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Gedatolisib in combination with palbociclib and endocrine therapy in women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the dose expansion groups of an open-label, phase 1b study

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Summary

Background

The PI3K–mTOR pathway is frequently dysregulated in breast cancer. Combining an inhibitor targeting all class I PI3K isoforms and mTOR complex 1 (mTORC1)–mTOR complex 2 (mTORC2) with endocrine therapy and a CDK4/6 inhibitor might provide more effective tumour control than standard-of-care therapy. To evaluate this hypothesis, gedatolisib, a pan-PI3K–mTOR inhibitor, was assessed in a phase 1b trial combined with palbociclib and endocrine therapy in patients with hormone receptor-positive, HER2-negative, advanced breast cancer. Results from the dose expansion portion of this trial are reported herein.

Methods

This multicentre, open-label, phase 1b study recruited female patients aged at least 18 years from 17 sites across the USA with hormone-receptor-positive, HER2-negative, advanced breast cancer and an Eastern Cooperative Oncology Group performance status of 0–1. Four patient groups were studied in the dose expansion portion of the study: treatment-naive in the advanced setting (first line; group A), progression on 1–2 lines of endocrine therapy but CDK4/6 inhibitor-naive (group B); and one or more previous lines (second-line and higher) of therapy, including a CDK4/6 inhibitor (groups C and D). Gedatolisib 180 mg was administered intravenously weekly in 28-day treatment cycles for groups A–C, and on days 1, 8, and 15 for group D. Letrozole (group A), fulvestrant (groups B–D), and palbociclib (all groups) were administered at standard doses and schedules. The primary endpoint was investigator-assessed objective response rate per RECIST version 1.1 in the evaluable analysis set. This trial is completed and registered with ClinicalTrials.gov, NCT02684032.

Findings

Between Dec 19, 2017, and June 19, 2019, 103 female participants were enrolled in the dose expansion groups A (n=31), B (n=13), C (n=32), and D (n=27). Median follow-up was 16·6 months (IQR 5·7–48·4) for group A, 11·0 months (7·6–16·9) for group B, 3·6 months (1·8–7·5) for group C, and 9·4 months (5·3–16·7) for group D for the primary endpoint. Gedatolisib, palbociclib, and endocrine therapy induced an objective response in 23 (85·2%; 90% CI 69·2–94·8) of 27 evaluable first-line participants (group A). In the second-line and higher setting, an objective response was observed in eight (61·5%; 90% CI 35·5–83·4) of 13 evaluable group B participants, seven (25·0%;

12·4–41·9) of 28 evaluable group C participants, and 15 (55·6%; 38·2–72·0) of 27 evaluable group D participants; this included participants with both wild-type and mutated *PIK3CA* tumours. The most common grade 3–4 treatment-related adverse events were neutropenia (65 [63%] of 103), stomatitis (28 [27%]), and rash (21 [20%]). Grade 3–4 hyperglycaemia was reported in six (6%) participants. 23 (22%) of 103 participants had a treatment-related serious adverse event, and there were no treatment-related deaths. Nine (9%) participants discontinued treatment because of a treatment-emergent adverse event.

Interpretation

Gedatolisib plus palbociclib and endocrine therapy showed a promising objective response rate compared with the published results for standard-of-care therapies and had an acceptable safety profile.

Funding

Pfizer and Celcuity.

Research in context

Evidence before this study

We searched PubMed from database inception to March 1, 2022, for clinical trials assessing combination therapies used for the treatment of advanced and metastatic breast cancer. Search terms included “gedatolisib” or “PI3K” or “AKT” or “mTOR” and “inhibitor” and “palbociclib” or “cyclin- dependent kinase” and “metastatic breast cancer” or “advanced breast cancer”. The PI3K inhibitor, alpelisib, is approved for use in combination with fulvestrant only for patients with PIK3CA- mutated, HR-positive, HER2-negative, advanced breast cancer following progression on endocrine therapy. The mTORC1 inhibitor, everolimus, in combination with exemestane is approved for patients with HR-positive, HER2-negative, advanced breast cancer following progression on letrozole or anastrozole. Everolimus combined with fulvestrant is also used in clinical practice on the basis of results from the PrECOG0102 study. After the initial submission of this manuscript, capivasertib in combination with fulvestrant received FDA approval on Nov 16, 2023, for patients with HR-positive, HER2- negative, advanced breast cancer whose tumours had one or more *PIK3CA*, *AKT1*, or *PTEN* alterations.

Added value of this study

To our knowledge this is the first clinical study to examine gedatolisib plus palbociclib and endocrine therapy in patients with HR-positive, HER2-negative, advanced breast cancer. The triplet combinations showed results that compared favourably with current standard-of-care first-line and second-line and higher regimens, regardless of *PIK3CA* mutation status or CDK4/6 inhibitor pretreatment. Only nine (9%) of 103 participants discontinued the study treatment owing to a treatment-related adverse event. This safety profile compares favourably to other available PI3K inhibitors used in this clinical setting.

Implications of all the available evidence

The overall positive benefit–risk ratio for the combination of gedatolisib with palbociclib and endocrine therapies indicates that further evaluation of gedatolisib is warranted for treatment-naive patients and patients previously treated for advanced breast cancer. This study provided the rationale for an ongoing phase 3 clinical trial (VIKTORIA-1) in patients with HR-positive, HER2-

negative, advanced breast cancer who were previously treated with endocrine therapy and a CDK4/6 inhibitor.

Introduction

Breast cancer is the leading cause of cancer death in women worldwide, and finding therapies with improved efficacy versus available standards of care remains a high unmet clinical need. The most common subtype of advanced breast cancer is hormone receptor (HR)-positive, HER2-negative. Approximately 70% of all breast cancer tumours express the oestrogen receptor, which, on activation, regulates the expression of various genes involved in tumour proliferation. Endocrine therapy, including aromatase inhibitors, selective oestrogen receptor modulators, or selective oestrogen receptor degraders is one of the most effective therapies for HR-positive, HER2-negative breast cancer.[1] However, resistance to endocrine therapy will develop in most tumours, posing a particular challenge in the metastatic setting.[2]

Inhibitors of the cyclin-dependent kinases 4 and 6 (CDK4/6) in combination with endocrine therapy have emerged as an effective treatment option for HR-positive, HER2-negative, advanced breast cancer. CDK4/6 signalling regulates the cell cycle by promoting the transition from the G1 to the S phase, which is associated with cell proliferation and tumour growth. Palbociclib was the first approved CDK4/6 inhibitor and was shown to improve progression-free survival in combination with endocrine therapy in both pre-menopausal and post-menopausal women with HR-positive advanced breast cancer with median progression-free survival of 27·6 months (95% CI 22·4–30·3) in first-line patients[3,4] and 9·5 months (9·2–11·0) in second-line and higher patients.[5] Two additional CDK4/6 inhibitors, ribociclib and abemaciclib, have been approved. Ribociclib was associated with median progression-free survival of 25·3 months (95% CI 23·0–30·3) in combination with letrozole in first-line patients[6] and 20·5 months (18·5–23·5) in combination with fulvestrant in first-line and second-line patients.[7] Abemaciclib was associated with median progression-free survival of 28·2 months in combination with a non-steroidal aromatase inhibitor in first-line patients[8] and 16·4 months in combination with fulvestrant in first-line and second-line patients.[9] Combined CDK4/6 inhibitor and endocrine therapy is now the standard of care for the treatment of patients with HR-positive, HER2-negative, advanced breast cancer who are treatment-naive or have received previous endocrine therapy.

As with endocrine therapy, patients with HR-positive, HER2-negative, advanced breast cancer become resistant to CDK4/6 inhibitors. Non-clinical data suggest that dysregulation of the

G1 to S phase checkpoint, which can occur through transient non-genomic changes in CCNE1 or loss of Rb1 might contribute to resistance to CDK4/6 inhibitors.[10] Additional suggested resistance mechanisms involve the interaction of the cell cycle and PI3K–AKT–mTOR pathways.[11] Addressing these resistance mechanisms remains a substantial clinical challenge, particularly in advanced breast cancer.[2]

Dysregulation of the PI3K–AKT and the mTOR signalling pathway is observed in many types of cancer, including breast cancer.[12] More than 70% of breast cancers have direct or indirect activation of the PI3K–mTOR pathway putatively through mechanisms such as deletion of *PTEN*, oncogenic mutations in *PIK3CA*, or HER2 or G protein-coupled receptor activation.[13] The upregulation of the PI3K–AKT–mTOR pathway promotes hormone-dependent and independent oestrogen receptor transcriptional activity, which contributes to endocrine resistance, leading to tumour cell growth, survival, motility, and metabolism. Clinical studies have shown that PI3K and mTOR inhibition can restore sensitivity to endocrine therapy.[14,15]

The PI3K–AKT–mTOR pathway, like many mitogenic pathways, can promote the activities of cyclin D and CDK4/6 to drive proliferative cell cycling.[16] Several preclinical studies have shown that CDK4/6 inhibitor resistance in breast cancer cell lines can be reversed by treatment with PI3K–AKT–mTOR inhibitors.[17,18]

The results of these studies provide a strong rationale for the addition of inhibitors that target the PI3K-AKT-mTOR pathway to endocrine therapy alone or in combination with a CDK4/6 inhibitor.

Three therapies targeting the PI3K–AKT–mTOR pathway have been shown to improve outcomes in patients with HR-positive, HER2-negative breast cancer. The mTOR inhibitor everolimus was approved in combination with exemestane for patients who had progressed on non-steroidal aromatase inhibitor therapy on the basis of the results of the BOLERO-2 trial, which reported median progression-free survival of 6·9 months (95% CI 6·4–8·1). In this study, 19% of participants discontinued everolimus owing to adverse events, with the most common being stomatitis and rash.[14] Alpelisib, a p110α subunit-selective PI3K inhibitor, combined with fulvestrant was approved to treat HR-positive, HER2-negative, *PIK3CA*-mutated, advanced breast cancer

following progression on or after previous endocrine therapy on the basis of the results of the SOLAR-1 phase 3 clinical trial, which reported median progression-free survival of 11·0 months (95% CI 7·5 to 14·5) in patients with *PIK3CA*-mutated cancer. Few participants enrolled in this study (35 [6·1%] of 572) had received previous CDK4/6 inhibitor therapy and 71 (25·0%) of 284 participants discontinued alpelisib owing to adverse events, with the most common being hyperglycaemia and rash.[15] A subsequent clinical trial, BYLieve, evaluated alpelisib and fulvestrant or letrozole in patients with HR-positive, HER2-negative, *PIK3CA*-mutated, advanced breast cancer who were previously treated with a CDK4/6 inhibitor and reported median progression-free survival of 7·3 months (95% CI 5·6–8·3) in cohort A (patients who had progressed on a CDK4/6 inhibitor plus aromatase inhibitor) and 5·6 months (5·4–8·1) in cohort C (patients who progressed after aromatase inhibitor and most recently treated with endocrine therapy or chemotherapy).[19,20] Capivasertib, an AKT inhibitor, has also been approved in combination with fulvestrant for patients with HR-positive, HER2-negative, advanced breast cancer with PI3K or AKT pathway mutations. The CAPItello-291 trial reported median progression-free survival of 5·5 months (95% CI 3·9 to 6·8) for capivasertib in the subgroup of patients who had progressed on a CDK4/6 inhibitor. In the overall population of this study, 46 (13%) of 355 participants discontinued capivasertib treatment owing to adverse events.[21]

The pan-Pl3K/mTOR inhibitor gedatolisib has shown broad anti-tumour activity in preclinical studies.[22] Because gedatolisib inhibits all class I PI3K isoforms and the two mTOR sub-complexes, mTORC1 and mTORC2, we hypothesised that gedatolisib would more effectively attenuate PI3K–AKT–mTOR activity by preventing activation of compensatory pathways, which has been shown to occur with inhibitors that target a single protein such as p110α, AKT, or mTORC1 alone.[14,13,23] Early-phase clinical trials have shown an acceptable safety profile and promising anti-tumour activity for gedatolisib alone or in combination with various therapies in patients with many advanced solid tumours.[24,25]

Herein, we report results from the dose expansion portion of a phase 1b trial that evaluated the activity and safety of gedatolisib plus palbociclib and either fulvestrant or letrozole in patients with HR-positive, HER2-negative, advanced breast cancer. The dose-escalation portion of this study has been presented and published elsewhere.[26]

Methods

Study design and participants

This was a multicentre, open-label, phase 1b trial that consisted of two dose-escalation groups and four dose expansion groups in female patients (aged at least 18 years) with HR-positive, HER2-negative, advanced breast cancer from 17 sites across the USA (appendix p 6). Key eligibility requirements for the dose expansion groups included measurable disease (per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST version 1.1]) following disease progression, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and to satisfy one of the following criteria: no previous endocrine therapy in the metastatic setting (group A), one or two previous lines of endocrine therapy in the metastatic setting with no previous CDK4/6 inhibitor (group B), and one or more previous lines of endocrine therapy in the metastatic setting, including previous treatment with a CDK4/6 inhibitor (groups C and D). One previous line of chemotherapy for advanced breast cancer was permitted. Previous treatment with an mTOR or PI3K inhibitor was not allowed. Written, informed consent was obtained from all participants before trial screening procedures and enrolment. The study was conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice. Approval of the protocol (appendix) and any modifications were obtained from independent ethics committees or institutional review boards. Further information about the study design, eligibility criteria, and details regarding the dose-escalation groups, is described in the appendix (p3).

Procedures

Eligible patients enrolled in the dose expansion groups received treatment in 28-day cycles as follows: group A received gedatolisib, palbociclib, and letrozole, and groups B, C, and D received gedatolisib, palbociclib, and fulvestrant. Gedatolisib 180 mg was administered intravenously weekly, except for group D, in which it was administered on days 1, 8, and 15 of each 28-day cycle (a 3-weeks-on–1-week-off [intermittent] schedule). Palbociclib 125 mg was administered orally once daily for 21 days followed by 7 days off and repeated in every 28-day cycle. Letrozole 2·5 mg was administered orally once daily on a continuous basis. Fulvestrant 500 mg was administered intramuscularly on days 1 and 15 of cycle 1 and on day 1 of each subsequent cycle. Treatment continued until disease progression, uncontrollable toxicity, a decision by the patient or investigator to discontinue, or study termination. Patients were followed for safety for 28–35 days.

Patients who continued to have toxicity after the safety follow-up period were followed-up at least every 4 weeks until resolution, or investigator assessment that no further improvement is expected. For patients who discontinued for reasons other than disease progression, tumour assessments continued until progression of disease was documented. Dose adjustments and interruptions were permitted to manage adverse events. Dose reductions for gedatolisib or palbociclib were recommended for haematological and non-haematological toxicities. Safety was monitored and assessed by adverse event evaluation continually from the time of informed consent to the follow-up visit after the last treatment. Safety laboratory tests, vital signs, and ECOG performance status assessment were done before first treatment administration, every 2 weeks for the first two treatment cycles, at the beginning of each treatment cycle thereafter, at the end of treatment, and per the investigator's discretion at the safety follow-up visit. Triplicate 12-lead electrocardiogram measurements were done at screening, for two cycles before and at the end of the first gedatolisib infusion cycle, and at the end of treatment visit.

Tumour assessments (CT or MRI) were done every 8 weeks for at least the first 18 months from the start of therapy until disease progression, death, start of a new anticancer therapy, loss to follow-up, or withdrawal of consent for activity follow-up. Objective response was assessed by the investigator and radiologically confirmed (CT or MRI) per RECIST version 1.1. Independent confirmation by masked independent central review was not done. Subsequent anticancer treatments after disease progression were not collected in the clinical database. After enrolment of group C was completed, the protocol was amended on Oct 8, 2018, to add group D. Enrolment of group B was also terminated. On April 29, 2020, 12 months after study enrolment was completed, the protocol was amended to allow tumour assessment to occur every 12–16 weeks. Analysis of *PIK3CA* mutational status was done from plasma samples as described in the appendix (p 4). Single-dose and multiple-dose pharmacokinetics of gedatolisib and palbociclib and multiple dose pharmacokinetic parameters for fulvestrant and letrozole were also assessed (appendix p 4). Data on race and ethnicity were collected from case report forms.

Outcomes

The primary objective of the dose-escalation groups was safety.[26] The primary objective of the dose expansion groups was to establish whether the triplet combination of gedatolisib plus palbociclib and endocrine therapy improved objective response rate in patients with advanced breast cancer

compared with historical control data of the doublet combination of palbociclib plus either letrozole or fulvestrant. The primary endpoint was objective response (radiologically confirmed complete response, partial response, stable disease, or progressive disease) as assessed by the investigator and confirmed by a subsequent radiological scan at least 4 weeks later per RECIST version 1.1 The objective response rate was determined in the response evaluable population.

The secondary objectives for the expansion groups included safety, activity, potential for QTc interval prolongation, and pharmacokinetics. Secondary endpoints were adverse events as characterised by type, frequency, severity as graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, timing, seriousness, and relationship to study therapy, and laboratory abnormalities as characterised by type, frequency, severity, and timing; progression-free survival from date of first treatment until document of progression or death due to any cause, and duration of response from time of first documentation of complete response or partial response to date of first documentation of progressive disease or death, whichever occurs first, as assessed by the investigator by means of the RECIST version 1.1, QTc interval, single and multiple dose pharmacokinetic parameters for gedatolisib and palbociclib, and multiple dose pharmacokinetic parameters for fulvestrant and letrozole.

Statistical analysis

The study was designed to establish whether each study group was superior to historical control data. The null and alternative hypotheses for objective response rate were 55% and 75% for group A, 20% and 40% for group B, 12% and 32% for group C, and 12% and 32% for group D. The sample size was calculated by a one group binomial hypothesis assuming at least 70% power on the basis of one-sided 0·05 significance level and the 90% Clopper–Pearson CIs. To test the null hypothesis for objective response rate, the study design required at least 26 response evaluable participants for group A, 28 for group B, 27 for group C, and 27 for group D.

The safety (full) analysis set included all dose expansion group participants who received at least one dose of gedatolisib and was used for the analysis of demographics, baseline disease characteristics, overall survival (post hoc), and secondary outcomes of safety, progression-free survival, and duration of response. Median progression- free survival, median duration of response, and quartiles were estimated on the basis of the Kaplan–Meier method for each treatment group. The Brookmeyer-Crowly method was used for the 95% CIs. 12-month progression- free survival

was also estimated in a prespecified analysis on the basis of the Kaplan–Meier method and was chosen based on the expected median progression-free survival for this patient population.

For time-to-event analyses, if disease progression was confirmed by RECIST version 1.1 or if a new anticancer therapy for the primary diagnosis before disease progression was initiated, participants were censored at the date of the last adequate disease assessment. Participants were censored at the first dose for inadequate baseline assessment or for no post-baseline disease assessment. If progression or death occurred after two or more missed tumour assessments, participants were censored at the date of the last scan immediately before the two missing tumour assessments.

The response evaluable analysis set was used for the primary outcome of objective response rate. Objective response was also assessed post hoc in the full analysis set and in the response evaluable set including patients with an unconfirmed partial response. Participants in the full analysis set were excluded from the response evaluable analysis set if they did not meet all of the following criteria: measurable disease, an adequate baseline assessment of disease, and at least one post- baseline measurable assessment of disease per RECIST version 1.1. Objective response rate was calculated as the proportion of patients with a complete response or partial response relative to the total number of response evaluable patients. The objective response rate was reported by group with the Clopper–Pearson 90% CI. All other statistical estimates were descriptive and presented with 95% CIs or SD where applicable. Analyses of objective response and 12-month progression-free survival were done by *PIK3CA* mutation status (prespecified exploratory analyses for group D and post- hoc analyses for groups A–C).

The full analysis set for groups C and D was used for a post-hoc analysis that compared group C and group D using a logistic regression model with a significant criterion of $p<0{\cdot}1$ for independent factors to remain on the model. Three independent factors met the $p<0{\cdot}1$ criterion and were tested in the final model by means of the formula

$$\text{ORR (Yes, No)} = \text{Intercept} + a1 \times (\text{dosing schedule}) + a2 \times (\text{previous chemotherapy}) + a3 \times (\text{number of previous lines of therapies}) + a4 \times (\text{duration of immediately previous therapy})$$

Coefficients: a1, a2, a3, a4

The data cutoff date was June 29, 2022, for all outcomes reported except for median progression-free survival and median duration of response, which were updated with the data cutoff of May 29, 2023, for the 11 participants who continued treatment under the Expanded

Access Protocol. Analyses were done with SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, NCT02684032.

Role of the funding source

The funders of the study had a role in study design, study conduct, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Dec 19, 2017, and June 19, 2019, 103 female participants were enrolled in the dose expansion groups A (n=31), B (n=13), C (n=32), and D (n=27)—the planned sample size was met for all groups except group B (figure 1). All enrolled participants were included in the full and safety analysis sets. Four patients in group A and four patients in group C were excluded from the response evaluable set owing to the lack of either measurable disease, adequate baseline assessment, or at least one post-baseline assessment (figure 1).

The median age was 57 years (IQR 46–64), and all participants had an ECOG performance status of 0–1. All participants had stage IV advanced breast cancer, and 90 (87%) of 103 participants had visceral metastasis (table 1). *PIK3CA* mutations were detected in 28 (28%) of 101 available participants' circulating tumour DNA samples (table 1).

Median follow-up was 16·6 months (IQR 5·7–48·4) for group A, 11·0 months (7·6–16·9) for group B, 3·6 months (1·8–7·5) for group C, and 9·4 months (5·3–16·7) for group D for objective response rate; 37·8 months (12·9–54·6), 53·9 months (53·9–53·9), not estimable (NE; 20·3–NE), and 31·6 months (16·7–44·4) for progression-free survival; and 45·0 months (16·8–50·9), 50·0 months (50·0–50·0), NE (18·6–NA), and 28·1 months (18·0–28·1) for duration of response (ie, responders).

An objective response was observed for 23 (85·2%, 90% CI 69·2–94·8) of 27 response evaluable group A participants, eight (61·5%, 35·5–83·4) of 13 response evaluable group B participants, seven (25·0%, 12·4–41·9) of 28 response evaluable group C participants, and 15 (55·6%, 38·2–72·0) of 27 response evaluable group D participants (table 2; figure 2). Median progression-free survival in the treatment-naive group (group A) was 48·4 months (95% CI 16·9–not reached) and median duration of response was 46·7 months (22·2–not reached). For second-line

and higher participants, median progression-free survival was 12·9 months (95% CI 7·6–38·3) in group B, 5·1 months (3·3–7·5) in group C, and 12·9 months (7·4–16·7) in group D (figure 3; table 2). Median duration of response was 12·2 months (95% CI 3·7–40·6) in group B, 16·6 months (3·7–not reached) in group C, and 12·6 months (95% CI 7·3–21·2) in group D (table 2; appendix pp 27–31). The median time to response was 2·1 months (IQR 1·8–5·7) for group A, 1·9 months (1·8–5·6) for group B, 1·8 months (1·7–1·9) for group C, and 1·8 months (1·7–5·6) for group D (appendix p 25). No group had reached median overall survival as of June 29, 2022.

An exploratory predefined analysis of objective response rate and a post-hoc analysis of 12-month progression-free survival according to *PIK3CA* mutation status indicated that activity was independent of *PIK3CA* mutation status (figure 2; table 2).

The median safety follow-up time was 17·5 months (IQR 5·9–38·7) for group A,11·1months (7·6–16·9) for group B, 3·7 months (1·9–8·0) for group C, and 9·8 months (5·8–17·5) for group D. At study closure, one dose-escalation participant and 11 dose expansion group participants (eight [26%] of 31 in group A, one [8%] of 13 in group B, and two [7%] of 27 in group D) were enrolled in an expanded access protocol or single patient Investigational New Drug application. As of the data cutoff, eight of these participants continued to receive gedatolisib in combination with palbociclib and either letrozole or fulvestrant. The most common reasons for treatment discontinuation were progression or relapse in 66 (64%) of 103 participants, study termination by the sponsor in 11 (11%) of 103 participants (all of whom continued treatment under the expanded access protocol), and adverse events in nine (9%) of 103 participants (figure 1).

Treatment-related adverse events for all dose expansion participants are summarised by grade in table 3 and by group in the appendix (pp 9–11). Treatment-emergent adverse events of any cause (appendix pp12–16) were of similar frequency and severity to treatment-related adverse events. Mean relative dose intensity for gedatolisib ranged from 83·2% (SD 7·30) to 92·5% (7·85) and from 86·0% (8·78) to 90·6 % (11·16) for palbociclib depending on the study group (appendix p 17). Gedatolisib dose was reduced in 23 group A participants, 11 group B participants, 15 group C participants, and 18 group D participants. Recommendations for toxicity management in this early development study were based on the known side-effects of palbociclib, whereby many dose reductions occur owing to neutropenia.[3] Although gedatolisib monotherapy has not been associated with myelosuppression,[24] the study protocol required dose reductions of gedatolisib for

grade 3 neutropenia, however, these events were probably related to palbociclib. All participants had an any grade, 80 (78%) of 103 participants had a grade 3, and 14 (14%) of 103 participants had a grade 4 treatment-related adverse event. Grade 3 neutropenia, a known adverse reaction for palbociclib, occurred in 55 (53%) of 103 participants, and grade 4 neutropenia occurred in ten (10%) of 103 participants. Hyperglycaemia was reported for 26 (25%) of 103 participants; four participants had grade 3 and two had grade 4 hyperglycaemia. The most common treatment-related adverse events were stomatitis (92 [89%]), nausea (79 [77%]), neutropenia (78 [76%]), fatigue (70 [68%]), and rash (54 [52%]; table 3). The most common grade 3–4 treatment-related adverse events were neutropenia (65 [63%] of 103 participants), stomatitis (28 [27%]), and rash (21 [20%]). Incidence of treatment-related adverse events was similar across all study groups (appendix p 9). For this study, no prophylaxis was included for stomatitis or rash. 23 (22%) of 103 expansion group participants had a treatment-related serious adverse event (eight [26%] of 31 in group A, four [31%] of 13 in group B, seven [22%] of 32 in group C, and four [15%] of 27 in group D). The most common treatment-related serious adverse events were febrile neutropenia (group A n=3, group B n=1, group D n=1) and acute kidney injury (group A n=2, group B n=1, group C n=1). There was much variability in participant QT interval data, however mean change in QTc interval from baseline was not clinically significant and generally less than 10 ms for all groups in total (appendix p 26). Across all treatment cycles, QT prolongation was reported as a grade 3 adverse event for only two participants (table 3). Study treatment was discontinued owing to an adverse event for three participants in group A, two in group B, three in group C, and one in group D (figure 1). No participants discontinued the study because of hyperglycaemia. Three deaths occurred, two participants in expansion group C and one participant in expansion group D. All deaths were not related to treatment and were considered related to disease progression.

The pharmacokinetics of all study drugs were characterised, and the parameters are presented in the appendix (pp 18–23). Gedatolisib plasma exposures were similar between groups, and no accumulation was observed after weekly administration (appendix pp 18–19); exposures were consistent with historical data in the single agent study.[21] Concomitant administration of gedatolisib did not affect the pharmacokinetics of palbociclib (appendix pp 20–21) or endocrine therapies (appendix pp 22–23).

In a post-hoc logistic regression analysis to assess the effect of different dosing schedules of gedatolisib in group C and D, three factors met the significance criteria: exposure to previous chemotherapy, number of previous lines of therapy, and time on the immediately previous therapy. Previous chemotherapy and number of previous lines of therapy for groups C and D are shown in table 1. The median time on immediately previous therapy was 5·2 months (95% CI 2·7–11·1) for group C and 13·5 months (4·5–21·5) for group D. The treatment effect, an odds ratio of 3·4 (90% CI 1·1–10·8), met the significance criterion suggesting that group D was 240% more likely to respond compared with group C, while controlling for three influential factors. Additionally, this analysis showed that the dosing schedule effect (group D over group C) is unchanged while testing within each of the three critical factors, confirming that the analysis of the dose schedule effect between the two non-randomised groups is robust (appendix pp 4, 24).

Discussion

Results from this phase 1b study show that gedatolisib combined with palbociclib and endocrine therapy resulted in clinically meaningful objective response rate and a median progression-free survival that compare well with the current standard-of-care therapies in patients with advanced breast cancer who have received previous lines of therapy as well as in treatment-naive patients. As of the data cutoff, the median overall survival was not reached in any study group.

Each expansion group achieved its primary endpoint target, with a higher objective response rate in the study group compared with the historical objective response rate observed in pivotal studies evaluating palbociclib in combination with either letrozole in treatment-naive patients or with fulvestrant following previous progression on first-line systemic therapy for metastatic disease. In group A, 23 (85·2%) of 27 treatment-naive participants had an objective response, which exceeded the expected upper target effect (75%). In response evaluable participants who had received previous hormonal therapy alone or in combination with a CDK4/6 inhibitor (expansion groups B–D), objective response rate ranged from 25·0% to 61·5%.

While cross-trial comparisons are subject to confounding, a comparison between the results from expansion group A to the PALOMA-2 study and the result from expansion group D to the PALOMA-3 study is informative. The PALOMA-2 study evaluated palbociclib plus letrozole as front-line therapy for patients with advanced breast cancer. The objective response rate and

median progression-free survival from expansion group A were substantially higher than those reported in the PALOMA-2 study (objective response in 187 [55%] of 338 patients;[3] median progression-free survival 27·6 months (22·4–30·3).[4] The PALOMA-3 study evaluated palbociclib plus fulvestrant in patients with advanced breast cancer who had progressed on previous endocrine therapy. The objective response rate reported in expansion group D exceeds the upper target effect of 32% and was substantially higher than the objective response rate reported in the PALOMA-3 study (10·4% [95% CI 7·4 to 14·1]),[33] despite nearly all group D participants receiving previous treatment with a CDK4/6 inhibitor.

Endocrine therapy in combination with a CDK4/6 inhibitor is the standard-of-care first-line therapy for HR-positive, HER2-negative, advanced breast cancer. However, most patients will have disease progression on this therapeutic regimen within 2–3 years. The standard second-line treatment options for patients with HR- positive, HER2-negative, advanced breast cancer who have progressed after treatment with a CDK4/6 inhibitor are fulvestrant or everolimus in combination with endocrine therapy (exemestane or fulvestrant) for patients regardless of breast cancer mutation status. For patients with *PIK3CA* mutations, alpelisib in combi nation with fulvestrant is the second-line standard of care, and capivasertib with fulvestrant is approved for patients with one or more *PIK3CA*, *AKT1*, or *PTEN* alterations. For patients with *ESR1* mutated breast cancer, elacestrant is approved for second-line therapy. Median progression-free survival for these treatments ranges from 1·9 months to 7·3 months.[14,19,20,27,28] Finding effective and well-tolerated therapy in the second-line setting remains an unmet clinical need for these patients.

In this study, gedatolisib in combination with palbociclib and fulvestrant showed a toxicity profile consistent with previous studies of gedatolisib in solid tumours.[24,25] Hyperglycaemia, a known adverse event for PI3K and mTOR inhibitors, was observed predominantly as a grade 1 or 2 adverse event, and no participants discontinued the study owing to hyperglycaemia. The frequency of hyperglycaemia observed in this study was 1 lower than that reported for alpelisib (in breast cancer)[15] and copanlisib (in haematological malignancies),[29] probably because of differences in chemical structure and volume of distribution of gedatolisib. Other adverse events were consistent with the class effect of PI3K and mTOR inhibitors but reported at lower incidence compared with other published data.[14,15,19,30]

Disease progression accounted for most treatment discontinuations. Overall, the safety profile for the combination therapy was acceptable with side-effects easily managed by standard-of-care treatment with a low percentage of expansion group participants discontinuing study treatment owing to an adverse event. The lowest frequency was observed in expansion group D, in which participants were treated with the intermittent schedule. The most common treatment-related adverse event was stomatitis–mucosal inflammation. It should be noted that stomatitis events that led to treatment discontinuation were observed in participants who did not receive prophylactic treatment with a steroid-based mouthwash. The SWISH study in patients treated with everolimus showed that the use of a dexamethasone mouth rinse for 8 weeks reduced grade 2 or higher stomatitis by 90%.[31] The use of prophylactic steroidal mouth rinse for at least two treatment cycles for all patients receiving gedatolisib will be prescribed in future studies. Additionally, roughly half of participants had treatment-related skin toxicity–rash of any grade, with no prophylactic treatment used. An antihistamine-based prophylaxis for rash will be recommended in future studies with gedatolisib as described previously.[32]

After enrolment was completed for group C, which used a weekly dosing schedule, group D was added to the study by means of a 3-weeks-on–1-week-off intermittent dosing schedule. This intermittent schedule improves patient convenience and lowers overall gedatolisib dose density per 28-day treatment cycle. Adverse event type, frequency, and grade were generally similar in groups C and D. From the standpoint of efficacy, similar intermittent dosing schedules in preclinical animal studies have been found to have similar anti-tumour activity to that of a weekly regimen.[34,35]

There were too few participants in expansion groups C and D to derive a definitive explanation for the lower objective response rate and progression-free survival in group C. However, differences in the patients' characteristics suggest that group C participants had more advanced disease than the group D participants and were thus potentially less responsive to subsequent therapy. Additionally, the exploratory regression model analysis of objective response rate in group C and group D suggests that the intermittent dosing schedule used in group D positively affected these group D outcomes. This is consistent with hypotheses that suggest that continuous exposure and pathway inhibition might lead to pathway reactivation via perturbation of pathway feedback mechanisms leading to reduced effect over time and that intermittent dosing

might allow a reset of pathway signalling.[35] The intermittent dosing schedule is under evaluation in the phase 3 VIKTORIA-1 study in patients with HR-positive, HER2-negative, advanced breast cancer.

Results from this study suggest that gedatolisib activity is independent of *PIK3CA* mutational status, with similar objective response rate and 12-month progression-free survival for participants with both wild-type and mutated *PIK3CA* status. This contrasts sharply with results from a previous study that evaluated alpelisib in combination with fulvestrant. In that study, an objective response rate of 29% was observed for participants with *PIK3CA* mutations and no objective tumour responses in participants whose cancers were *PIK3CA* wild type.[30]

As a pan-PI3K and mTOR inhibitor, gedatolisib more completely inactivates multiple nodes of the pathway (eg, PI3K Class I isoforms and mTORC1 and 2),[22] which prevents the feedback and crosstalk that can lead to resistance to therapies that target only a single node of the pathway (eg, PI3K-α, Akt, or mTOR).[13,16,36,37] This can explain the activity of gedatolisib in patients regardless of the *PIK3CA* mutation status of their tumours. There are multiple direct and indirect mechanisms by which the PI3K–AKT–mTOR pathway can be dysregulated in breast cancer, which probably explains why drugs that target single nodes of the pathway (e.g. p110α, AKT, mTOR) have modest efficacy,[14,15,19,20] even in tumours with PI3K-related alterations.

Limitations of this study include a non-randomised design with no control groups and the protocol requirement for participants to have measurable disease, which might lead to systematic bias affecting generalisability of group A results, given that a large proportion of patients with newly diagnosed metastatic breast cancer might present with non-measurable disease. Furthermore, the primary objective specified analysis of response rate in the response-evaluable population. The exclusion of participants who discontinued the study early regardless of reason can inflate the objective response rate. In our analysis (per protocol), eight participants in group A (n=4) and in group C (n=4) were not considered response evaluable. Although the total number of participants treated in this study was 138, each treatment group ranged between 13 and 32 participants, and the results should be considered hypothesis generating.

Despite these limitations, our results show that further study is warranted for gedatolisib in combination with palbociclib and either letrozole or fulvestrant for patients with HR-positive, HER2-negative, advanced breast cancer. Promising objective response rate and median progression-free survival results were observed, independently of *PIK3CA* mutation status, in participants who were pretreated with CDK4/6 inhibitors and who were treatment-naive. Gedatolisib in combination with palbociclib and endocrine therapy showed acceptable safety with no new safety signals emerging relative to previous studies with gedatolisib. The safety data compare favourably to results for other available therapies for patients in this setting. The intermittent (3 weeks on–1 week off) gedatolisib dosing schedule had a similar safety profile and seemed to be more active versus the weekly dosing schedule in the second-line and higher setting and will be further evaluated in future studies. The ongoing VIKTORIA-1 phase 3 study (NCT05501886) in patients with HR-positive, HER2- negative, advanced breast cancer previously treated with a CDK4/6 inhibitor is seeking to confirm these results. On the basis of the results in treatment-naive participants, further study in the first-line setting is also warranted.

Contributors

RW, RML, HSH, HSR, EMS-R, JMS, ECD, and PK were responsible for patient recruitment and collection of data. SS wrote the statistical analysis plan and analysed the data. RML, RW, SCM, BFS, and IG oversaw drafting of the manuscript and have accessed and verified the reported data. SS and SCM produced the tables and figures. All authors had full access to the data, participated in manuscript development, and approved the submitted version.

Declaration of interests

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Data sharing

On request, and subject to certain criteria, conditions, and exceptions, Celcuity will provide access to individual deidentified participant data from Celcuity-sponsored interventional clinical studies done for medicines either for indications that have been approved, or (where development has been terminated, or both. A brief research proposal will be assessed and form the basis of a data-sharing agreement. Data requests can be submitted by use of the form provided on the Celcuity website.

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References

1. Rugo HS, Rumble RB, Macrae E, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016; 34: 3069–103.
2. Hartkopf AD, Grischke E-M, Brucker SY. Endocrine-Resistant Breast Cancer: Mechanisms and Treatment. Breast Care 2020; 15: 347–54.
3. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016; 375: 1925–36.
4. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat 2019; 174: 719–29.
5. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016; 17: 425–39.

6. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018; 29: 1541–7.
7. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol 2018; 36: 2465–72.
8. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. npj Breast Cancer 2019; 5: 1–8.
9. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017; 35: 2875–84.
10. Yang C, Li Z, Bhatt T, et al. Acquired CDK6 amplification promotes breast cancer resistance to CDK4/6 inhibitors and loss of ER signaling and dependence. Oncogene 2017; 36: 2255–64.
11. Alves CL, Ditzel HJ. Drugging the PI3K/AKT/mTOR Pathway in ER+ Breast Cancer. Int J Mol Sci 2023; 24.
12. Baselga J. Targeting the phosphoinositide-3 (PI3) kinase pathway in breast cancer. Oncologist 2011; 16 Suppl 1: 12–9.
13. Elkabets M, Vora S, Juric D, et al. mTORC1 inhibition is required for sensitivity to PI3K p110α inhibitors in PIK3CA-mutant breast cancer. Sci Transl Med 2013; 5: 196ra99.
14. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012; 366: 520–9.
15. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. N Engl J Med 2019; 380: 1929–40.
16. Vora SR, Juric D, Kim N, et al. CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors. Cancer Cell 2014; 26: 136–49.
17. Michaloglou C, Crafter C, Siersbaek R, et al. Combined Inhibition of mTOR and CDK4/6 Is Required for Optimal Blockade of E2F Function and Long-term Growth Inhibition in Estrogen Receptor-positive Breast Cancer. Mol Cancer Ther 2018; 17: 908–20.
18. O'Brien NA, McDermott MSJ, Conklin D, et al. Targeting activated PI3K/mTOR signaling overcomes acquired resistance to CDK4/6-based therapies in preclinical models of hormone receptor-positive breast cancer. Breast Cancer Res 2020; 22: 89.
19. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol 2021; 22: 489–98.
20. Rugo HS, Neven P, Saffie I, et al. Abstract PD13-05: Alpelisib + fulvestrant in patients with PIK3CA-mutated, HR+, HER2— advanced breast cancer (ABC) who received chemotherapy or endocrine therapy (ET) as immediate prior treatment: BYLieve Cohort C primary results and exploratory biomarker analyses. Cancer Res 2022; 82: PD13-05.
21. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2023; 388: 2058–70.
22. Mallon R, Feldberg LR, Lucas J, et al. Antitumor Efficacy of PKI-587, a Highly Potent Dual PI3K/mTOR Kinase Inhibitor. Clin Cancer Res 2011; 17: 3193–203.
23. Bago R, Sommer E, Castel P, et al. The hVps34-SGK3 pathway alleviates sustained PI3K/Akt inhibition by stimulating mTORC1 and tumour growth. EMBO J 2016; 35: 1902–22.
24. Shapiro GI, Bell-McGuinn KM, Molina JR, et al. First-in-Human Study of PF-05212384 (PKI-587), a Small-Molecule, Intravenous, Dual Inhibitor of PI3K and mTOR in Patients with Advanced Cancer. Clin Cancer Res 2015; 21: 1888–95.

25. Curigliano G, Shapiro GI, Kristeleit RS, et al. A Phase 1B open-label study of gedatolisib (PF-05212384) in combination with other anti-tumour agents for patients with advanced solid tumours and triple-negative breast cancer. Br J Cancer 2023; 128: 30–41.
26. Forero-Torres A, Han H, Dees EC, et al. Phase Ib study of gedatolisib in combination with palbociclib and endocrine therapy (ET) in women with estrogen receptor (ER) positive (+) metastatic breast cancer (MBC) (B2151009). J Clin Oncol 2018; 36: 1040–1040.
27. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. J Clin Oncol 2022; 40: 3246–56.
28. Lindeman GJ, Fernando TM, Bowen R, et al. VERONICA: Randomized Phase II Study of Fulvestrant and Venetoclax in ER-Positive Metastatic Breast Cancer Post-CDK4/6 Inhibitors - Efficacy, Safety, and Biomarker Results. Clin Cancer Res 2022; 28: 3256–67.
29. Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ. Aliqopa (copanlisib) for injection [prescribing information]. 2022; published online Feb.
30. Juric D, Janku F, Rodón J, et al. Alpelisib Plus Fulvestrant in PIK3CA-Altered and PIK3CA-Wild-Type Estrogen Receptor-Positive Advanced Breast Cancer: A Phase 1b Clinical Trial. JAMA Oncol 2019; 5: e184475.
31. Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017; 18: 654–62.
32. Rugo HS, Lacouture ME, Goncalves MD, Masharani U, Aapro MS, O'Shaughnessy JA. A multidisciplinary approach to optimizing care of patients treated with alpelisib. Breast 2022; 61: 156–67.
33. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med 2015; 373: 209–19.
34. Yang W, Hosford SR, Dillon LM, et al. Strategically Timing Inhibition of Phosphatidylinositol 3-Kinase to Maximize Therapeutic Index in Estrogen Receptor Alpha-Positive, PIK3CA-Mutant Breast Cancer. Clin Cancer Res 2016; 22: 2250–60.
35. Hudson K, Hancox UJ, Trigwell C, et al. Intermittent High-Dose Scheduling of AZD8835, a Novel Selective Inhibitor of PI3Kα and PI3Kδ, Demonstrates Treatment Strategies for PIK3CA-Dependent Breast Cancers. Mol Cancer Ther 2016; 15: 877–89.
36. Fruman DA, Chiu H, Hopkins BD, Bagrodia S, Cantley LC, Abraham RT. The PI3K Pathway in Human Disease. Cell 2017; 170: 605–35.
37. Castel P, Ellis H, Bago R, et al. PDK1-SGK1 Signaling Sustains AKT-Independent mTORC1 Activation and Confers Resistance to PI3Kα Inhibition. Cancer Cell 2016; 30: 229–42.

Table 1. Demographics and baseline characteristics (n=103)

	Group A (n=31)	Group B (n=13)	Group C (n=32)	Group D (n=27)
Age, years	54 (42 to 61)	62 (49 to 67)	60 (50 to 66)	59 (50 to 63)
Race, n (%)				
Asian	0	1 (8%)	1 (3%)	0
Black or African American	4 (13%)	1 (8%)	3 (9%)	3 (11%)
White	25 (81%)	10 (77%)	27 (84%)	24 (89%)
Other	2 (7%)	1 (8%)	1 (3%)	0
Ethnicity				
Hispanic or Latinx	0	0	1 (3%)	0
Not Hispanic or Latinx	31 (100%)	12 (92%)	31 (97%)	27 (100%)
Not reported	0	1 (8%)	0	0
BMI, kg/m^2	28·5 (20·4 to 49·2)	26·1 (19·1 to 38·9)	25·6 (19·1 to 56·2)	28·9 (19·3 to 50·3)
TNM current stage IV	31 (100%)	13 (100%)	32 (100%)	27 (100%)
PIK3CA mutational status*				
Wild type	25 (81%)	9 (69%)	24 (75%)	15 (56%)
Mutant type	5 (16%)	4 (31%)	8 (25%)	11 (41%)
Unknown/missing	1 (3%)	0	0	1 (4%)
ECOG performance status				
0	20 (65%)	7 (54%)	16 (50%)	14 (52%)
1	11 (36%)	6 (46%)	16 (50%)	13 (48%)
Time from first previous systemic therapy, months	62·5 (2·9 to 181·8); n=20	93·6 (1·4 to 211·7); n=13	49·7 (9·6 to 240·1); n=32	36·7 (6·4 to 294·4); n=27
Time from the last previous therapy, months	26·1 (-6·4 to 181·7); n=20	1·1 (0·5 to 2·9); n=13	0·9 (0·3 to 26·6); n=32	0·8 (0·4 to 19·2); n=27
Number of disease sites involved				
1	5 (16%)	0	3 (9%)	3 (11%)
2	12 (39%)	6 (46%)	10 (31%)	12 (44%)
3	9 (29%)	5 (38%)	13 (41%)	9 (33%)
≥4	5 (16%)	2 (15%)	6 (19%)	3 (11%)

Metastatic disease site involved				
Bone Only	0	0	0	0
Bone	18 (58%)	11 (85%)	25 (78%)	18 (67%)
Brain	0	0	1 (3%)	0
Liver	14 (45%)	10 (77%)	20 (63%)	17 (63%)
Lung	7 (23%)	3 (23%)	7 (22%)	6 (22%)
Lymph Node	8 (26%)	2 (15%)	9 (28%)	2 (7%)
Pleural Effusion	4 (13%)	0	3 (9%)	2 (7%)
Skin	1 (3%)	0	1 (3%)	0
Other	26 (84%)	10 (77%)	20 (63%)	21 (78%)
Visceral Metastasis[†]				
Yes	28 (90%)	12 (92%)	28 (88%)	22 (81%)
No	3 (10%)	1 (8%)	4 (13%)	5 (19%)
Number of previous systemic therapies for advanced breast cancer	0	1 (0 to 2)	2 (1 to 2)	1 (1 to 2)
0	30 (97%)	2 (15%)	0	0
1	1 (3%)	9 (69%)	15 (47%)	18 (67%)
2	0	2 (15%)	11 (34%)	8 (30%)
≥3	0	0	6 (19%)	1 (4%)
Prior therapies for Advanced Breast Cancer, n (%)				
Chemotherapy	1 (3%)	4 (31%)	15 (47%)	5 (19%)
Selective oestrogen receptor degrader or selective oestrogen receptor modulator[‡]	0	5 (39%)	14 (44%)	10 (37%)
Aromatase inhibitor therapy	0	7 (54%)	25 (78%)	19 (70%)
CDK4/6 inhibitor	0	0	32 (100%)	26 (96%)

Data are median (range) or n (%). Expansion group A=gedatolisib plus palbociclib plus letrozole (in first-line therapy patients). Expansion group B=gedatolisib plus palbociclib plus fulvestrant (in second-line or higher therapy CDK4/6-naive patients). Expansion group C=gedatolisib plus palbociclib plus fulvestrant (in patients pretreated with CDK4/6 inhibitors as second-line or higher therapy). Expansion group D=gedatolisib plus palbociclib plus fulvestrant (in patients pretreated with CDK4/6 inhibitors as second-line and higher therapy). ECOG=Eastern Cooperative Oncology Group. All participants received gedatolisib weekly except for those in expansion group D, who received gedatolisib on day 1, 8, and 15 of every 28-day cycle. *Established by analysis of DNA isolated from plasma samples collected before dosing on cycle 1 day 1 (appendix p 4). †Included participants with lung, liver, adrenal glands, pleura, and peri2to0neal metastases. ‡Previous selective oestrogen receptor degrader therapy for advanced breast cancer included fulvestrant. Previous selective oestrogen receptor modulators included tamoxifen, raloxifene, and toremifene.

Table 1: Summary of endpoints

	Group A	**Group B**	**Group C**	**Group D**
Previous Therapy	First-line; CDK inhibitor-naive	1-2 previous lines; CDK inhibitor-naive	Second-line and higher; CDK inhibitor-pretreated	Second-line and higher; CDK inhibitor-pretreated
N				
Full analysis set	31	13	32	27
Response evaluable set	27	13	28	27
Study Treatment (gedatolisib dosing schedule)	Gedatolisib, palbociclib, and letrozole (weekly)	Gedatolisib, palbociclib, and fulvestrant (weekly)	Gedatolisib, palbociclib, and fulvestrant (weekly)	Gedatolisib, palbociclib, and fulvestrant (3 weeks on - 1 week off)
Objective response, full analysis set	23 (74·2%; 58·2-86·5)	8 (61·5%; 35·5-83·4)	7 (21·9%; 10·7-37·2)	15 (55·6%; 38·2-72·0)
Objective response, response evaluable set	23 (85·2%; 69·2-94·8)	8 (61·5%; 35·5-83·4)	7 (25·0%; 12·4-41·9)	15 (55·6%; 38·2-72·0)
Objective response, response evaluable including unconfirmed partial response	23 (85·2%; 69·2-94·8)	10 (76·9%; 50·5-93·4)	10 (35·7%; 20·8-53·0)	17 (63·0%; 45·3-78·3)
Median progression-free survival,* months (95% CI)	48·4 (16·9-NR)	12·9 (7·6-38·3)	5·1 (3·3-7·5)	12·9 (7·4-16·7)
Progression-free survival at 12 months, % (95% CI)	72·1% (50·1-85·7)	54·5% (22·9-78·0)	23·6% (9·8-40·8)	53·2% (31·5-70·9)
Median duration of response* months (95% CI)	46·7 (22·2-NR)	12·2 (3·7-40·6)	16·6 (3·7-NR)	12·6 (7·3-21·2)
PIK3CA status				
Wild type	25 (81%)	9 (69%)	24 (75%)	15 (56%)
Mutant	5 (16%)	4 (31%)	8 (25%)	11 (41%)
Objective response by *PIK3CA* status (response evaluable set)				
Wild type	17 (81%)[†]	6 (67%)	4 (20%)[‡]	8 (53%)
Mutant	5 (100%)	2 (50%)	3 (38%)	7 (64%)

	Group A	Group B	Group C	Group D
Objective response by *PIK3CA* status (response evaluable set including unconfirmed partial response)				
Wild type	17 (81%)	7 (78%)	5 (25%)	9 (60%)
Mutant	5 (100%)	3 (75%)	5 (63%)	8 (73%)
Progression-free survival at 12 months by *PIK3CA* status, % (95% CI)				
Wild type	74.1% (48·2-88·4)	50.0% (15·2-77·5)	21.8% (7·1-41·6)	48.5% (21·0-71·5)
Mutant	60.0% (12·6-88·2)	66.7% (5·4-94·5)	29.2% (4·2-61·9)	60.0% (25·3-82·7)

Data are n (%) or n (%; 90% CI), unless stated otherwise. Data as of June 29, 2022, database lock, unless otherwise noted. NR=not reached. *Median progression-free survival and median duration of response updated with data cutoff May 29, 2023. †Only 21 are response evaluable. ‡Only 20 were response evaluable.

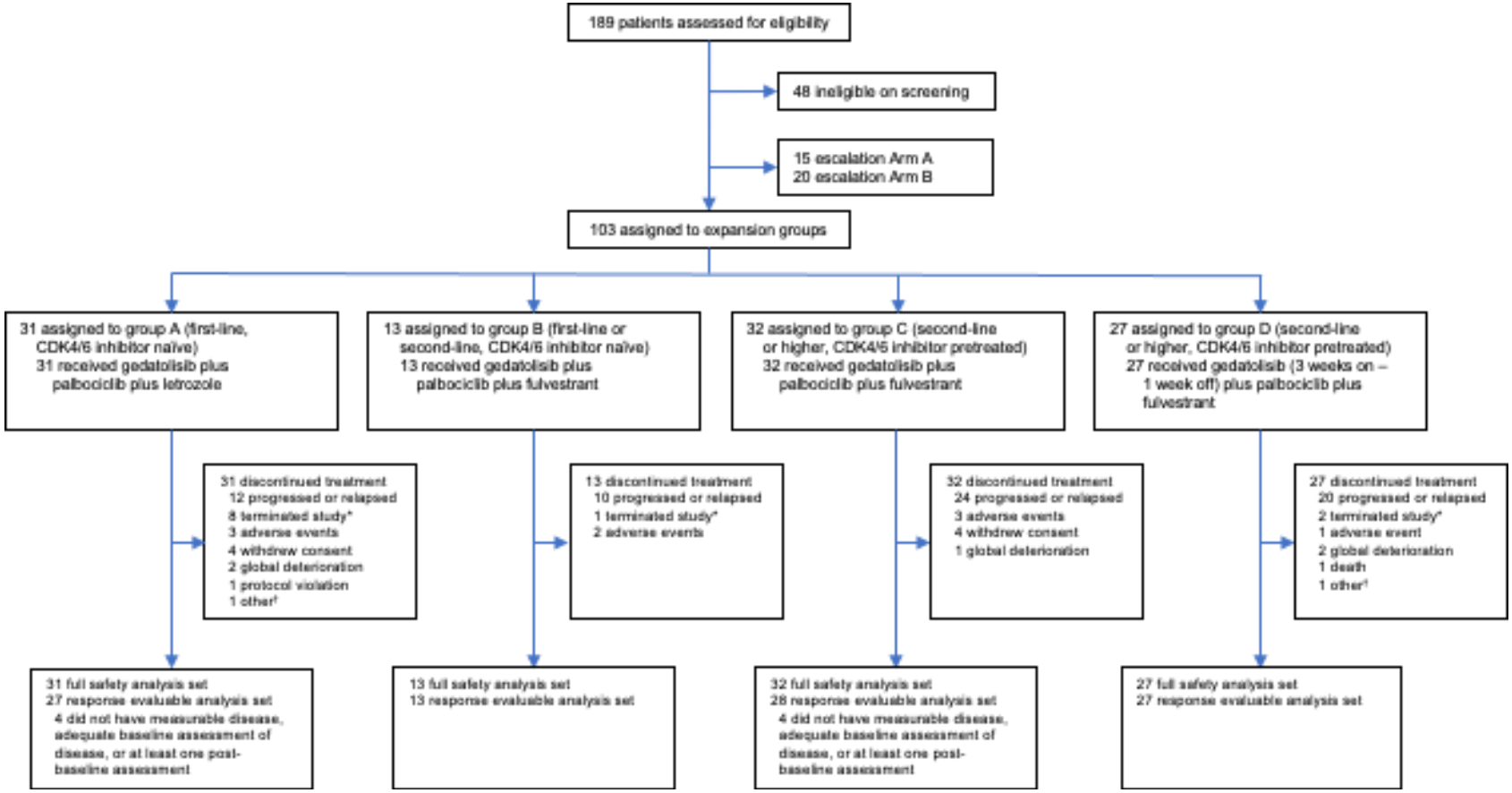
Table 3. Summary of treatment-related adverse events (safety analysis set; n=103)

	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis or mucosal inflammation*	21 (20%)	43 (42%)	28 (27%)	0
Nausea	44 (43%)	35 (34%)	0	0
Neutropenia or neutrophil count decreased*	1 (1%)	12 (12%)	55 (53%)	10 (10%)
Fatigue	22 (21%)	37 (36%)	11 (11%)	0
Rash*†	22 (21%)	11 (11%)	21 (20%)	0
Dysgeusia	44 (43%)	3 (3%)	0	0
Vomiting	33 (32%)	13 (13%)	1 (1%)	0
Anaemia or haemoglobin decrease*	11 (11%)	18 (17%)	12 (12%)	0
White blood cell count decreased or leukopenia*	4 (4%)	16 (16%)	15 (15%)	4 (4%)
Diarrhoea	24 (23%)	9 (9%)	3 (3%)	0
Decreased appetite	24 (23%)	9 (9%)	0	0
Dry mouth	26 (25%)	2 (2%)	0	0
Constipation	21 (20%)	5 (5%)	1 (1%)	0
Pruritus	14 (14%)	8 (8%)	5 (5%)	0
Hyperglycaemia or Blood glucose increased*	14 (14%)	6 (6%)	4 (4%)	2 (2%)
Headache	19 (18%)	6 (6%)	0	0
Infusion-related reaction	17 (17%)	6 (6%)	0	0
Lymphocyte count decreased	3 (3%)	5 (5%)	12 (12%)	1 (1%)
Aspartate aminotransferase or alanine aminotransferase increased*	13 (13%)	3 (3%)	3 (3%)	0
Epistaxis	18 (17%)	0	0	0
Hot flush	16 (16%)	1 (1%)	0	0
Platelet count decreased	15 (15%)	2 (2%)	0	0
Dizziness	14 (14%)	2 (2%)	0	0
Dry skin	12 (12%)	4 (4%)	0	0
Urinary tract infection	1 (1%)	15 (15%)	0	0
Arthralgia	12 (12%)	2 (2%)	1 (1%)	0
Oral pain	9 (9%)	5 (5%)	0	0
Alopecia	12 (12%)	1 (1%)	0	0
Hypomagnesaemia	11 (11%)	2 (2%)	0	0
Myalgia	12 (12%)	1 (1%)	0	0
Weight decreased	8 (8%)	5 (5%)	0	0
Hypokalaemia	9 (9%)	1 (1%)	2 (2%)	0
Oropharyngeal pain	11 (11%)	1 (1%)	0	0
Upper respiratory tract infection	0	11 (11%)	0	0

	Grade 1	Grade 2	Grade 3	Grade 4
Dyspnoea	5 (5%)	2 (2%)	2 (2%)	0
Dermatitis acneiform	4 (4%)	1 (1%)	2 (2%)	0
Pyrexia	4 (4%)	1 (1%)	2 (2%)	0
Thrombocytopenia	4 (4%)	2 (2%)	1 (1%)	0
Acute kidney injury	0	2 (2%)	4 (4%)	0
Febrile neutropenia	0	0	6 (6%)	0
Pulmonary embolism	0	1 (1%)	5 (5%)	0
Blood creatinine increased	3 (3%)	1 (1%)	1 (1%)	0
Hypophosphataemia	3 (3%)	1 (1%)	1 (1%)	0
Activated partial thromboplastin time prolonged	3 (3%)	0	1 (1%)	0
Dehydration	0	3 (3%)	1 (1%)	0
Electrocardiogram QT prolonged	0	2 (2%)	2 (2%)	0
Proteinuria	0	3 (3%)	1 (1%)	0
Glycosylated haemoglobin increased	1 (1%)	1 (1%)	1 (1%)	0
Hypertension	0	1 (1%)	2 (2%)	0
Pneumonitis	1 (1%)	0	2 (2%)	0
Urticaria	2 (2%)	0	1 (1%)	0
Embolism	0	0	2 (2%)	0
Pain in jaw	1 (1%)	0	1 (1%)	0
Pyelonephritis	0	0	2 (2%)	0
Sinus pain	1 (1%)	0	1 (1%)	0
Chronic obstructive pulmonary disease	0	0	1 (1%)	0
Escherichia infection	0	0	1 (1%)	0
Mucosal infection	0	0	1 (1%)	0
Pneumonia	0	0	1 (1%)	0
Premature menopause	0	0	1 (1%)	0
Psoriasis	0	0	1 (1%)	0
Pyelonephritis acute	0	0	1 (1%)	0

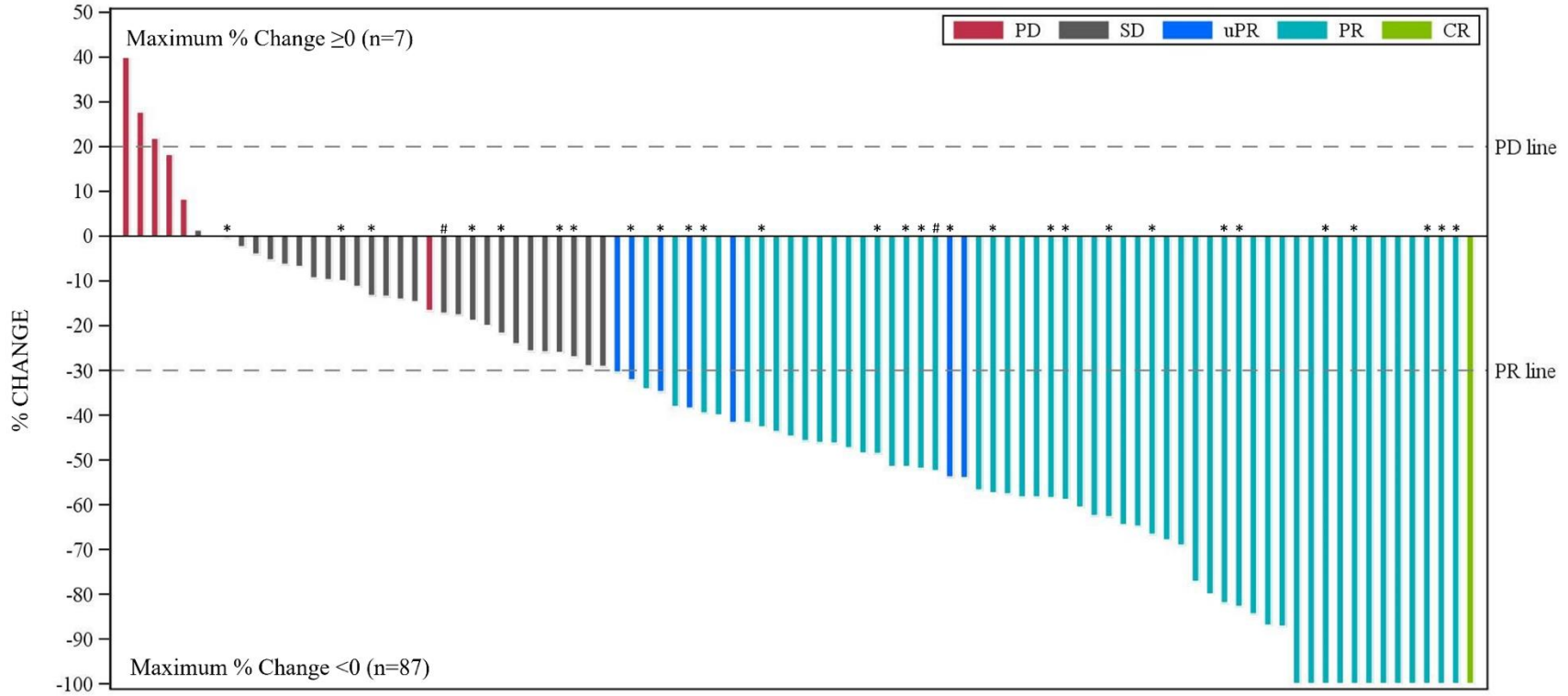
Data are n (%). CTCAE=Common Terminology Criteria for Adverse Events. Adverse events are by preferred term and maximum CTCAE grade in decreasing frequency order in participants treated with gedatolisib plus palbociclib and letrozole or fulvestrant. Adverse events were graded according to CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities. Adverse events that were related to treatment are shown here. All causality adverse events are shown in the appendix (pp 12–16). *Number of participants with at least one of the terms. If a participant had multiple terms, we counted once for the highest grade. †Rash, rash maculo-papular, rash pruritic, rash pustular, rash papular, rash erythematous, or rash vesicular.

Figure 1. Trial profile



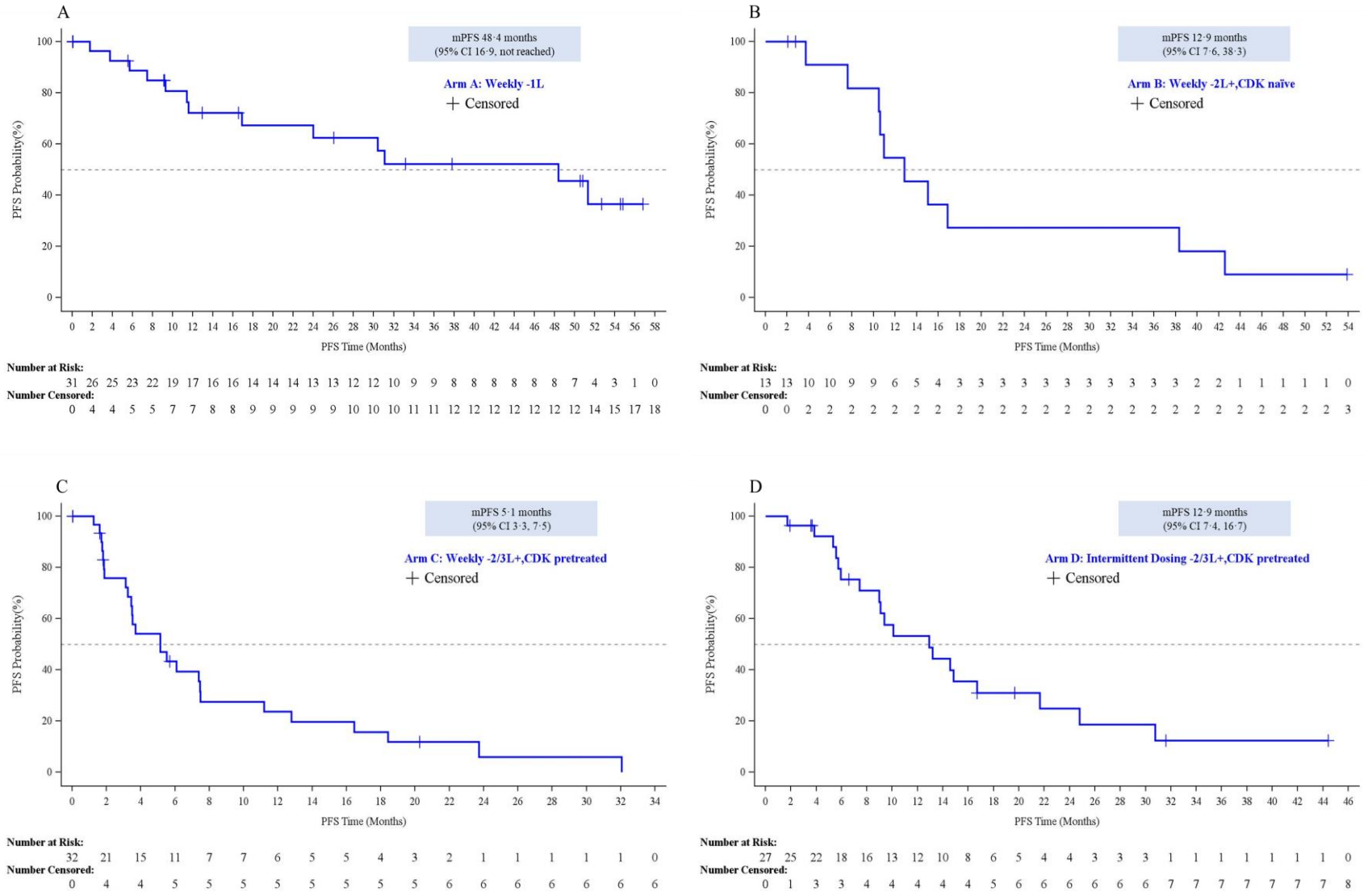
*All patients listed as terminated study continued treatment in an expanded access programme. †Other reasons for treatment discontinuation: new diagnosis of renal cell cancer (group A) and too many missed visits and assessments due to transportation issues or the COVID-19 pandemic (group D). All participants received gedatolisib weekly except for participants in expansion group D, who received gedatolisib on days 1, 8, and 15 of every 28-day cycle (a 3-weeks-on–1-week-off schedule). 138 total participants were enrolled, n=35 participants were enrolled in the dose escalation portion across groups A (gedatolisib plus palbociclib plus letrozole; n=15) and B (gedatolisib plus palbociclib plus fulvestrant; n=20). 103 participants were enrolled in the dose expansion portion across groups A, B, C, and D. Baseline characteristics for escalation group participants are shown in the appendix (pp 7–8).

Figure 2. Best response



Percentage change from baseline in the sum of the diameter of all target lesions at the time of best response is shown for each participant in the response evaluable analysis set (n=94). One participant in group C was excluded from this plot owing to a target lesion being indeterminate. The sum of diameters could not be calculated, although the overall assessment was progressive disease because of new target lesions. Only tumour assessments done before the start of any further anticancer treatment and before documented progression were considered. Twelve participants with 100% maximum improvement were considered partial response rather than complete response owing to the presence of stable non-target lesions. **PIK3CA* mutation detected. [#]No *PIK3CA* data.

Figure 3. Progression-free survival for all expansion groups



(A) Expansion group A, treatment-naive participants, weekly gedatolisib dosing. (B) Expansion group B, 1–2 lines of previous therapy, CDK4/6 inhibitor naive participants, weekly gedatolisib dosing. (C) Expansion group C, second-line and higher participants, CDK4/6 pretreated, weekly gedatolisib dosing. (D) Expansion group D, second-line and higher participants, CDK4/6 pretreated, 3-weeks-on–1-week-off gedatolisib dosing. Updated as of May 29, 2023 data cutoff.