# **SUPPLEMENTARY APPENDIX**

# This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Lu YS, Lee KS, Chao TY, et al. Phase 1b Study of Alpelisib or Buparlisib in Premenopausal Women With HR+, HER2– Advanced Breast Cancer

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**Methods for laboratory assessments:**

Fasting plasma glucose, C-peptide, lipase, and lipid profile were tested at screening, pre-dose on Day 1 and Day 15 of Cycle 1, Day 1 and Day 15 of Cycle 2, on Day 1 of each subsequent cycle, and at end of treatment (EOT); overnight fasting of ≥10 hours was required. Glycated hemoglobin A1c was tested at screening, on Day 1 of every third cycle starting on Cycle 3, and at EOT. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, and creatinine testing were performed on Cycle 1 and 2; Days 8, 15, and 22; and at safety follow-up.

**Supplementary Table S1. Patient demographics and disease characteristics (Full Analysis Set)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | **Alpelisib + tamoxifen + goserelin (n=16)** | **Buparlisib + tamoxifen + goserelin (n=13)** | **Control: Tamoxifen + goserelin (n=10)** | **Total  (N=39)** |
| Age, years | Mean | 44.7 | 45.8 | 45.6 | 45.3 |
| Median (range) | 45.5 (28-54) | 46.0 (36-54) | 47.5 (34-53) | 46.0 (28-54) |
| BMI, kg/m2 | Mean | 23.43 | 23.78 | 20.97 | 22.92 |
| ECOG performance status, n (%) | 0 | 15 (93.8) | 9 (69.2) | 6 (60.0) | 30 (76.9) |
| 1 | 1 (6.3) | 4 (30.8) | 4 (40.0) | 9 (23.1) |
| Disease status, n (%) | Metastatic | 15 (93.8) | 13 (100) | 9 (90.0) | 37 (94.9) |
| De novo | 7 (43.8) | 6 (46.2) | 5 (40.0) | 18 (46.2) |
| Recurrent | 8 (50.0) | 7 (53.8) | 4 (50.0) | 19 (48.7) |
| Locally advanced | 1 (6.3) | 0 | 1 (10.0) | 2 (5.1) |
| Liver and/or lung disease, n (%) | Present | 9 (56.3) | 7 (53.8) | 7 (70.0) | 23 (59.0) |
| Absent | 7 (43.8) | 6 (46.2) | 3 (30.0) | 16 (41.0) |
| Measurable disease, per RECIST version 1.1, n (%) | Yes | 16 (100) | 11 (84.6) | 10 (100) | 37 (94.9) |
| No | 0 | 2 (15.4) | 0 | 2 (5.1) |
| Bone-only metastases, n (%) | Yes | 5 (33.3) | 1 (7.7) | 2 (22.2) | 8 (21.6) |
| No | 10 (66.7) | 12 (92.3) | 7 (77.8) | 29 (78.4) |
| Previous chemotherapy, n (%) | Metastatic setting | 1 (6.3) | 0 | 1 (10.0) | 2 (5.1) |
| Adjuvant/ neoadjuvant only | 6 (37.5) | 7 (53.8) | 3 (30.0) | 16 (41.0) |
| None | 9 (56.3) | 6 (46.2) | 6 (60.0) | 21 (53.8) |
| Previous ET in adjuvant setting, n (%) | Yes | 5 (31.3) | 3 (23.1) | 2 (20.0) | 10 (25.6) |
| No | 11 (68.8) | 10 (76.9) | 8 (80.0) | 29 (74.4) |
| Previous treatment with tamoxifen in adjuvant setting, n (%) | Yes | 5 (31.3) | 3 (23.1) | 1 (10.0) | 9 (23.1) |
| No | 11 (68.8) | 10 (76.9) | 9 (90.0) | 30 (76.9) |
| Tamoxifen-resistant disease, n (%)a | Yes | 4 (25.0) | 2 (15.4) | 1 (10.0) | 7 (17.9) |
| Underwent primary surgery for breast cancer, n (%) | Lumpectomy | 2 (12.5) | 2 (15.4) | 1 (10.0) | 5 (12.8) |
| Mastectomy | 6 (37.5) | 6 (46.2) | 3 (30.0) | 15 (38.5) |
| Axillary LN dissection | 0 (0) | 3 (23.1) | 0 (0) | 3 (7.7) |
| None | 8 (50.0) | 2 (15.4) | 5 (10.0) | 15 (38.5) |
| Previous radiotherapy, n (%) | Adjuvant | 3 (18.8) | 3 (23.1) | 1 (10.0) | 7 (17.9) |
| Metastatic | 0 (0) | 1 (7.7) | 2 (20.0) | 3 (7.7) |
| None | 13 (81.3) | 9 (69.2) | 7 (70.0) | 29 (74.4) |
| Histology/cytology, n (%) | Invasive ductal carcinoma | 13 (81.3) | 10 (76.9) | 10 (100.0) | 33 (84.6) |
| Invasive lobular carcinoma | 3 (18.8) | 2 (15.4) | 0 | 5 (12.8) |
| Other | 0 | 1 (7.7) | 0 | 1 (2.6) |
| Histologic differentiation, n (%) | Well | 4 (25.0) | 1 (7.7) | 3 (30.0) | 8 (20.5) |
| Moderate | 5 (31.3) | 7 (53.8) | 4 (40.0) | 16 (41.0) |
| Poor | 0 | 1 (7.7) | 0 | 1 (2.6) |
| Unknown | 7 (43.8) | 4 (30.8) | 3 (30.0) | 14 (35.9) |
| Percentages were calculated using the FAS as the denominator, except for sites of metastatic disease. Percentages of patients with a recorded site of metastatic disease were calculated using the number patients with any metastatic disease as the denominator.  aTamoxifen-resistant disease is defined as disease recurrence during treatment with tamoxifen in the adjuvant setting.  BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; LN, lymph node; RECIST, Response Evaluation Criteria in Solid Tumors; SD, standard deviation. | | | | | |

### **Supplementary Table S2.** **Treatment-emergent adverse events (≥20% in any group) by preferred term (Safety Analysis Set)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Preferred term, n (%)** | **Alpelisib + tamoxifen + goserelin**  **(n=16)** | **Buparlisib + tamoxifen + goserelin**  **(n=13)** | **Control: Tamoxifen + goserelin (n=10)** | **Total**  **(N=39)** |
| Patients with at least 1 TEAE | 16 (100) | 13 (100) | 10 (100) | 39 (100) |
| Rash | 7 (43.8) | 8 (61.5) | 2 (20.0) | 17 (43.6) |
| Decreased appetite | 9 (56.3) | 4 (30.8 | 0 | 13 (33.3) |
| Stomatitis | 6 (37.5) | 6 (46.2) | 0 | 12 (30.8) |
| Nausea | 6 (37.5) | 3 (23.1) | 2 (20.0) | 11 (28.2) |
| Hyperglycemia | 5 (31.3) | 6 (46.2) | 0 | 11 (28.2) |
| Alopecia | 7 (43.8 | 2 (15.4 | 1 (10.0) | 10 (25.6) |
| Hot flush | 7 (43.8) | 1 (7.7) | 1 (10.0) | 9 (23.1) |
| Diarrhea | 6 (37.5) | 2 (15.4) | 1 (10.0) | 9 (23.1) |
| Fatigue | 5 (31.3) | 3 (23.1) | 1 (10.0) | 9 (23.1) |
| ALT increased | 2 (12.5) | 6 (46.2) | 1 (10.0) | 9 (23.1) |
| Pruritus | 3 (18.8) | 5 (38.5) | 1 (10.0) | 9 (23.1) |
| AST increased | 1 (6.3) | 6 (46.2) | 1 (10.0) | 8 (20.5) |
| Weight decreased | 8 (50.0) | 0 | 0 | 8 (20.5) |
| Dizziness | 3 (18.8) | 3 (23.1) | 1 (10.0) | 7 (17.9) |
| Edema peripheral | 2 (12.5) | 2 (15.4) | 2 (20.0) | 6 (15.4) |
| Insomnia | 0 | 4 (30.8) | 2 (20.0) | 6 (15.4) |
| Arthralgia | 1 (6.3) | 2 (15.4) | 2 (20.0) | 5 (12.8) |
| Abdominal pain upper | 1 (6.3) | 3 (23.1) | 0 | 4 (10.3) |
| Face edema | 4 (25.0) | 0 | 0 | 4 (10.3) |
| Noncardiac chest pain | 1 (6.3) | 1 (7.7) | 2 (20.0) | 4 (10.3) |
| Pain in extremity | 2 (12.5) | 0 | 2 (20.0) | 4 (10.3) |
| Hypertension | 1 (6.3) | 3 (23.1) | 0 | 4 (10.3) |
| Anemia | 1 (6.3) | 0 | 2 (20.0) | 3 (7.7) |
| Neutrophil count decreased | 0 | 1 (7.7) | 2 (20.0) | 3 (7.7) |
| Percentages (%) were calculated using the SAF as the denominator.  Treatment-emergent AEs were defined as events that started or worsened after the first administration of the study treatment until the date of last dose of study treatment + 28 days. Patients with multiple occurrences of TEAE under a treatment were counted only once in the TEAE category for that treatment. Patients with multiple TEAEs within a PT were counted only once for that PT; PTs are presented in descending order of frequency overall.  AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, preferred term; SAF, safety analysis set; TEAE, treatment-emergent adverse event. | | | | |

**Supplementary Table S3. Best overall response (confirmed) over the treatment period (Full Analysis Set)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Best response category** | **Alpelisib + tamoxifen + goserelin**  **(n=16)**  **n (%)** | **Buparlisib + tamoxifen + goserelin**  **(n=13)**  **n (%)** | **Control: Tamoxifen + goserelin (n=10)**  **n (%)** | **Total**  **(N=39)**  **n (%)** |
| **Best overall response (confirmed)** | | | | |
| PR | 8 (50.0) | 3 (23.1) | 0 | 11 (28.2) |
| SD | 4 (25.0) | 9 (69.2) | 5 (50.0) | 18 (46.2) |
| PD | 3 (18.8) | 0 | 5 (50.0) | 8 (20.5) |
| Non-CR/non-PD | 0 | 1 (7.7) | 0 | 1 (2.6) |
| Not evaluable | 1 (6.3) | 0 | 0 | 1 (2.6) |
| Best overall response (confirmed) was the RECIST-confirmed result, which required confirmation of CR and PR assessments.  Best response categories (PR, SD, PD, and non-CR/non-PD) were defined according to RECIST v1.1 criteria; non-CR/non-PD was defined for patients with non-target lesions only, as a response of neither CR or PD.  A best response category of “not evaluable” was recorded if there were insufficient data to categorize a response as either CR, PR, SD, PD, or non-CR/non-PD.  Percentages were calculated using the FAS as the denominator.  CR, complete response; FAS, full analysis set; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease. | | | | |

**Supplementary Table S4. Clinical benefit rate (Full Analysis Set)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical benefit ratea** | **Alpelisib + tamoxifen + goserelin**  **(n=16)** | **Buparlisib + tamoxifen + goserelin**  **(n=13)** | **Control:**  **Tamoxifen + goserelin**  **(n=10)** |
| **n (%)b** | 9 (0.56) | 6 (0.46) | 5 (0.50) |
| **95% CI** | 0.30, 0.80 | 0.19, 0.75 | 0.19, 0.81 |
| Proportions are calculated using the FAS as the denominator.  The 95% CI was computed using the exact binomial method (Clopper-Pearson).  aDefined as a best overall response (observed) of CR, PR, or SD lasting 24 weeks or longer, according to RECIST v1.1 criteria.  bThe number of patients with a best overall response as per the clinical benefit rate definition.  CI, confidence interval; CR, complete response; FAS, full analysis set; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease. | | | |

**Supplementary Table S5.** **EuroQol-5D questionnaire responses of 3 or 4 during the study (Safety Analysis Set)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Visit/**  **response category** | **Alpelisib + tamoxifen + goserelin**  **(n=16)** | | **Buparlisib + tamoxifen + goserelin**  **(n=13)** | | **Control:**  **Tamoxifen + goserelin**  **(n=10)** | |
|  | **n (%)a** | **Score** | **n (%)a** | **Score** | **n (%)a** | **Score** |
| **Cycle 14 Day 1**  Usual activity  Anxiety/depression |  | | | | | |
| 8 (50.0) | 1 | 5 (38.5) | 1 | 3 (30.0) | 3 |
| 8 (50.0) | 1 | 5 (38.5) | 1 | 3 (30.0) | 3 |
| **Cycle 26 Day 1**  Pain/discomfort  Anxiety/depression |  | | | | | |
| 4 (25.0) | 2 | 2 (15.4) | 2 | 1 (10.0) | 3 |
| 4 (25.0) | 2 | 2 (15.4) | 2 | 1 (10.0) | 3 |
| **Cycle 29 Day 1**  Anxiety/depression |  | | | | | |
| 3 (18.8) | 2 | 1 (7.7) | 2 | 1 (10.0) | 3 |
| **Cycle 31 Day 1**  Pain/discomfort  Anxiety/depression |  | | | | | |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| **Cycle 32 Day 1**  Pain/discomfort  Anxiety/depression |  | | | | | |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| 2 (12.5) | 2 | 1 (7.7) | 2 | 1 (10.0) | 3 |
| **Cycle 34 Day 1**  Pain/discomfort  Anxiety/depression |  | | | | | |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| 2 (12.5) | 2 | 1 (7.7) | 2 | 1 (10.0) | 3 |
| **Cycle 35 Day 1**  Mobility  Usual activity  Pain/discomfort  Anxiety/depression |  | | | | | |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 4 |
| 2 (12.5) | 1 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 4 |
| 2 (12.5) | 2 | 1 (7.7) | 2 | 1 (10.0) | 4 |
| **Cycle 36 Day 1**  Pain/discomfort  Anxiety/depression |  | | | | | |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| 2 (12.5) | 2 | 1 (7.7) | 2 | 1 (10.0) | 4 |
| **Cycle 37 Day 1**  Pain/discomfort |  | | | | | |
| 2 (12.5) | 2 | 1 (7.7) | 1 | 1 (10.0) | 3 |
| aPatients with a response; percentages were calculated using FAS as the denominator.  FAS, full analysis set. | | | | | | |

**Supplementary Table S6.** **Patient Health Questionnaire-9 depression score from baseline to the worst postbaseline score (Safety Analysis Set)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Baseline to worst postbaseline scorea** | **Alpelisib + tamoxifen + goserelin**  **(n=16)**  **n (%)** | **Buparlisib + tamoxifen + goserelin**  **(n=13)**  **n (%)** | **Control:**  **Tamoxifen + goserelin**  **(n=10)**  **n (%)** |
| None to moderate | 0 | 3 (23.1) | 0 |
| None to severe | 0 | 1 (7.7) | 0 |
| Mild to moderate | 0 | 1 (7.7) | 0 |
| Mild to severe | 0 | 0 | 0 |
| Missing | 13 (81.3) | 0 | 5 (50.0) |
| aOnly shifts from baseline to moderate or severe (in any treatment group) are presented. Baseline was defined as the last nonmissing evaluation, scheduled or unscheduled, before first dose of study drug. A patient was only counted once for the worst severity score using total score during the treatment period. Percentages were calculated using SAF as the denominator.  SAF, safety analysis set. | | | |

**Supplementary Table S7. Criteria for defining dose-limiting toxicities**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Alpelisib Phase 1a Study (1)** | **Buparlisib Phase 1 Study (2)** | **B-YOND Study** |
| **Timing of evaluation** | First treatment cycle (28 days) | First treatment cycle (28 days) | First treatment cycle (28 days) |
| **CTCAE version** | CTCAE version 4.0 | CTCAE version 3.0 | CTCAE version 4.03 |
| **DLT assessments** | * Grade ≥ 2 hyperglycemia * Grade ≥ 2 photosensitivity * Specified grade ≥ 3 hematologic, renal, hepatic, metabolic, or subcutaneous AEs lasting for > 7 days * Any other grade ≥ 3 toxicity | * Non-CTCAE grade 2 hyperglycemia not resolved to grade 0 within 14 consecutive days of initiation of oral antihyperglycemia medications, non-CTCAE grade ≥ 3 hyperglycemia * Grade ≥ 2 pancreatitis * ≥ 1 grade level increase in neurotoxicity * Grade ≥ 2 phototoxicity or skin rash necessitating treatment interruption for > 21 consecutive days * Grade 2 mood alteration not resolved to grade 1 within 14 days despite medical treatment (grade 2 anxiety was considered a DLT only if worsened from baseline), and grade ≥ 3 mood alteration * Grade ≥ 3 hematologic or nonhematologic toxicity | * Febrile neutropenia * Grade ≥ 3 neutropenia for > 7 consecutive days, grade 3 thrombocytopenia for > 7 consecutive days and/or thrombocytopenia requiring platelet transfusion, grade 4 thrombocytopenia * Serum creatinine ≥ 2.0 × ULN to ≤ 3.0 × ULN for > 7 consecutive days; grade ≥ 3 serum creatinine * Total bilirubin ≥ 2.0 × ULN to < 3.0 × ULN for > 7 consecutive days, grade ≥ 3 total bilirubin, grade 3 AST or ALT for > 7 consecutive days, grade 4 AST or ALT, grade ≥ 3 AST or ALT with a grade ≥ 2 bilirubin elevation of any duration * Grade 3 asymptomatic amylase and/or lipase, not reversible to ≤ grade 2 for > 7 consecutive days, grade 4 asymptomatic amylase and/or lipase * Grade 2 hyperglycemia that does not resolve to grade 0 within 14 consecutive days after appropriate treatment, grade ≥ 3 hyperglycemia * Grade ≥ 3 pancreatitis * Cardiac toxicity grade ≥ 3 or cardiac event that is symptomatic or requires medical intervention, clinical signs of cardiac disease, such as unstable angina or myocardial infarction, or troponin grade 3 * Nervous system disorders grade ≥ 2 and ≥ 1 grade level increase of pre-existing neurotoxicity * Grade ≥ 2 photosensitivity, grade 3 rash for > 7 consecutive days despite skin toxicity treatment,   grade 4 rash   * Other grade ≥ 3 AEs (excluding ≥ CTCAE grade 3 elevations in ALP) |
| AEs, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; ULN, upper limit of normal. | | | |

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