Pictilisib PI3Kinase inhibitor (a phosphatidylinositol 3-kinase [PI3K] inhibitor) plus paclitaxel for the treatment of hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study

Annals of Oncology Advance Access published August 29, 2016

Pictilisib plus paclitaxel for the treatment of hormone receptor-positive, HER2-negative, locally recurrent, or metastatic breast cancer: interim analysis of the multicentre, placebo-controlled, phase II randomised PEGGY study

P. Vuylsteke[1,*], M. Huizing[2,*], K. Petrakova[3], R. Roylance[4], R. Laing[5], S. Chan[6], F. Abell[7], S. Gendreau[8], I. Rooney[9], D. Apt[10], J. Zhou[11], S. Singel[9] & L. Fehrenbacher[12]

[1]Department of Medical Oncology, Université Catholique de Louvain, CHU UCL Namur, Sainte-Elisabeth, Belgium

[2]Multidisciplinary Breast and Gynaecological Oncology Unit, Universitair Ziekenhuis Antwerpen, Wilrijkstraat 10, Antwerp, Belgium

[3]Department of Medical Oncology, Masaryk Memorial Cancer Institute, Brno, Czech Republic

[4]Department of Medical Oncology, Barts Health NHS Trust and Barts Cancer Institute, Queen Mary University of London, London, UK

[5]Department of Oncology, The Royal Surrey County Hospital, Guildford, UK

[6]Department of Clinical Oncology, Nottingham University Hospitals NHS Trust, Nottingham, UK

[7]Department of Medical Oncology, Calvary Mater Hospital Newcastle, New South Wales, Australia

[8]Oncology Biomarker Development, Genentech Inc., South San Francisco, CA, USA

[9]Product Development Oncology, Genentech Inc., South San Francisco, CA, USA

[10]BioOncology, Genentech Inc., South San Francisco, CA, USA

[11]Product Development Biometrics Biostatistics Department, Genentech Inc., South San Francisco, CA, USA

[12]Kaiser Permanente, Northern California, Vallejo, CA, USA.

Corresponding author: Dr Peter Vuylsteke, Medical Oncologist, Université Catholique de Louvain, CHU UCL Namur, Site Sainte-Elisabeth, Medical Oncology, Place Louise Godin 15, B-5000 Namur, Belgium, Tel: +32 (0)81 70 2547, E-mail: peter.vuylsteke@cmsenamur.be

*These authors have contributed equally to this work.

Key message: The PEGGY study failed to meet its primary endpoint, with no improvement in progression-free survival in patients who received pictilisib plus paclitaxel versus placebo plus paclitaxel in either the intention-to-treat population or in patients with *PIK3CA*-mutated tumours.

Abstract

Background: ~40% of hormone receptor-positive, HER2-negative breast cancers (BCs) are associated with activating mutations of the phosphatidylinositol 3-kinase (PI3K) pathway. Pictilisib, a potent and highly specific class I pan-PI3K inhibitor, demonstrated preclinical activity in BC cell lines and may potentiate the effect of taxanes, benefiting patients with or without aberrant activation of the PI3K pathway. PEGGY (NCT01740336), a randomised, placebo-controlled phase II trial, examined whether pictilisib augments the anti-tumour activity of paclitaxel in patients with hormone receptor-positive, HER2-negative locally recurrent or metastatic BC (mBC). We report results from the protocol-specified interim analysis.

Patients and methods: 183 eligible patients were randomised (1:1) to receive paclitaxel (90 mg/m^2 weekly for 3 weeks in every 28-day cycle) with either 260 mg pictilisib or placebo (daily on Days 1–5 every week). The primary endpoint was progression-free survival (PFS) in the intention-to-treat (ITT) population and patients with *PIK3CA*-mutated tumours. Secondary endpoints included overall response rate (ORR), duration of response and safety.

Results: In the ITT population, median PFS was 8.2 months with pictilisib (*n* = 91) versus 7.8 months with placebo (*n* = 92) (hazard ratio [HR] for progression or death, 0.95; 95% confidence interval [CI] 0.62–1.46; *P* = 0.83). In patients with *PIK3CA*-mutated tumours, median PFS was 7.3 months for pictilisib (*n* = 32) versus 5.8 months with placebo (*n* = 30) (HR, 1.06; 95% CI 0.52–2.12; *P* = 0.88). ORR was similar between treatment arms. The safety profile of pictilisib was consistent with previous reports, with no new safety signals. Proportions of patients with grade ≥3 adverse events (AEs), serious AEs, and dose reductions/discontinuations due to AEs were higher with pictilisib.

Conclusions: PEGGY did not meet its primary endpoint, revealing no significant benefit from adding pictilisib to paclitaxel for patients with hormone receptor-positive, HER2-negative locally recurrent or mBC.

Word count: 298/300 words

Clinical trial number: NCT01740336

Key words for indexing: HER2-negative, hormone receptor-positive, metastatic breast cancer, PI3K, pictilisib, PIK3CA

Introduction

Treatment of HER2-negative breast cancer (BC) remains challenging, despite improved outcomes, and single-agent cytotoxic chemotherapeutic agents, including paclitaxel, are primary options for patients with HER2-negative locally recurrent or metastatic BC (mBC) [1, 2]. Alterations in the phosphatidylinositol 3-kinase (PI3K) signalling pathway occur frequently in BC and include amplification and/or mutation of the genes encoding receptor tyrosine kinases, such as the catalytic subunit of PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha [*PIK3CA*]), protein kinase B (*AKT*) or phosphatase and tensin homologue (*PTEN*) [3, 4]. The majority of BCs are oestrogen receptor (ER)-positive and activation of the PI3K pathway has been linked to resistance to endocrine therapy [3, 5]. Mutations in *PIK3CA* are detected in ~40% of patients with ER-positive BC [6].

Pictilisib (GDC-0941) is a potent, selective, orally available pan-inhibitor of class I PI3K family members that inhibits the p110α, p110β, p110δ, and p110γ subunits of PI3K [7]. Pictilisib binds the adenosine triphosphate (ATP)-binding pocket of PI3K and prevents formation of phosphatidylinositol (3,4,5)-trisphosphate (PIP_3), a key signalling intermediary that transmits signals downstream of PI3K [7]. BC cell lines and xenograft models harbouring *PIK3CA* mutations were reported to be sensitive to the anti-tumour effects of pictilisib, while models lacking this mutation also showed sensitivity [8]. When given in combination with docetaxel, pictilisib enhanced drug-induced apoptosis in a xenograft model of BC, suggesting that cancer cells challenged with chemotherapy may be dependent on the PI3K pathway for survival [9].

Pictilisib demonstrated anti-tumour activity, on-target pharmacodynamic activity and an acceptable safety profile at doses of ≥100 mg in a phase I, open-label dose-

escalation study of patients with advanced solid tumours [10]. The addition of pictilisib to anastrozole in patients with preoperative early BC (OPPORTUNE) was associated with a significantly increased anti-proliferative response compared with anastrozole alone [11]. Additionally, pictilisib at dose ranges of ≤330 mg combined with weekly paclitaxel was generally well tolerated and demonstrated anti-tumour activity in patients with BC [12]. We now report results of a pre-specified interim analysis of PEGGY, a phase II trial evaluating the addition of pictilisib to paclitaxel compared with placebo plus paclitaxel in the treatment of patients with locally recurrent or metastatic HER2-negative, hormone receptor-positive BC.

Patients and methods

Study design and treatment

PEGGY (NCT01740336) was a multicentre, randomised, placebo-controlled phase II trial. Eligible patients were pre- and postmenopausal females aged ≥18 years with histologically or cytologically confirmed locally recurrent or mBC. Inclusion criteria specified that patients had HER2-negative, hormone receptor-positive disease defined by local clinical guidelines and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Adequate haematological and end-organ function were required and prior chemotherapy was not permitted, with the exception of capecitabine for locally recurrent or metastatic disease, or prior treatment with a PI3K inhibitor for advanced or mBC. Patients with a history of intolerance to a taxane-containing therapy or clinically significant cardiac or pulmonary dysfunction were ineligible.

This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and all patients provided written informed consent.

Approval for the protocol and any accompanying material provided to the patient was obtained from independent ethics committees at participating institutions.

Randomisation and masking

Patients were randomly assigned (1:1 ratio) to receive paclitaxel with either pictilisib or placebo. Stratification factors were: (i) prior treatment with mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus); (ii) prior treatment with capecitabine for mBC; and (iii) prior treatment with adjuvant chemotherapy. Sponsor, investigators, and patients were blinded to treatment assignment of pictilisib or placebo, unless necessary for patient management.

Procedures

The treatment schedule is shown in Supplementary Figure S1. Patients received 28-day cycles of intravenous paclitaxel (90 mg/m^2 weekly for 3 of every 4 weeks each cycle) with either 260 mg pictilisib given orally (pictilisib arm) or placebo (placebo arm) daily on Days 1–5 every week. Study treatment was received until progression of disease (PD), unacceptable toxicity, study withdrawal, or study completion or termination, and patients who discontinued one treatment component for any reason could continue to participate in the study and receive single-agent treatment until progression. Patients in the placebo arm who progressed were permitted to cross over to receive paclitaxel plus open-label pictilisib or single-agent pictilisib, provided they still met the eligibility criteria, until unacceptable toxicity, elective withdrawal from the study, or study completion or termination.

Tumour assessments were performed according to the modified Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST v1.1) every 12 weeks until PD (determined by investigator assessment), regardless of whether patients received study treatment.

Interim efficacy and safety analyses were planned to be performed after 60 progression-free survival (PFS) events of PD or “on study” death in the intention-to-treat (ITT) population.

Safety assessment

The incidence and severity of adverse events (AEs) and serious AEs (SAEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4. The safety assessment period included the period between randomisation and 30 days after the last blinded treatment, prior to the crossover period (if applicable).

Mutation analysis for PIK3CA

PIK3CA-mutation status in tumour tissue was analysed at a central laboratory using allele-specific quantitative real-time polymerase chain reaction (cobas® *PIK3CA* Mutation Test, Roche Molecular Diagnostics, Pleasanton, CA, USA) for activating missense mutations and nucleotide substitutions that result in the following amino acid changes: R88Q (exon 1), N345K (exon 4), C420R (exon 7), E542K (exon 9), E545K/A/G/D (exon 9), Q546K/E/R/L (exon 9), M1043I (exon 20), H1047R/L/Y (exon 20), H1049R (exon 20).

Statistical analyses

The primary endpoint was PFS based on investigator assessment in the ITT population and in patients with *PIK3CA*-mutated tumours (the “*PIK3CA*-mutant” subgroup). Secondary endpoints included overall response rate (ORR), duration of response (DoR) and safety.

Per protocol, primary (PFS) and secondary efficacy endpoints (ORR, DoR) were analysed in all randomised patients (ITT population), patients with a *PIK3CA*-mutated

tumour and additional subgroups. PFS was defined as the time from randomisation to the first occurrence of PD or “on-study” death from any cause (≤30 days after the last dose of study treatment). DoR was defined as time from first observation of objective response until first observation of PD or “on-study” death. The blinded period before crossover was included in all analyses. Safety analyses included all patients who received at least one dose of study treatment during the blinded period, prior to crossover.

The PEGGY study was hypothesis-generating and not powered to detect minimal clinically meaningful differences between treatment arms at a statistically significant type I error level of 5%. The PEGGY study was designed to obtain meaningful estimates for the hazard ratio of the pictilisib arm (versus the placebo arm) in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit-alpha (*PIK3CA*)-mutant and *PIK3CA*-wild-type subgroups, as well as in the intention-to-treat (ITT) population. In the *PIK3CA*-mutant subgroup, 40 events were required to trigger final analysis and, at a targeted hazard ratio of 0.53, a two-sided upper 90% confidence interval of 0.32–0.89 would be considered meaningful. The interim analysis was planned to occur after 60 events were reported in the ITT population. In the ITT population, it was estimated that 180 patients would be required for final analysis based on projections that 15% of randomised patients would be unevaluable for efficacy, 35% of patients would have *PIK3CA* mutations and 75% of efficacy-evaluable patients would have a progression event. 120 events were expected in the ITT population by the time 40 events had been observed in the *PIK3CA*-mutant subgroup.

Results

Patient characteristics

183 patients were randomised to receive paclitaxel treatment combined with either pictilisib (*n* = 91) or placebo (*n* = 92) (February 2013–May 2014). All randomised patients received at least one dose of study treatment and were analysed in the ITT and safety populations (Supplementary Figure S1). At data cut-off (12 September 2014), 65.6% of patients had discontinued blinded treatment, 70.3% in the pictilisib arm and 60.9% in the placebo arm (Figure 1). Baseline characteristics were generally well balanced across the treatment groups (Table 1). Approximately one-third of patients in each arm had detectable *PIK3CA* mutations (pictilisib 35.2%, placebo 32.6%; Supplementary Table S1).

Treatment exposure

Overall, treatment exposure was comparable between arms (Supplementary Table S2). The median duration of treatment in the pictilisib arm was 5.4 months (range, 0–16 months) for pictilisib and 5.1 months (range, 0–16 months) for paclitaxel. In the placebo arm, the median duration of treatment was 5.8 months (range, 0–15 months) for placebo and 5.1 months (range, 0–15 months) for paclitaxel. Median dose intensity for pictilisib/placebo differed slightly between arms, and was 91.7% (range, 23–105%) in the pictilisib arm and 98.6% (range, 41–103%) in the placebo arm. Mean dose intensity also differed between arms and was 85.9% (standard deviation [SD], 15.9%) in the pictilisib arm and 94.8% (SD, 9.4%) in the placebo arm. The number of patients with dose reductions for pictilisib/placebo was notably higher in the pictilisib arm (39.6% [*n* = 36] versus 7.6% [*n* = 7] in the placebo arm); dose reduction for paclitaxel treatment was comparable between arms (Table 2).

Efficacy at interim analysis

At interim analysis, 88 PFS events had occurred, representing 73% of the expected 120 PFS events for final analysis. In the *PIK3CA*-mutated subgroup of patients, 32 of 40 PFS events had occurred (80%).

Progression-free survival

Eighty-eight patients in the ITT population (42 [46.2%] in the pictilisib arm and 46 [50.0%] in the placebo arm) and 32 patients in the *PIK3CA*-mutant population had PFS events (17 [53.1%] in the pictilisib arm and 15 [50.0%] in the placebo arm). Overall, there was no significant PFS difference between arms in the ITT population or patients with *PIK3CA*-mutated tumours. The median PFS in the pictilisib arm was 8.2 months (*n* = 91) versus 7.8 months in the placebo arm (*n* = 92) (Figure 2A; hazard ratio [HR], 0.95; 95% confidence interval [CI] 0.62–1.46; *P* = 0.83). The median PFS in patients with *PIK3CA*-mutated tumours (Figure 2B) was 7.3 months in the pictilisib arm (*n* = 32) and 5.8 months in the placebo arm (*n* = 30) (HR, 1.06; 95% CI 0.52–2.12; *P* = 0.88). Analysis of PFS in pre-specified subgroups did not show differences between arms (Figure 3).

Overall response rate and duration of response (ITT population)

The ORR was 22.0% (20/91 patients; 95% CI 14.0–31.9) in the pictilisib arm and 19.6% (18/92 patients; 95% CI 12.0–29.2) in the placebo arm. All responses were partial. Five of the 20 responders in the pictilisib arm and three of the 18 responders in the placebo arm had PFS events. Median DoR was 6.8 months (95% CI 5.2–not estimable [NE]) in the pictilisib arm and 5.6 months (95% CI 4.9–NE) in the placebo arm.

Safety

During the blinded period, the safety profile of pictilisib in combination with paclitaxel was consistent with previous reports of single-agent and combination therapy [10, 12, 13]. The incidence of treatment-emergent AEs is summarised in Table 2. The proportions of grade ≥3 AEs, SAEs and dose modifications/discontinuations due to AEs were higher in the pictilisib arm compared with the placebo arm.

The most common grade ≥3 AEs in either arm were neutropenia, peripheral neuropathy, anaemia and diarrhoea (a known AE associated with pictilisib treatment) (Supplementary Table S3). Hyperglycaemia, hypertension (deemed non-serious by investigators) and maculopapular rash were also reported in the pictilisib arm only (Supplementary Table S3). The most common SAEs in either arm were pyrexia, BC and pneumonitis (Supplementary Table S4). SAEs reported in the pictilisib arm only were maculopapular rash, dyspnoea, febrile neutropenia and gastroenteritis (Supplementary Table S4). The most common AE leading to dose reduction was maculopapular rash in the pictilisib arm (seven patients [7.7%]), while the most common AEs leading to pictilisib/placebo withdrawal were pneumonitis (two patients in each arm) and allergic dermatitis (two patients in the pictilisib arm).

Rash, comprising the AEs: rash, erythematous rash, follicular rash, generalised rash, macular rash, maculopapular rash, maculovesicular rash, morbilliform rash, papular rash, papulosquamous rash, pruritic rash, pustular rash, and vesicular rash, was common (48.4% of patients in the pictilisib arm versus 33.7% of patients in the placebo arm of any grade) and the main cause of study drug dose modification, leading to more drug interruptions (11.0% versus 1.1%), reductions (14.3% versus 0), and withdrawals (2.2% versus 0) in the pictilisib arm compared with the placebo arm, respectively (Supplementary Table S5).

AEs of special interest to pictilisib therapy were reported in 10 patients (11.0%) in the pictilisib arm and two patients (2.2%) in the placebo arm (Supplementary Table S6). Of these, grade 3 rash and grade 2 pneumonitis were detected in the pictilisib arm only.

There were four AEs leading to death during blinded drug treatment and within 30 days after the last blinded dose; one in the pictilisib arm (one case of progressive disease) and three in the placebo arm (one case of hepatic haemorrhage and two cases of progressive disease).

Discussion

The PEGGY study examined whether the pan-PI3K inhibitor pictilisib enhances the anti-tumour activity of paclitaxel in patients with advanced HER2-negative, hormone receptor-positive BC. At interim analysis, pictilisib plus paclitaxel did not improve PFS in either the ITT population (median PFS of 8.2 months in the pictilisib arm versus 7.8 months in the placebo arm; $P = 0.83$) or the *PIK3CA*-mutated subgroup (median PFS of 7.3 months in the pictilisib arm versus 5.8 months in the placebo arm; $P = 0.88$).

Previous clinical trials of pictilisib have produced varying results. The first-in-human phase I dose escalation study of single-agent pictilisib demonstrated anti-tumour activity with an acceptable safety profile in patients with advanced solid tumours [10]. The addition of pictilisib to anastrozole in the OPPORTUNE study significantly increased the anti-proliferative response in patients with early BC [11], while treatment of patients with ER-positive locally advanced or mBC in the phase II FERGI trial (pictilisib plus fulvestrant versus placebo plus fulvestrant) was not

associated with a significant increase in PFS at a pictilisib dose of 260 mg or 340 mg [14].

Effectively combining a PI3K pathway inhibitor with chemotherapy is challenging and the high number of pictilisib dose modifications and the lower pictilisib dose compared with the FERGI study (260 mg versus 340 mg, respectively) may have resulted in a lack of consistent pharmacodynamic activity in the PEGGY study. Due to the significant dose modifications it is therefore still not clear whether a PI3K inhibitor can exert a synergistic effect on paclitaxel if a dose high enough to sustain PI3K pathway inhibition can be achieved. In addition, *PIK3CA*-mutation status did not provide evidence to differentiate PFS benefit for pictilisib. Investigators from OPPORTUNE and FERGI also reported little or no association between *PIK3CA* mutation status and outcome [11, 14].

While the PI3K signalling pathway represents an attractive therapeutic target, its complexity makes selection of the patient group most likely to benefit from this type of intervention challenging. The PI3K pathway is targetable; however, escape pathways involving proteins such as KRAS or MEK/ERK may be activated by its inhibition, leading to resistance [15-17]. Thus, targeting multiple pathways with a combination of agents may be key to developing more promising therapies [15-17]. Current strategies include targeting the α subunit of PI3K specifically or combining PI3K in combination with endocrine therapy.

In conclusion, the PEGGY study did not meet its primary endpoint in either the ITT population or in patients with *PIK3CA*-mutated tumours, and revealed no significant benefit from adding pictilisib to paclitaxel for patients with hormone receptor-positive, HER2-negative locally recurrent or mBC.

Acknowledgements

We would like to thank the patients, their families, the nurses, and the investigators who participated in this study. Support for third-party writing assistance for this manuscript, furnished by Islay Steele, PhD, was provided by F. Hoffmann-La Roche Ltd.

Funding

This work was supported by F. Hoffmann-La Roche Ltd/Genentech Inc., a member of the Roche Group (no grant number is applicable).

Disclosure: conflicts of interest

PV and MH have received honoraria for advisory boards from Roche Belgium. JZ, IR and SS are employees of Genentech Inc. SG is an employee of Roche and holds shares in Roche. DA was an employee of Genentech, Inc. All remaining authors have declared no conflicts of interest.

References

1. Cardoso F, Costa A, Norton L et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014; 23: 489-502.

2. Gradishar WJ, Anderson BO, Balassanian R et al. Breast cancer version 2.2015. J Natl Compr Canc Netw 2015; 13: 448-475.

3. Miller TW, Balko JM, Arteaga CL. Phosphatidylinositol 3-kinase and antiestrogen resistance in breast cancer. J Clin Oncol 2011; 29: 4452-4461.

4. Lauring J, Park BH, Wolff AC. The phosphoinositide-3-kinase-Akt-mTOR pathway as a therapeutic target in breast cancer. J Natl Compr Canc Netw 2013; 11: 670-678.

5. Yang SX, Polley E, Lipkowitz S. New insights on PI3K/AKT pathway alterations and clinical outcomes in breast cancer. Cancer Treat Rev 2016; 45: 87-96.

6. Arthur LM, Turnbull AK, Renshaw L et al. Changes in PIK3CA mutation status are not associated with recurrence, metastatic disease or progression in endocrine-treated breast cancer. Breast Cancer Res Treat 2014; 147: 211-219.

7. Folkes AJ, Ahmadi K, Alderton WK et al. The identification of 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine (GDC-0941) as a potent, selective, orally bioavailable inhibitor of class I PI3 kinase for the treatment of cancer. J Med Chem 2008; 51: 5522-5532.

8. O'Brien C, Wallin JJ, Sampath D et al. Predictive biomarkers of sensitivity to the phosphatidylinositol 3' kinase inhibitor GDC-0941 in breast cancer preclinical models. Clin Cancer Res 2010; 16: 3670-3683.

9. Wallin JJ, Guan J, Prior WW et al. GDC-0941, a novel class I selective PI3K inhibitor, enhances the efficacy of docetaxel in human breast cancer models by increasing cell death in vitro and in vivo. Clin Cancer Res 2012; 18: 3901-3911.

10. Sarker D, Ang JE, Baird R et al. First-in-human phase I study of pictilisib (GDC-0941), a potent pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor, in patients with advanced solid tumors. Clin Cancer Res 2015; 21: 77-86.

11. Schmid P, Pinder SE, Wheatley D et al. Phase II randomized preoperative window-of-opportunity study of the PI3K inhibitor pictilisib plus anastrozole compared with anastrozole alone in patients with estrogen receptor-positive breast cancer. J Clin Oncol 2016; 34: 1987-1994.

12. Schöffski P, Cresta S, Mayer IA et al. Tolerability and anti-tumor activity of the oral PI3K inhibitor GDC-0941 in combination with paclitaxel, with and without bevacizumab or trastuzumab in patients with locally recurrent or metastatic breast cancer. Cancer Res 2015; 75: Abstract P5-19-10 (and associated poster presentation).

13. Von Hoff D, LoRusso P, Demetri GD et al. A phase I dose-escalation study to evaluate GDC-0941, a pan-PI3K inhibitor, administered QD or BID in patients with advanced or metastatic solid tumors. J Clin Oncol 2011; 29 (20 May suppl.): Abstract 3052.

14. Krop IE, Mayer IA, Ganju V et al. Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): a

randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016; 17; 811-821.

15. Carracedo A, Ma L, Teruya-Feldstein J et al. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. J Clin Invest 2008; 118: 3065-3074.

16. Paplomata E, O'Regan R. The PI3K/AKT/mTOR pathway in breast cancer: targets, trials and biomarkers. Ther Adv Med Oncol 2014; 6: 154-166.

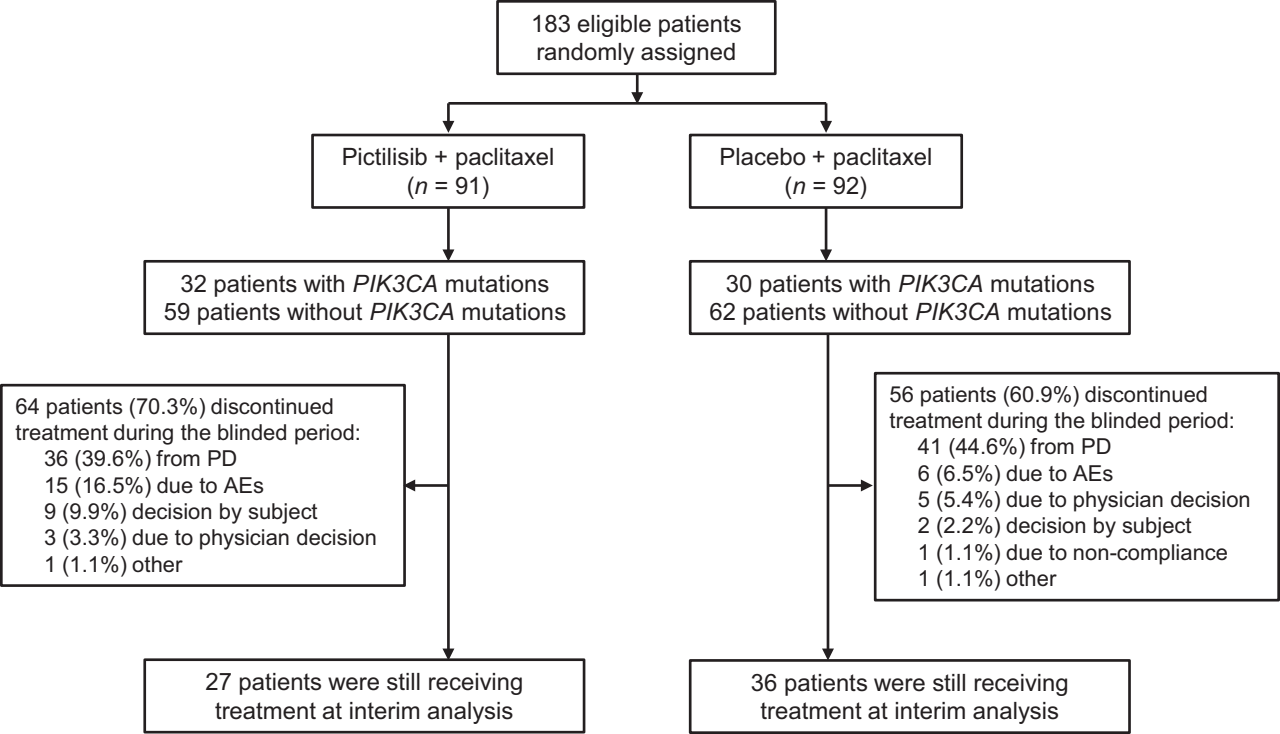
17. Rozengurt E, Soares HP, Sinnet-Smith J. Suppression of feedback loops mediated by PI3K/mTOR induces multiple overactivation of compensatory pathways: an unintended consequence leading to drug resistance. Mol Cancer Ther 2014; 13: 2477-2488.

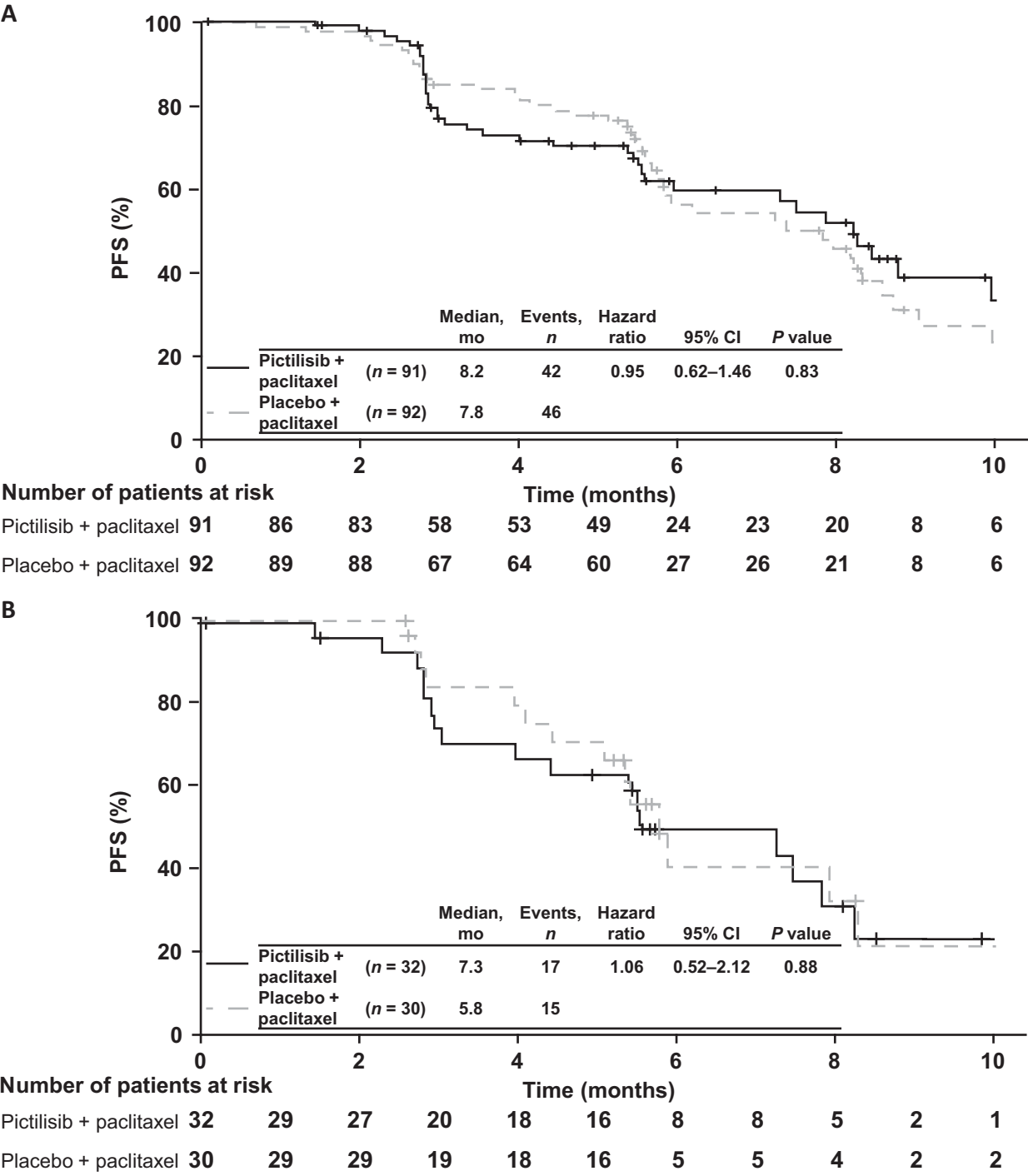
Figure legends

Figure 1. Participant flow diagram. AE, adverse event; ITT, intention-to-treat; PD, progressive disease.

Figure 2. PFS in (A) the ITT population and (B) patients with *PIK3CA*-mutated tumours. Kaplan-Meier curves for PFS by treatment group in (A) the ITT population and (B) patients with *PIK3CA*-mutated tumours. Patients who had neither progressed at the date of their last assessment nor died were censored. Tick marks indicate the times at which events were recorded. CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Figure 3. Hazard ratios for PFS in different subgroups. Hazard ratios and 95% CIs for PFS in all pre-specified subgroups according to baseline characteristics. [a]Samples were defined as progesterone receptor-positive if ≥10% of cells were positive by immunocytochemistry. [b]Visceral disease was defined as presence of disease in the lung, liver, adrenal glands, bone marrow or CNS; visceral disease was "unknown" if present in the mediastinum, abdomen or pelvis. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NE, not estimable; PFS, progression-free survival.


183 eligible patients randomly assigned
Pictilisib + paclitaxel (n = 91)
Placebo + paclitaxel (n = 92)
32 patients with PIK3CA mutations
59 patients without PIK3CA mutations
30 patients with PIK3CA mutations
62 patients without PIK3CA mutations
64 patients (70.3%) discontinued treatment during the blinded period:
36 (39.6%) from PD
15 (16.5%) due to AEs
9 (9.9%) decision by subject
3 (3.3%) due to physician decision
1 (1.1%) other
56 patients (60.9%) discontinued treatment during the blinded period:
41 (44.6%) from PD
6 (6.5%) due to AEs
5 (5.4%) due to physician decision
2 (2.2%) decision by subject
1 (1.1%) due to non-compliance
1 (1.1%) other
27 patients were still receiving treatment at interim analysis
36 patients were still receiving treatment at interim analysis


A
PFS (%)
100
80
60
40
20
0
Median, mo
Events, n
Hazard ratio
95% CI
P value
Pictilisib + paclitaxel (n = 91) 8.2 42 0.95 0.62–1.46 0.83
Placebo + paclitaxel (n = 92) 7.8 46
0
2
4
6
8
10
Time (months)
Number of patients at risk
Pictilisib + paclitaxel 91 86 83 58 53 49 24 23 20 8 6
Placebo + paclitaxel 92 89 88 67 64 60 27 26 21 8 6
B
PFS (%)
100
80
60
40
20
0
Median, mo
Events, n
Hazard ratio
95% CI
P value
Pictilisib + paclitaxel (n = 32) 7.3 17 1.06 0.52–2.12 0.88
Placebo + paclitaxel (n = 30) 5.8 15
0
2
4
6
8
10
Time (months)
Number of patients at risk
Pictilisib + paclitaxel 32 29 27 20 18 16 8 8 5 2 1
Placebo + paclitaxel 30 29 29 19 18 16 5 5 4 2 2

Baseline risk factors	Total, *n*	Placebo (*n* = 92) Events/*n*	Placebo (*n* = 92) Median PFS, mo	Pictilisib (*n* = 91) Events/*n*	Pictilisib (*n* = 91) Median PFS, mo	HR	95% CI
All patients	183	46/92	7.8	42/91	8.2	0.95	(0.62–1.46)
***PIK3CA* mutation status**							
Positive	62	15/30	5.8	17/32	7.3	1.06	(0.52–2.12)
Negative	106	27/53	8.1	22/53	9.9	0.76	(0.43–1.36)
Unknown	15	4/9	6.7	3/6	8.4	1.07	(0.19–6.11)
Baseline ECOG PS							
0	95	20/43	8.1	25/52	7.8	1.22	(0.67–2.22)
1	86	26/49	7.3	15/37	9.9	0.67	(0.36–1.28)
2	2			2/2	5.6	NE	(NE–NE)
Prior treatment with mTOR inhibitors							
No	163	41/84	7.8	34/79	8.2	0.88	(0.56–1.40)
Yes	20	5/8	7.0	8/12	5.3	1.57	(0.47–5.31)
Prior capecitabine treatment for mBC							
No	157	40/81	7.3	37/76	7.8	1.06	(0.68–1.67)
Yes	26	6/11	7.8	5/15	8.7	0.47	(0.13–1.67)
Prior treatment with adjuvant chemotherapy							
No	79	20/40	7.3	17/39	8.2	0.76	(0.40–1.47)
Yes	104	26/52	8.1	25/52	7.8	1.15	(0.66–2.00)
Progesterone receptor status – central[a]							
Positive	97	21/46	7.8	24/51	7.5	1.19	(0.66–2.15)
Negative	48	15/27	5.8	12/21	8.4	0.82	(0.38–1.77)
Unknown	38	10/19	5.8	6/19	14	0.62	(0.21–1.82)
Visceral disease							
No	63	18/36	8.5	8/27	11.1	0.78	(0.34–1.81)
Yes	118	27/55	7.3	34/63	8.2	0.91	(0.54–1.53)
Unknown	2	1/1	5.6	0/1	NE	NE	(NE–NE)
Bone-only disease							
No	151	37/73	7.2	39/78	8.2	0.85	(0.54–1.34)
Yes	32	9/19	9.9	3/13	11.1	0.86	(0.23–3.23)
Baseline histological subtype – lobular							
No	155	36/74	7.9	37/81	8.2	1.00	(0.63–1.59)
Yes	28	10/18	5.8	5/10	5.9	1.03	(0.34–3.06)

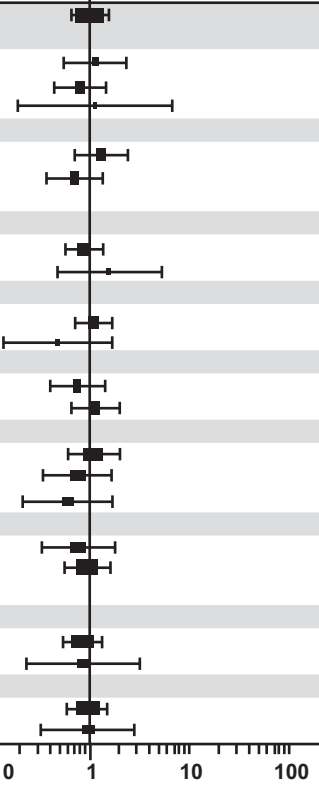


Table 1. Baseline demographic and clinical characteristics (ITT population)

	Pictilisib + paclitaxel (*n* = 91)	Placebo + paclitaxel (*n* = 92)
Median age, years (range)	55.0 (30–78)	58.0 (33–80)
Race, *n* (%)		
White	76 (83.5)	79 (85.9)
Asian	10 (11.0)	9 (9.8)
Black or African American	3 (3.3)	2 (2.2)
American Indian or Alaskan native	1 (1.1)	0
Native Hawaiian or other Pacific Islander	1 (1.1)	0
Other	0	2 (2.2)
Baseline ECOG PS, *n* (%)		
0	52 (57.1)	43 (46.7)
1	37 (40.7)	49 (53.3)
2	2 (2.2)	0
Stratification factors, *n* (%)		
Prior treatment with adjuvant chemotherapy	52 (57.1)	52 (56.5)
Prior treatment with capecitabine for mBC	15 (16.5)	11 (12.0)
Prior treatment with mTOR inhibitors	12 (13.2)	8 (8.7)
Progesterone receptor status[a] (central testing), *n* (%)		
Negative	21 (23.1)	27 (29.3)
Positive	51 (56.0)	46 (50.0)
Unknown	19 (20.9)	19 (20.7)
PIK3CA mutation status, *n* (%)		
Negative	53 (58.2)	53 (57.6)
Positive	32 (35.2)	30 (32.6)
Unknown	6 (6.6)	9 (9.8)
Visceral disease,[b] *n* (%)		
Yes	63 (69.2)	55 (59.8)
No	27 (29.7)	36 (39.1)
Unknown	1 (1.1)	1 (1.1)
Bone-only disease, *n* (%)		
Yes	13 (14.3)	19 (20.7)
No	78 (85.7)	73 (79.3)
Baseline histological subtype – lobular, *n* (%)		
Yes	10 (11.0)	18 (19.6)
No	81 (89.0)	74 (80.4)
Median time from histological diagnosis, months (range)	64.0 (0.3–333.4)	51.7 (0.5–373.5)

Median time from diagnosis of metastatic disease, months	7.6 (0.1–154.2)	2.2 (-0.5–112.2)
Baseline stage, *n* (%)		
I	7 (7.7)	10 (10.9)
IIA	20 (22.0)	16 (17.4)
IIB	10 (11.0)	10 (10.9)
IIIA	18 (19.8)	16 (17.4)
IIIB	4 (4.4)	2 (2.2)
IIIC	9 (9.9)	10 (10.9)
IV	16 (17.6)	18 (19.6)
Unknown	7 (7.7)	10 (10.9)
Baseline histological grade, *n* (%)		
Well differentiated	8 (8.8)	10 (10.9)
Moderately differentiated	37 (40.7)	40 (43.5)
Poorly differentiated	24 (26.4)	25 (27.2)
Anaplastic	0	1 (1.1)
Unknown	22 (24.2)	16 (17.4)

Data are median (range) or number (%). [a]Samples were defined as progesterone receptor-positive if ≥10% of cells were positive by immunocytochemistry. [b]Visceral disease was defined as presence of disease in the lung, liver, adrenal glands, bone marrow or CNS; visceral disease was “unknown” if present in the mediastinum, abdomen or pelvis. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; mBC, metastatic breast cancer; mTOR, mammalian target of rapamycin.

Table 2. Safety overview (safety population)

	Pictilisib + paclitaxel (*n* = 91)	Placebo + paclitaxel (*n* = 92)
AEs	90 (98.9)	92 (100.0)
Grade ≥3 AEs	61 (67.0)	46 (50.0)
SAEs	33 (36.3)	23 (25.0)
AE leading to any drug dose interruption	53 (58.2)	45 (48.9)
AE leading to pictilisib/placebo dose interruption	46 (50.5)	34 (37.0)
AE leading to paclitaxel dose interruption	43 (47.3)	33 (35.9)
Number of patients with dose reduction		
Pictilisib/placebo	36 (39.6)	7 (7.6)
Paclitaxel dose	29 (31.9)	25 (27.2)
AE leading to dose reduction of any treatment	45 (49.5)	21 (22.8)
AE leading to pictilisib/placebo dose reduction	28 (30.8)	7 (7.6)
AE leading to paclitaxel dose reduction	29 (31.9)	19 (20.7)
AE leading to discontinuation of any treatment	23 (25.3)	14 (15.2)
AE leading to pictilisib/placebo discontinuation	16 (17.6)	6 (6.5)
AE leading to paclitaxel discontinuation	17 (18.7)	13 (14.1)

Data are number (%). AE, adverse event; SAE, serious adverse event.