# Phase II, randomized, parallel-cohort study of neoadjuvant buparlisib (BKM120) in combination with trastuzumab and paclitaxel in women with HER2-positive, *PIK3CA* mutant and *PIK3CA* wild-type primary breast cancer – NeoPHOEBE


**Sibylle Loibl[1,2], Lorena de la Pena[3], Valentina Nekljudova[1], Dimitrios Zardavas[4], Stefan Michiels[5], Carsten Denkert[6], Mahdi Rezai[7], Begoña Bermejo[8], Lee Soo Chin[9], Sabine Turri[10], Patrick Urban[10], Sherko Kümmel[11], Michael Lux[12], Martine Piccart[4,13], Gunter Von Minckwitz[1], José Baselga[3,14], Sherene Loi[15]**

[1]German Breast Group, Neu-Isenburg, Germany; [2]Sana-Klinikum Offenbach, Germany; [3]SOLTI Breast Cancer Research Group, Barcelona, Spain; [4]Breast International Group, Brussels, Belgium; [5]Institut Gustave Roussy, Villejuif, France; [6]Pathology Charité, Berlin, Gemany; [7]Luisenkrankenhaus Düsseldorf, Germany; [8]Hospital Clinico Universitario de Valencia; [9]Department of Haematology-Oncology, National University Cancer Institute Singapore; [10]Novartis Pharma AG, Basel, Switzerland; [11]Kliniken Essen-Mitte, Essen, Germany; [12]Women University Hospital Erlangen, Germany; [13]Institut Jules Bordet, Brussels, Belgium; [14]Memorial Sloan-Kettering Cancer Center, New York, USA; [15]Peter MacCallum Cancer Centre, East Melbourne, Australia;


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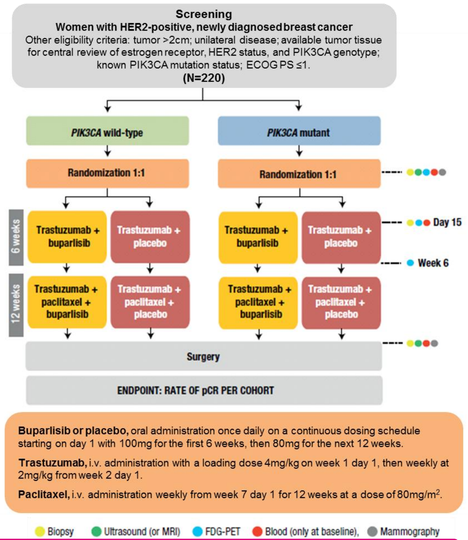
## Background

- The PI3K/Akt/mTOR pathway is frequently dysregulated in breast cancer (BC) and has been identified as a mediator of resistance to HER2 blockade in HER2-positive tumors.[1,2]
- Buparlisib is an oral pan-PI3K inhibitor targeting all isoforms of class I PI3K (α, β, γ, δ).[3]
- Clinical activity was observed using buparlisib in advanced BC as a single agent, and combined with paclitaxel and/or trastuzumab.[4,5]

### Figure 1: NeoPHOEBE study design




## References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2. Nahta R et al. Clin Breast Cancer. 2010;10 Suppl 3:S72-8.
3. Maira SM et al. Mol Cancer Ther. 2012; 11:317-28.
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## Objectives

**Primary Objective: Pathologic complete response (pCR; ypT0/is) at surgery**

Secondary Objectives: **Objective response rate (ORR) at the end of week 6,** pCR by other definitions. ORR prior to surgery, pCR and ORR by estrogen receptor (ER) status, patients with node-negative disease at surgery, rate of breast conserving surgery, safety, tolerability and compliance.

Translational objectives: Correlation of pCR with PTEN, Ki67, apoptosis rates, and tumor infiltrating lymphocytes (TIL), and by phenotype of 50% TIL at baseline.

## Materials and Methods

**NeoPHOEBE (NCT01816594) is a phase II, randomized, double-blind, placebo-controlled, parallel cohort study of neoadjuvant buparlisib/ placebo plus trastuzumab and paclitaxel in women with primary HER2+ BC.**

Patients were stratified upfront in 2 independent cohorts according to *PIK3CA* mutation status and, in each cohort, randomized stratified by ER status to buparlisib or placebo with trastuzumab followed by buparlisib or placebo with trastuzumab and paclitaxel **(Figure 1)**.

**Statistical considerations:** Sample size was based on a minimax 2-stage randomized phase II design with a prospective control, allowing for early stopping if the desired efficacy was not observed at stage 1. Cohorts were powered (80%) to detect a clinically meaningful 18% pCR increase (one-sided α=0.15).

## Results

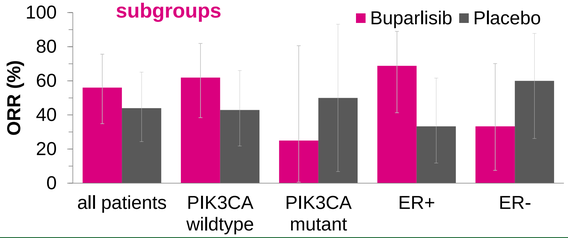
**Table 1: Patient and tumor characteristics**

| Parameter | | Buparlisib (N=25) N (valid %) | Placebo (N=25) N (valid %) | Overall (N=50) N (valid %) |
|---|---|---|---|---|
| **Age, years, median (range)** | | 50 (35, 72) | 50 (26, 78) | 50 (26, 78) |
| **cT1/2** | | 24 (96.0) | 25 (100.0) | 49 (98.0) |
| **cN+** | | 8 (32.0) | 9 (36.0) | 17 (34.0) |
| **ER positive** | | 16 (64.0) | 15 (60.0) | 31 (62.0) |
| **PgR positive** | | 10 (40.0) | 12 (48.0) | 22 (44.0) |
| ***PIK3CA* mutant** | | 4 (16.0) | 4 (16.0) | 8 (16.0) |
| **Tumor grade 3** | | 14 (56.0) | 17 (68.0) | 31 (62.0) |
| **Ki67 >20%** | | 22 (88.0) | 21 (84.0) | 43 (86.0) |
| **ypT0/is,** | **overall** | **8 (32.0)** | **10 (40.0)** | **18 (36.0)** |
| | *PIK3CA* wildtype | 7 (33.3) | 9 (42.9) | 16 (33.3) |
| | *PIK3CA* mutant | 1 (25.0) | 1 (25.0) | 2 (25.0) |
| | ER+ | 5 (31.3) | 4 (26.7) | 9 (29) |
| | ER- | 3 (33.3) | 6 (60) | 9 (47.4) |

**Table 2: Non-hematological AEs according to treatment**

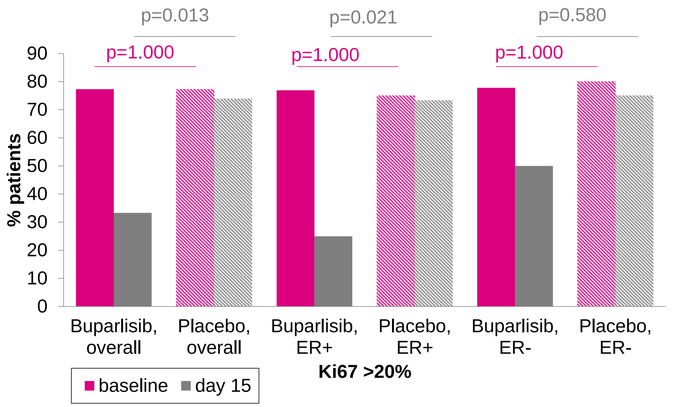
| Adverse Event | Grade | Buparlisib (N=25) N (valid %) | Placebo (N=25) N (valid %) | Overall (N=50) N (valid %) | p-value |
|---|---|---|---|---|---|
| **Increased AST** | any | 19 (76.0) | 9 (36.0) | 28 (56.0) | **0.005** |
| | 3-4 | 7 (28.0) | 0 (0.0) | 7 (14.0) | **0.005** |
| **Increased ALT** | any | 21 (84.0) | 18 (72.0) | 39 (78.0) | 0.248 |
| | 3-4 | 12 (48.0) | 2 (8.0) | 14 (28.0) | **0.002** |
| **Mucositis** | any | 19 (76.0) | 12 (48.0) | 31 (62.0) | **0.040** |
| | 3-4 | 2 (8.0) | 0 (0.0) | 2 (4.0) | 0.245 |
| **Rash maculo-papular** | any | 15 (60.0) | 12 (48.0) | 27 (54.0) | 0.285 |
| | 3 | 5 (20.0) | 0 (0.0) | 5 (10.0) | **0.025** |

### Figure 2: ORR after week 6 overall and in stratified subgroups

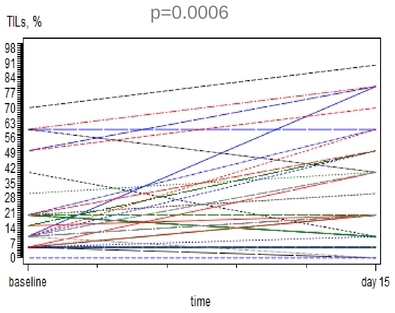



- Between 9/2013 and 10/2014, 50 patients were randomized in 17 sites in 4 countries (**Table 1**). Recruitment was suspended due to toxicity and resulting early therapy discontinuations.
- pCR rates were not significantly different between treatments, overall and according to stratified subgroups (**Table 1**). ORR after week 6 was not different between treatments overall, but there was a trend for better ORR with buparlisib in the ER+ subgroup (p=0.053; interaction buparlisib and ER status p=0.032) (**Figure 2**).
- Relevant non-hematological adverse events (AEs) are shown in **Table 2**. Hematological AEs did not differ between treatments. More patients discontinued buparlisib (9 due to AE, 2 patient/investigator decision) compared to placebo (2 local progress) (p<0.001). 9 patients reported a serious AE with buparlisib (3 with hepatotoxicity).
- Buparlisib led to a decrease in Ki67 from baseline to day 15 in all patients and the ER+ subgroup (**Figure 3**). TILs increased significantly from baseline to day 15 (**Figure 4**). Absolute changes from baseline to day 15 in TILs (OR 1.94, 95%CI 1.14-3.28; p=0.014), but not in Ki67 (OR 1.08, 0.67-1.73; p=0.764) independently predicted pCR.

### Figure 3: Exploratory analysis - Ki67 at baseline and day 15




### Figure 4: TILs at baseline and day 15




## Conclusions

**NeoPHOEBE was stopped prematurely. Adding a pan-PIK3 inhibitor to taxane-trastuzumab-based neoadjuvant therapy did not increase pCR rates compared to placebo overall and in subgroups of *PIK3CA* mutation or ER status, but led to higher toxicity. The higher ORR after week 6 is intriguing and further investigation of the addition of PI3K inhibitor to anti-HER2 therapy in the ER+/HER2+ group is warranted.**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