EPIK-B5: A Phase III, Randomized Study of Alpelisib (ALP) + Fulvestrant (FUL) in Patients With Hormone Receptor–Positive (HR+), Human Epidermal Growth Factor Receptor 2–Negative (HER2–), PIK3CA-Mutated Advanced Breast Cancer (ABC) Progressing On/After an Aromatase Inhibitor (AI) With a Cyclin-Dependent Kinase 4/6 Inhibitor (CDK4/6i)

Michelino De Laurentiis,1 Luis Costa,2 Joseph Gligorov,3 Ann Knop,4 Elżbieta Senkus,5 Jose A. García-Sáenz,6 Peter Schmid,7 Aurelia Heniquez,8 Paolo Serra,9 Albert Reising,8 Sherko Kuemmel10

1Istituto Nazionale Tumori IRCCS “Fondazione G. Pascale”-Breast Oncology Unit, Naples, Italy; 2Hospital Santa Maria, Lisbon, Portugal; 3Institut Universitaire de Cancérologie AP-HP, Sorbonne Université, Paris, France; 4Copenhagen University Hospital, Copenhagen, Denmark; 5Medical University of Gdansk, Gdansk, Poland; 6Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain; 7Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK; 8Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 9Novartis Pharma AG, Basel, Switzerland; 10Kliniken Essen-Mitte, Essen, Germany, Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany

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Introduction (1 of 2)

- Endocrine therapy (ET) + cyclin-dependent kinase 4 or 6 inhibitor (CDK4/6i) is a standard of care for hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC)\(^1\). However, both de novo and acquired resistance to treatment with CDK4/6i + ET have been observed, ultimately leading to treatment failure and disease relapse\(^2,3\)

- Progression-free survival (PFS) for ≥2L ET monotherapy post CDK4/6i is poor; prognosis may be worse in patients with phosphoinositide-3-kinase catalytic subunit alpha gene (PIK3CA)-mutation\(^4\)

- Alpelisib (ALP), an inhibitor of alpha-specific class I phosphatidylinositol-3-kinase (PI3K\(\alpha\)) (Figure 1),\(^5,6\) in combination with fulvestrant (FUL) has shown consistent clinical benefit and manageable toxicity profile in SOLAR-1 (n=9) and BYLieve Cohort A (n=121) in patients with HR+, HER2– ABC who had prior CDK4/6i treatment\(^7-10\)
  - In a small subpopulation in SOLAR-1 patients with prior CDK4/6i use, ALP + FUL was associated with a 6-month PFS of 44% and median PFS of 5.5 months
  - In BYLieve cohort A, ALP + FUL was associated with a 6-month PFS of 50.4% and median PFS of 7.3 months

- The value of above data from SOLAR-1 and BYLieve cohort A is however limited by the small sample size and absence of a comparator group in the BYLieve study\(^7-10\)

- EPIK-B5 (NCT05038735) trial aims to confirm the efficacy and safety of ALP + FUL in a larger population with HR+, HER2–, PIK3CA-mutated ABC pretreated with CDK4/6i + aromatase inhibitor (AI)
Introduction (2 of 2)

Figure 1. Alpelisib (BYL719): Oral PI3Kα inhibitor

4EBP1, eukaryotic initiation factor 4E-binding protein 1; AKT, protein kinase B; B-RAF, serine/threonine-protein kinase B-raf; ER, estrogen receptor; ERK1/2, extracellular signal-related kinase 1/2; IGF, insulin-like growth factor; MEK, mitogen-activated protein/ERK kinase; mTORC, mammalian target of rapamycin complex; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol 3-kinase; PI3Kα, phosphatidylinositol-3-kinase alpha; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RAS, rat sarcoma virus; S6K, S6 kinase; TGF-α, transforming growth factor-alpha; VEGF, vascular endothelial growth factor.
Objectives

- EPIK-B5 trial will assess the efficacy and safety of ALP + FUL compared to placebo + FUL in men and postmenopausal women with HR+, HER2–, ABC with a PIK3CA mutation, who progressed on or after an AI + CDK4/6i
- Trial endpoints are described in Table 1

Table 1. EPIK-B5 endpoints

<table>
<thead>
<tr>
<th>Endpoint measures</th>
<th>Primary</th>
<th>Secondary</th>
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<tr>
<td></td>
<td>PFS based on BIRC assessments and using RECIST v1.1 criteria</td>
<td>OS</td>
<td>Gene expression or genetic alteration analysis in tumor tissue and/or ctDNA collected prior to study treatment and association with clinical efficacy endpoint (such as PFS, OS)</td>
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<td>ORR, CBR, and DOR with confirmed response; TTR based on BIRC assessment and RECIST v1.1.</td>
<td>Safety and tolerability</td>
<td>Molecular analysis of ctDNA samples collected prior to study treatment and at the disease progression and its correlation with clinical efficacy</td>
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<td>PFS based on BIRC assessment and using RECIST v1.1 criteria for participants by PIK3CA mutation status assessed in ctDNA at baseline</td>
<td>Time to definitive deterioration of ECOG performance status from baseline</td>
<td>Change from baseline in overall health status of the EQ 5D-5L index score and VAS, worst pain item of BPI-SF</td>
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<td>Change from baseline in GHS/QoL and symptom scale scores of the EORTC QLQ-C30</td>
<td>Time to definitive (10%) deterioration in the GHS/QoL and symptom scale scores of the EORTC QLQ-C30</td>
<td>Time to start of first subsequent chemotherapy</td>
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<td>Time from randomization to objective tumor progression on next line treatment or death from any cause (PFS2)</td>
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ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; BIRC, Blinded Independent Review Committee; BPI-SF, Brief Pain Inventory-Short Form; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4 or 6 inhibitor; ctDNA, circulating tumor deoxyribonucleic acid; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ 5D-5L, EuroQol 5-level instrument; FUL, fulvestrant; GHS, global health status; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QoL, quality of life; RECIST, response evaluation criteria in solid tumors; TTR, time to response; VAS, visual analog scale.
EPIK-B5 is a phase III, randomized (1:1), double-blind, placebo-controlled, international, multi-center study to assess the efficacy and safety of ALP + FUL compared with placebo + FUL in men or postmenopausal women with HR+, HER2–, ABC with a PIK3CA mutation who progressed or relapsed on or after treatment with an AI + CDK4/6i, allowing ≤1 line of prior chemotherapy in the advanced/metastatic setting (Figure 2).

Methods (1 of 4)

**Trial Design**

- **EPIK-B5** is a phase III, randomized (1:1), double-blind, placebo-controlled, international, multi-center study to assess the efficacy and safety of ALP + FUL compared with placebo + FUL in men or postmenopausal women with HR+, HER2–, ABC with a PIK3CA mutation who progressed or relapsed on or after treatment with an AI + CDK4/6i, allowing ≤1 line of prior chemotherapy in the advanced/metastatic setting (Figure 2).

**Figure 2. EPIK-B5 study design**

**Endpoints**

**Primary:**
- PFS based on BIRC assessment

**Secondary:**
- OS
- ORR, CBR, DOR, TTR based on BIRC assessment
- PFS based on BIRC assessment, by PIK3CA mut status in cDNA
- Safety and tolerability
- TTD of E6006
- Change from baseline and TTD in QoL, and symptom scale scores in EORTC QLQ-C30
- PFS2

**Stratification Factors**
- Presence of lung and/or liver metastases (yes versus no)
- Setting at last prior CDK4/6i therapy (adjuvant versus metastatic)

**Patient population (N=234)**
- Adult postmenopausal women and men with HR+, HER2–
- ABC with PIK3CA mutation who progressed or relapsed on or after CDK4/6i and AI
- ≥1 measurable lesion per RECIST v1.1
- ≤1 line of prior CT treatment (except neoadjuvant or adjuvant CT)
- Adequate tumor tissue available for assessment of PIK3CA mutation status by central laboratory

**Arm 1 (n=117)**
- Alpelisib (300 mg PO QD) + fulvestrant (500 mg IM on D1 and D15 of cycle 1, and then D1 of each subsequent 28-day cycle)

**Arm 2 (n=117)**
- Alpelisib matching placebo + fulvestrant (500 mg IM on D1 and D15 of cycle 1, and then D1 of each subsequent 28-day cycle)

**Cross-over from the placebo arm to the alpelisib arm is permitted at time of PD as assessed per RECIST v1.1 by BIRC**

**Figure 2. EPIK-B5 study design**

**ABC**, advanced breast cancer; **AI**, aromatase inhibitor; **ALP**, alpelisib; **BIRC**, blinded independent review committee; **CBR**, clinical benefit rate; **CDK4/6i**, cyclin-dependent kinase 4 or 6 inhibitor; **cDNA**, circulating tumor deoxyribonucleic acid; **DOR**, duration of response; **ECOG-PS**, Eastern Cooperative Oncology Group performance status; **EORTC QLQ-C30**, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; **FUL**, fulvestrant; **HER2–**, human epidermal growth factor receptor-2–negative; **HR+**, hormone receptor–positive; **IM**, intramuscular; **ORR**, overall response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PFS2**, time from date of randomization to the first documented progression on next line therapy or death; **PIK3CA**, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; **PO**, orally; **QD**, once daily; **QoL**, quality of life; **R**, randomization; **RECIST v1.1**, response evaluation criterion version 1.1; **TTD**, time to definitive deterioration, **TTR**, time to response.
Methods (2 of 4)

**Assessments**

- **Efficacy:** Imaging assessments per response evaluation criteria in solid tumors (RECIST) 1.1 will be performed at screening (28 days prior to randomization) as well as every 8 weeks for the first 18 months and every 12 weeks thereafter, until 36 months, then change to as clinically indicated until disease progression per blinded independent review committee (BIRC) assessment, death, lost to follow-up, or withdrawal of consent. Tumor response will be assessed locally and centrally.

- **Safety:** Adverse events and serious adverse events will be monitored and collected at every visit. Additional routine safety monitoring will be performed including physical examination, Eastern Cooperative Oncology Group (ECOG) performance status assessment, electrocardiogram, cardiac function evaluation by magnetic resonance imaging /echocardiography/multiple gated acquisition scan, and laboratory evaluations (hematology, serum chemistry, coagulation, fasting lipid panel/glucose, HbA1c and urinalysis).

- **Patient-reported outcomes (PRO):** The European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30), EuroQoL 5-level instrument (EQ-5D-5L), and Brief Pain Inventory-Short Form (BPI-SF) questionnaires will be used to evaluate PRO measures of health-related quality of life (QoL), functioning, disease symptoms, treatment-related side effects, global health status, and cancer related pain. The PROs will be completed every 8 weeks after randomization during the first 18 months and every 12 weeks thereafter until 36 months. After the disease progression, PROs will be collected within 14 days of the reported progression at end of treatment (EOT) visit, then at 30 days post follow up and again 8 and 16 weeks post progression.

HbA1C, glycosylated hemoglobin.
Biomarkers: Tumor tissue collected at prescreening and blood samples collected at cycle 1 day 1 pre-dose and at the time of progression, respectively, will be used to assess potential resistance mechanisms to CDK4/6i based therapies, to identify potential biomarkers that may be predictive of benefit from treatment with ALP + FUL, and for additional PIK3CA mutation analysis (by next generation sequencing panel) as well as for assessing its potential impact on clinical outcome.

Follow-up: After EOT, patients will continue to be followed for safety (30 days after study treatment discontinuation), efficacy (tumor assessment until progression), PRO assessment (8 and 16 weeks post progression after the end of safety follow-up), and survival (every 12 weeks after the end of post treatment safety and efficacy follow-ups).

Statistical analysis: The primary efficacy analysis comparing the two treatment groups will be performed using a stratified log-rank test at a one-sided 2.5% level of significance. The PFS distribution will be estimated using the Kaplan-Meier method. A stratified Cox regression model will be used to estimate PFS hazard ratio (and 95% confidence interval) using the same stratification factors as for the log-rank test.
Methods (4 of 4)

Trial Status

- EPIK-B5 is recruiting; the first patient first visit occurred in November 2021
- Approximately 234 patients are expected to be randomized at 98 sites in 17 countries (Figure 3)
- The estimated primary completion date is anticipated in the last quarter of 2026

Figure 3. Geographic regions and enrollment sites
Conclusions

• ET + CDK4/6i is a standard of care for HR+, HER2–, ABC; however, CDK4/6i resistance, in which the PI3K pathway has a key role, remains challenging

• The results from SOLAR-1 and BYLieve cohort A support ALP + FUL combination as an active therapeutic option with manageable safety profile in patients with HR+, HER2– PIK3CA-mutated ABC in the post-CDK4/6i + AI setting; however, the data is limited by small sample size and absence of a comparator group in the BYLieve study

• EPIK-B5 will complement the data from SOLAR-1 and BYLieve Cohort A studies and obtain more comprehensive data on the efficacy and safety of ALP + FUL in participants with HR+, HER2–, ABC, with a PIK3CA mutation, who progressed on or after AI and a CDK4/6i

ABC, advanced breast cancer; AI, aromatase inhibitor; ALP, alpelisib; CDK4/6i, cyclin-dependent kinase 4 or 6 inhibitor; ET, endocrine therapy; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; HR+, hormone receptor–positive; PI3K, phosphatidylinositol 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
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References

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