the primary endpoint, 169 progression-free survival events occurred in the intention-to-treat population: 56 (33%) in group A, 61 (36%) in group B, and 52 (31%) in group C (figure 2), taking into account censoring. The median follow-up was 19·0 months (IQR 14·7–25·1). Median progression-free survival was 8·3 months (95% CI 5·9–12·6) in group A versus 5·7 months (5·4–7·0) in group C (HR 0·67; 95% CI 0·45–1·00; p=0·051). This increase was significant at the prespecified two-sided α of 0·2. The median progression-free survival in group B was 5·7 months (95% CI 4·2–7·2) and was not significantly different from the median progression-free survival in group C (HR 0·94; 95% CI 0·64–1·38; p=0·77). Additional subgroup analyses of group A versus C and group B versus C were generally consistent with overall results (appendix pp 10–11). At the time of the progression-free survival analysis, overall survival data were immature with a total of 93 deaths (31 [39%] patients in group A, 30 [38%] patients in group B, and 32 [41%] patients in group C) and will be reported later. Overall response was also significantly higher in group A versus group C in both the intention-to-treat population and in the post-hoc analysis in patients with measurable disease (tables 3, 4).

The post-hoc, exploratory analysis according to BICR included 128 progression-free survival events: 48 (61%) of 79 patients in group A, 43 (54%) of 79 patients in group B, and 37 (47%) of 79 patients in group C. No difference was observed between groups A and C (median progression-free survival 7·1 months *vs* 6·9 months; HR 0·883; 95% CI 0·565–1·380; two-sided p=0·59 stratified) or between groups B and C (median progression-free survival 7·9 months *vs* 6·9 months; HR 0·876; 95% CI 0·560–1·368; two-sided p=0·56 stratified). Results were consistent with investigator's assessment for the secondary endpoint of overall response (group A: 30% [95% CI 20–41; group B: 17% [8–25]; group C: 11% [4–18]). There were 41 fewer events overall observed for the BICR of progression-free survival than in the investigator's assessment, with the biggest discrepancy being in group C. Discordance at the patient level for progression status between the BICR and the investigator assessment was 21 (29%) of 73 patients with non-missing assessments in group A, 17 (24%) of 72 patients in group B, and 23 (34%) of 68 patients in group C.

A post-hoc analysis reported 37 (16%) of 237 patients had a history of brain metastases at study entry. A total of 25 (11%) of 237 patients had progressive disease due to brain lesions or received on-study or post-discontinuation intervention for brain metastases. These numbers are too small to reach any definitive conclusions (appendix p 12).

The safety population comprised 227 patients (table 5). Of these, 73 (94%) of 78 patients in group A, 75 (97%) of 77 in group B, and 67 (93%) of 72 in group C had at least one treatment-emergent adverse event of grade 1–4. Patients with at least one treatment-emergent adverse event of grade 3 or 4 were reported in all groups, with group A reporting the greatest number of patients (53 [68%] of 78). Neutropenia was the most frequently reported treatment-emergent adverse event of grade 3 or 4, reported in 21 (27%) of 78 in group A, 17 (22%) of 77 in group B, and 19 (26%) of 72 patients in group C.

	Group A (n=79)	Group B (n=79)	Group C (n=79)
Age, years	55 (47–62)	54 (47–62)	57 (47–67)
Geographical distribution			
Asia Pacific	13 (16%)	13 (16%)	12 (15%)
Europe	30 (38%)	45 (57%)	36 (46%)
North America	24 (30%)	13 (16%)	24 (30%)
South America	12 (15%)	8 (10%)	7 (9%)
Metastatic site			
Visceral	58 (73%)	56 (71%)	48 (61%)
Lung	35 (44%)	31 (39%)	22 (28%)
Liver	32 (41%)	32 (41%)	22 (28%)
Bone only	7 (9%)	3 (4%)	7 (9%)
Other	13 (16%)	18 (23%)	16 (20%)
Measurable disease	70 (89%)	68 (86%)	69 (87%)
Previous systemic therapies for advanced breast cancer			
2–3	35 (44%)	44 (56%)	40 (51%)
>3	44 (56%)	35 (44%)	39 (49%)
Previous endocrine therapy			
Neoadjuvant endocrine therapy	2 (3%)	2 (3%)	2 (3%)
Adjuvant endocrine therapy	29 (37%)	39 (49%)	35 (44%)
Endocrine therapy for metastatic disease	46 (58%)	36 (46%)	42 (53%)
Tamoxifen in any setting	35 (44%)	45 (57%)	37 (47%)
Aromatase inhibitors in any setting	46 (58%)	42 (53%)	42 (53%)
Overall*	63 (80%)	60 (76%)	60 (76%)
Previous HER2 therapies for advanced breast cancer			
Trastuzumab	77 (97%)	76 (96%)	79 (100%)
Trastuzumab emtansine	77 (97%)	78 (99%)	77 (97%)
Pertuzumab	43 (54%)	37 (47%)	39 (49%)
Lapatinib	35 (44%)	37 (47%)	31 (39%)

Data are median (IQR) or n (%). *Any of the following: letrozole (64 [27%] of 237 patients), tamoxifen (42 [18%] patients), exemestane (34 [14%] patients), or anastrozole (32 [14%] patients).Group A=abemaciclib, trastuzumab, and fulvestrant. Group B=abemaciclib and trastuzumab. Group C=standard-of-care chemotherapy and trastuzumab.

Table 1: **Baseline characteristics**

	Group A (n=78)	Group B (n=77)	Group C (n=72)
Number of treatment cycles	10 (5–21)	8 (3–15)	8 (2–16)
Number of patients receiving concomitant filgrastim	3 (4%)	2 (3%)	9 (13%)
Dose reductions*	39 (50%)	32 (42%)	20 (28%)
Reasons leading to dose reductions reported for ≥5% of patients			
Any adverse event	37 (47%)	30 (39%)	20 (28%)
Diarrhoea	10 (13%)	12 (16%)	1 (1%)
Neutropenia	8 (10%)	9 (12%)	12 (17%)

Data are median (IQR) or n (%). Group A=abemaciclib, trastuzumab, and fulvestrant. Group B=abemaciclib and trastuzumab. Group C=standard-of-care chemotherapy and trastuzumab. *Dose reduction of abemaciclib: 36 (46%) of 78 patients in group A and 32 (42%) of 77 patients in group B.

Table 2: **Summary of drug exposure and dose adjustments**

The most common serious adverse events that occurred in more than 1% of the safety population were: in group A, pyrexia (three [4%] of 78 patients), diarrhoea (two [3%]), urinary tract infection (two [3%]), and acute kidney injury (two [3%]); in group B, diarrhoea (two [3%] of 77 patients), and pneumonitis (two [3%]); and in group C, neutropenia (four [6%] of 72 patients) and pleural effusion (two [3%]). Additional safety results on adverse events of special interest can be found in appendix pp 2–3.

Six patients in group A, 11 patients in group B, and six patients in group C discontinued at least one study treatment owing to adverse events (figure 1). Of these, six patients in group A and five in group B discontinued abemaciclib treatment only owing to adverse events. Four patients in group B and three patients in group C discontinued all treatments in the study regimen owing to adverse events and no patients in group A discontinued all treatments in the triplet combination. Of the six patients in group A and the six patients in group C, adverse events unique to each patient led to treatment discontinuation. Two of the eleven patients in group B discontinued at least one study treatment owing to cardiac failure, and two additional patients in group B discontinued study treatment owing to decreased neutrophil count.

31 (40%) of 78 patients in group A, 29 (38%) of 77 patients in group B, and 31 (43%) of 72 patients in group C died before data cutoff (appendix p 14). The number of deaths on therapy or within 30 days of treatment discontinuation were similar across the three groups. Deaths on study treatment due to adverse events included two patients in group A (cardiopulmonary arrest, dyspnoea), one in group B (pulmonary fibrosis), and one in group C (febrile neutropenia). Each death in groups B and C was attributed to study treatment.

Compliance to the patient-reported health-related quality-of-life questionnaires was 100% at baseline, at least 90% on therapy, and at least 70% at short-term follow-up and was similar between treatment groups (Eli Lilly and Company data on file). The most common specified reason for non-compliance was study site failed to administer (Eli Lilly and Company data on file). Symptom detriment in group A versus C (least squares mean change from baseline) was reported for EORTC QLQ-C30 diarrhoea (significant and clinically meaningful) and nausea and vomiting (significant but not clinically meaningful; appendix p 15). However, symptom benefit in group A versus C was reported for EORTC QLQ-C30 pain and insomnia, which were significant but not clinically meaningful. No other significant differences were observed between groups A and C for EORTC QLQ-C30 scales (appendix pp 4–5). Group A and C longitudinal data from EORTC QLQ-C30 pain, insomnia, nausea and vomiting, and diarrhoea are presented in the appendix (pp 6–7). At the

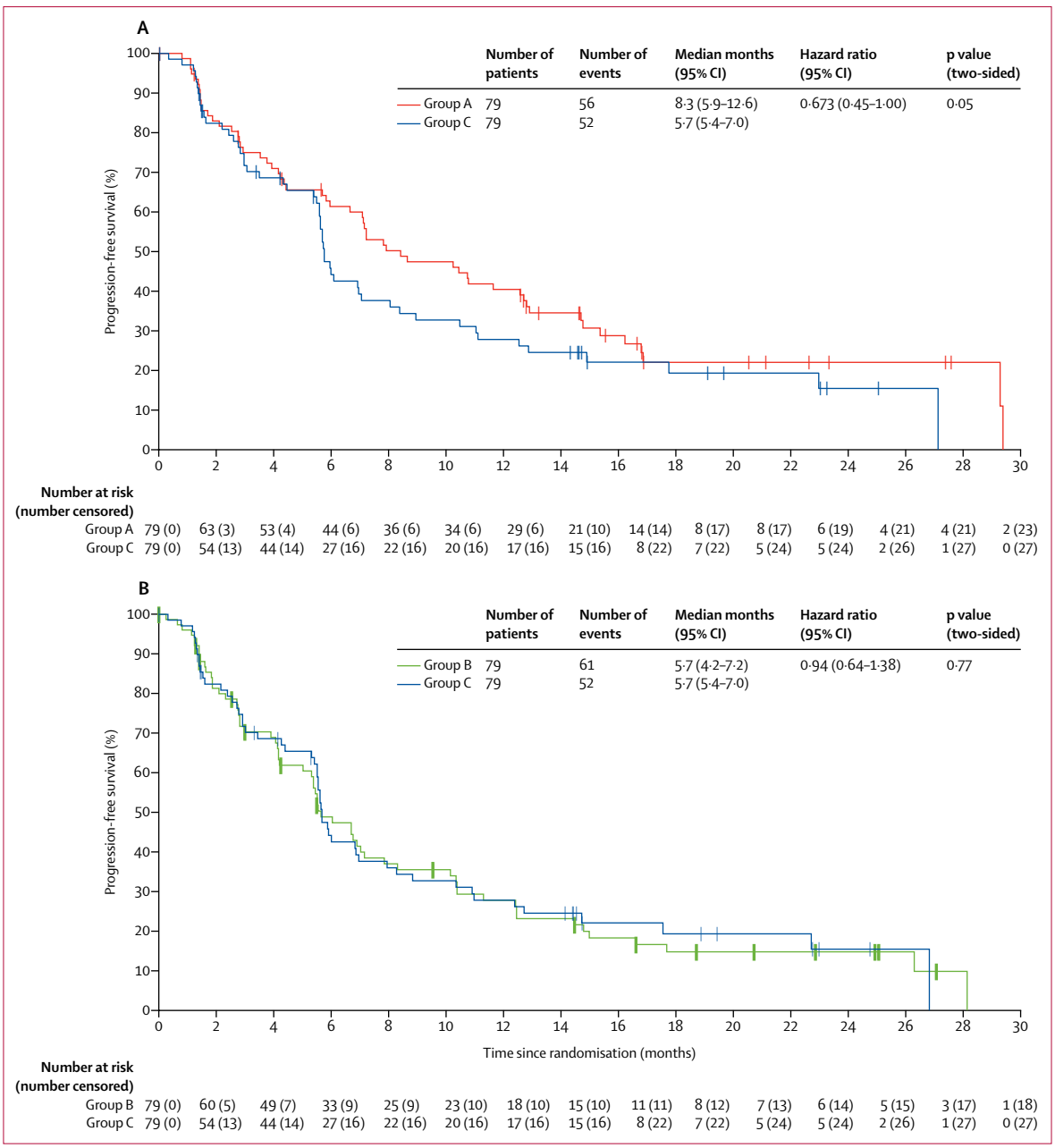

Figure 2: **Kaplan-Meier estimates of progression-free survival in group A versus C (A) and group B versus C (B)**
Group A=abemaciclib, trastuzumab, and fulvestrant. Group B=abemaciclib and trastuzumab. Group C=standard-of-care chemotherapy and trastuzumab.

post-therapy follow-up visit, a significant but not clinically meaningful change from baseline benefit for group A compared with group C was seen for fatigue (–9·62 [4·87]; p=0·050) and nausea and vomiting (–8·44 [3·57]; p=0·020; appendix p 15). On the basis of time to sustained deterioration analyses, patients in group A reported a significant delay in the worsening of physical and emotional functioning compared with patients in group C. No significant differences in time to sustained deterioration were observed for the remaining EORTC QLQ-C30 scales or the mBPI-sf worst pain item (appendix p 8).

Similar exposures of abemaciclib, its two major active metabolites, M2 and M20, and trastuzumab were observed between groups A and B (appendix p 9).

Discussion

To our knowledge, this trial is the first randomised study of a CDK4 and CDK6 inhibitor to report positive results in combination with endocrine therapy and HER2-targeted

	Group A (n=79)	Group B (n=79)	Group C (n=79)	Group A *vs* group C: odds ratio (95% CI); p value
Duration of response, months	12·5 (6·5–23·5)	9·5 (2·8–22·7)	NR	..
Time to first confirmed response, months	2·8 (1·6–5·5)	4·2 (1·5–5·6)	1·6 (1·3–2·8)	..
Complete response	1 (1%; 0–4)	0	0	..
Partial response	25 (32%; 21–42)	11 (14%; 6–22)	11 (14%; 6–22)	..
Stable disease	36 (46%; 35–57)	48 (61%; 50–72)	42 (53%; 42–64)	..
Stable disease for ≥6 months	20 (25%; 16–35)	25 (32%; 21–42)	19 (24%; 15–34)	..
Progressive disease	10 (13%; 5–20)	13 (17%; 8–25)	14 (18%; 9–26)	..
Overall response (complete response + partial response)	26 (33%; 23–43)	11 (14%; 6–22)	11 (14%; 6–22)	3·2 (1·4–7·1); p=0·0042
Disease control (complete response + partial response + stable disease)	62 (79%; 70–88)	59 (75%; 65–84)	53 (67%; 57–78)	2·1 (1·0–4·3); p=0·065
Clinical benefit (complete response + partial response + stable disease ≥6 months)	46 (58%; 47–69)	36 (46%; 35–57)	30 (38%) 27–49	2·7 (1·4–5·3); p=0·0032

Data are median (IQR) or n (%; 95% CI), unless otherwise stated. NR=not reached.

Table 3: **Response outcomes in the intention-to-treat population**

	Group A (n=70)	Group B (n=68)	Group C (n=69)	Group A *vs* group C: odds ratio (95% CI); p value
Duration of response, months	10·4 (6·5–23·5)	9·5 (2·8–22·7)	NR	..
Complete response	0	0	0	..
Partial response	25 (36%; 25–47)	11 (16%; 7–25)	11 (16%; 7– 25)	..
Stable disease	30 (43%; 31–55)	39 (57%; 46–69)	33 (48%; 36–60)	..
Stable disease for ≥6 months	15 (21%; 12–31)	21 (31%; 20–42)	12 (17%; 8–26)	..
Progressive disease	9 (13%; 5–21)	11 (16%; 7–25)	13 (19%; 10–28)	..
Overall response (complete response + partial response)	25 (36%; 25–47)	11 (16%; 7–25)	11 (16%; 7–25)	3·0 (1·3–6·6); p=0·011
Disease control (complete response + partial response + stable disease)	55 (79%; 69–88)	50 (74%; 63–84)	44 (64%; 52–75)	2·2 (1·0–4·7); p=0·056
Clinical benefit (complete response + partial response + stable disease ≥6 months)	40 (57%; 46–69)	32 (47%; 35–59)	23 (33%; 22–44)	2·8 (1·4–5·5); p=0·0057

Data are median (IQR) or n (%; 95% CI), unless otherwise stated. NR=not reached. Group A=abemaciclib, trastuzumab, and fulvestrant. Group B=abemaciclib and trastuzumab. Group C=standard-of-care chemotherapy and trastuzumab.

Table 4: **Response outcomes in patients with measurable disease (n=207)**

therapy compared with standard-of-care chemotherapy with trastuzumab in patients pretreated with at least two HER2-targeted treatments. monarcHER showed an improved progression-free survival in group A (abemaciblib, trastuzumab, and fulvestrant) compared with group C (standard-of-care chemotherapy and trastuzumab) in women with hormone receptor-positive, HER2-positive advanced breast cancer. This improvement was significant at the prespecified two-sided α of 0·2. The confirmed overall responses in both the intention-to-treat population and the subset with measurable disease were more than doubled in group A versus group C.

The treatment landscape for patients with HER2-positive advanced breast cancer is rapidly evolving. In 2019, Saura and colleagues[22] showed a benefit for the tyrosine kinase inhibitor neratinib in combination with capecitabine compared with lapatinib plus capecitabine, with an HR for progression-free-survival of 0·76 (95% CI 0·63–0·93; p=0·006). Margetuximab, a chimeric IgG monoclonal antibody, in combination with physician's choice standard-of-care chemotherapy versus trastuzumab plus physician's choice standard-of-care chemotherapy resulted in a median progression-free survival of 5·8 months versus 4·9 months (HR 0·76; p=0·033) and an overall response rate of 22% versus 16% (p=0·060).[23] A study of tucatinib, an investigational, oral tyrosine kinase inhibitor, in combination with capecitabine and trastuzumab reported a median progression-free survival of 7·8 months versus 5·6 months with placebo plus capecitabine and trastuzumab (HR 0·54, 95% CI 0·42–0·71; p<0·001).[24] Finally, an open-label; single-arm, phase 2 study of the novel antibody–drug conjugate, trastuzumab deruxtecan (DS8201) showed a confirmed overall response of 60·9% (95% CI 53·4–68·0).[25] Other novel targeted agents are being explored in patients with HER2-positive disease (NCT04208178).

The monarcHER results are noteworthy because they show a superior progression-free survival and higher

	Group A (n=78)			Group B (n=77)			Group C (n=72)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Patients with ≥1 treatment-emergent adverse event	20 (26%)	49 (63%)	4 (5%)	36 (47%)	38 (49.4)	1 (1%)	32 (44%)	29 (40.3)	6 (8%)
Diarrhoea	55 (71%)	7 (9%)	0	55 (71%)	5 (7%)	0	16 (22%)	2 (3%)	0
Fatigue	38 (49%)	3 (4%)	0	34 (44%)	5 (7%)	0	31 (43%)	1 (1%)	0
Neutropenia	16 (21%)	20 (26%)	1 (1%)	9 (12%)	17 (22%)	0	9 (13%)	14 (19%)	5 (7%)
Nausea	32 (41%)	3 (4%)	0	30 (39%)	2 (3%)	0	24 (33%)	0	0
Anaemia	20 (26%)	7 (9%)	0	18 (23%)	3 (4%)	0	14 (19%)	3 (4%)	0
Thrombocytopenia	14 (18%)	6 (8%)	2 (3%)	18 (23%)	5 (7%)	0	3 (4%)	2 (3%)	0
Abdominal pain	20 (26%)	1 (1%)	0	17 (22%)	0	0	12 (17%)	1 (1%)	0
Vomiting	18 (23%)	1 (1%)	0	20 (26%)	2 (3%)	0	9 (13%)	1 (1%)	0
Leucopenia	10 (13%)	8 (10%)	0	6 (8%)	2 (3%)	0	3 (4%)	5 (7%)	2 (3%)
Cough	18 (23%)	0	0	11 (14%)	0	0	8 (11%)	0	0
Decreased appetite	16 (21%)	0	0	17 (22%)	0	0	12 (17%)	1 (1%)	0
Pyrexia	13 (17%)	2 (3%)	0	5 (6%)	0	0	8 (11%)	2 (3%)	0
Upper respiratory tract infection	12 (15%)	1 (1%)	0	4 (5%)	0	0	7 (10%)	0	0
Headache	12 (15%)	1 (1%)	0	11 (14%)	0	0	11 (15%)	2 (3%)	0
Dyspnoea	9 (12%)	3 (4%)	0	7 (9%)	1 (1%)	0	10 (14%)	2 (3%)	0
Pruritus	12 (15%)	0	0	10 (13%)	0	0	3 (4%)	0	0
Blood creatinine increased	10 (13%)	0	0	11 (14%)	0	0	0	0	0
AST increased	9 (12%)	0	0	6 (8%)	1 (1%)	0	8 (11%)	0	0
Arthralgia	8 (10%)	1 (1%)	0	5 (6%)	0	0	5 (7%)	1 (1%)	0
Rash maculopapular	8 (10%)	0	0	7 (9%)	0	0	6 (8%)	0	0

The table shows adverse events of all grades occurring in ≥10% of the safety population in any group. Data are n (%), listed by decreasing frequency (all grades) in group A (abemaciclib + trastuzumab + fulvestrant). Deaths (grade 5 events) occurred in all three groups: two patients in group A (cardiopulmonary arrest and dyspnoea), one in group B (pulmonary fibrosis), and one in group C (febrile neutropenia). The deaths in group A were not attributed to study treatment. Each death in group B and C was attributed to treatment (appendix p 14). AST=aspartate aminotransferase. Group A=abemaciclib, trastuzumab, and fulvestrant. Group B=abemaciclib and trastuzumab. Group C=standard-of-care chemotherapy and trastuzumab.

Table 5: **Treatment-emergent adverse events**

overall response rate with a chemotherapy-free regimen of abemaciclib, trastuzumab, and fulvestrant compared with standard-of-care chemotherapy plus trastuzumab. A chemotherapy-free treatment option in an advanced and heavily pretreated patient population would probably be of interest to both patients and their physicians. Further larger studies are warranted. We did not analyse time to subsequent chemotherapy because all the patients had advanced disease and any such analysis would be confounded by the number of patients who died before receiving subsequent treatment.

The patients participating in monarcHER represent a heavily pretreated population; 183 (77%) of 237 patients received at least one previous endocrine therapy. There was no significant improvement in progression-free survival for group B (abemaciclib and trastuzumab) compared with group C (standard-of-care chemotherapy and trastuzumab). Notably, the abemaciclib–trastuzumab doublet (group B) showed similar benefit to that of chemotherapy–trastuzumab (group C), indicating activity for abemaciclib in this patient population. The improvement in progression-free survival in group A versus group C is unlikely to be from the addition of endocrine therapy alone. It could be anticipated that the progression-free survival benefit observed with endocrine therapy in earlier lines of therapy might be better than those observed in the refractory setting of monarcHER. In 2009, Kaufman and colleagues[26] reported a median progression-free survival of 4·8 months versus 2·4 months for the combination of anastrozole plus trastuzumab versus anastrozole alone in patients for whom up to one line of previous endocrine therapy was allowed for advanced breast cancer. Also in 2009, Johnston and colleagues[27] reported a median progression-free survival of 8·2 months versus 3·0 months for the combination of letrozole plus lapatinib versus letrozole alone in patients for whom no previous therapy for advanced breast cancer was permitted. A subgroup analysis of the CALGB 40302 trial[28] reported a median progression-free survival of 5·9 months versus 3·3 months for fulvestrant plus lapatinib versus fulvestrant alone in patients who had received up to one previous chemotherapy and up to two previous endocrine therapies. The control groups of these studies show the low clinical activity of endocrine therapy alone (including fulvestrant) and that the addition of an anti-HER2 agent adds modestly to the outcome even among patients with less heavily pretreated disease. On review of all available data, including the activity of abemaciclib plus trastuzumab seen with group B, the historical data outlined above, and in association with in vitro observations from O'Brien and

colleagues,[15] it is reasonable to suppose the superiority of group A compared with group C is owing to the synergism rather than the addition of fulvestrant alone.

The pharmacokinetics of abemaciclib and its two major metabolites are consistent with those associated with efficacy in MONARCH 2 and MONARCH 3. These steady-state exposures of abemaciclib are similar to those associated with target inhibition and tumour growth reduction in xenograft models.[29] For the combination treatments, the pharmacokinetics of fulvestrant were similar to exposures observed in the monotherapy and combination treatment groups in MONARCH 2, and the pharmacokinetics of trastuzumab in combination with abemaciclib was similar to the pharmacokinetics of trastuzumab monotherapy.[30] Overall, these results suggest that abemaciclib does not have an effect on trastuzumab or fulvestrant pharmacokinetics, nor does the combination affect the pharmacokinetics of abemaciclib.

Abemaciclib was generally well tolerated; however, the incidence of thrombocytopenia was higher than that previously reported in MONARCH 1 and MONARCH 2.[10,12] Notably, previous trastuzumab emtansine use in the intention-to-treat population was 77 (97%) in group A, 78 (99%) in group B, and 77 (97%) in group C. The proportion of patients reporting grade 3 and 4 neutropenia was lower than anticipated in group C, which might be attributed to the imbalance in the use of filgrastim between groups. Group A had a longer duration of treatment than group C, potentially contributing to the greater number of grade 3 and worse adverse events observed. Although there were numerically more adverse events, deaths on treatment and dose discontinuations from adverse events were balanced between groups A and C.

Significant detriments in group A compared with group C were reported for nausea and vomiting, and diarrhoea. The detriment reported in diarrhoea was also clinically meaningful and consistent with the adverse event profile. These gastrointestinal-related symptoms were typically transient and returned to near baseline by the post-therapy follow-up visit. Finally, significant benefits in change from baseline for pain and insomnia, as well as nausea and vomiting at post-therapy follow-up, and delayed time to sustained deterioration for physical and emotional functioning provide patient-reported insight from a chemotherapy-free setting.

The monarcHER study has several limitations. The design did not allow isolation of the contributing treatment effect of fulvestrant. To do so would require a fourth treatment group examining the combination of fulvestrant and trastuzumab. Although this idea was considered during study development, there were concerns regarding its clinical applicability and potential effect on trial recruitment and data interpretation. The fulvestrant and trastuzumab doublet was not a standard of care in 2015 and was not seen as a potential treatment option by many physicians, resulting in this treatment group not being included. An additional limitation of the study design was that monarcHER was designed at an experimental two-sided α of 0·2, and therefore was not as rigorous as a registration phase 3 trial, which usually uses an α of 0·05. Furthermore, monarcHER was not designed to examine the CNS activity of any of the drug combinations. There were no preplanned analyses to evaluate the effect of the treatment groups on brain metastases. Although we did a post-hoc analysis of patients with a history of brain metastases at study entry, the numbers of patients involved were too small to reach any definitive conclusions. Finally, previous treatment with pertuzumab not being required at study entry is another potential limitation. monarcHER recruited globally between May 31, 2016, and Feb 28, 2018, with 61 (26%) of 237 patients recruited in North America, including the USA. The 119 (50%) patients with previous exposure to pertuzumab is likely to be reflective of the global recruitment in a period during which pertuzumab was not widely available or accessible outside of the USA.

Following our results, the question remains: what is the optimal role for CDK4 and CDK6 inhibitors in patients with hormone receptor-positive, HER2-positive breast cancer? Even in a rapidly changing environment with multiple new molecules entering the market, there remains an unmet medical need for patients with advanced disease who might wish to have a chemotherapy-free option available. With recurrence in the brain being of particular concern for patients with HER2-positive disease, prospective, adequately controlled studies to examine the effects of the combination of abemaciclib, trastuzumab, and fulvestrant on CNS activity are warranted. CDK4 and CDK6 inhibitors are being investigated in the adjuvant setting in patients with hormone receptor-positive, HER2-negative early breast cancer with outcomes awaited from ongoing trials. Consideration should be given to exploring their use in patients with hormone receptor-positive, HER2-positive early breast cancer who remain at high risk of recurrence despite optimal therapy.

Contributors

SMT, SG, and GLP contributed to the conception. SMT and GLP contributed to the design. SMT, AMW, SZ, JFH, TAT-S, FR, S-AI, S-BK, SRDJ, AC, KC, and ZY contributed to the acquisition of data. AC, SCC, ZY, and MCG contributed to the analysis. AMW, TAT-S, FR, S-AI, S-BK, SRDJ, AC, SG, SCC, GLP, ZY, MCG, and FA contributed to interpretation of data. SMT, AMW, SCC, GLP, ZY, MCG, and FA contributed to the drafting of the manuscript. AMW, SZ, JFH, TAT-S, FR, S-AI, S-BK, SRDJ, AC, SG, KC, SCC, GLP, ZY, MCG, and FA contributed to critical revision of the manuscript for intellectual content.

Declaration of interests

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Data sharing

Eli Lilly provides access, after anonymisation, to all individual participant data collected during the trial, except for pharmacokinetic and genetic data. Data can be requested 6 months after the indication studied has been approved in the USA and EU or after primary publication acceptance, whichever is later. No expiration date for data requests is set once the data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the online instructions.

For **data request instructions** see https://vivli.org

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