EPIK-B4: A Phase 2, Randomized TiP of Metformin (MET) Extended Release (XR) +/- Dapagliflozin (DAPA) to Prevent Hyperglycemia (HG) in Patients (pts) With Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2-), PIK3CA-Mutated (mut) Advanced Breast Cancer (ABC) Treated With Alpelisib (ALP) and Fulvestrant (FUL)

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Introduction (1 of 3)

• Mutations of the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene, inducing hyperactivation of the alpha isoform (p110α) of phosphatidylinositol 3-kinase (PI3K) occur in 28% to 46% of pts with HR+, HER2– ABC1

• First-line treatment for HR+, HER2– ABC includes endocrine therapy (ET) with or without a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). However, acquired resistance to ET because of PIK3CA mutations remains a challenge2

• ALP (an α-selective PI3K inhibitor and degrader, Figure 1)3,4 is indicated in combination with FUL for the treatment of men and postmenopausal women with HR+, HER2–, PIK3CA-mut ABC following progression on or after an endocrine-based regimen2,5

• In the pivotal SOLAR-1 trial, among ALP-treated pts, 65% developed HG of any grade and 37% developed severe (grade ≥3) HG1. Among these severe hyperglycemic pts, 87% developed the events within the first two cycles of treatment6

ABC, advanced breast cancer; ALP, alpelisib; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; HG, hyperglycemia; HR+, hormone receptor–positive; mut, mutated.
Introduction (2 of 3)

- HG is a known adverse event (AE) linked to the mechanism of action of ALP as a PI3Kα inhibitor. This is largely manageable with the use of MET and dose interruptions/reductions, and reversible upon discontinuation. In some pts, HG may lead to dose discontinuation; hence, there remains an unmet need for management strategies beyond MET that offer earlier and more sustained improvement of HG\textsuperscript{7,8}

- Preclinical data from rats support the use of the combination of DAPA (SGLT2 inhibitor) and MET for ALP-induced HG. The combination significantly reduced blood glucose levels, without any drug-drug interaction and while maintaining the efficacy of ALP\textsuperscript{8}

ALP, alpelisib; DAPA, dapagliflozin; FUL, fulvestrant; HG, hyperglycemia; MET, metformin; PI3K, phosphoinositide 3-kinase; SGLT2, sodium-glucose transport protein 2.
Introduction (3 of 3)

Figure 1. Alpelisib (BYL719): Oral PI3Kα inhibitor

4EBP1, eukaryotic translation 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; 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

- The EPIK-B4 (NCT04899349) trial will assess the safety and efficacy of DAPA + MET XR versus MET XR during treatment with ALP in combination with FUL in pts with HR+, HER2– ABC with a PIK3CA mutation following progression on/after ET

- Trial endpoints are described in Table 1

Table 1. EPIK-B4 trial endpoints

<table>
<thead>
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<th>Endpoint Measures</th>
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<tr>
<td><strong>Primary</strong></td>
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<tr>
<td>Occurrence of severe HG (grade ≥3, based on glucose laboratory values) over the first 8 weeks of ALP + FUL treatment (from C1D8 to C3D8)</td>
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<tr>
<td><strong>Secondary</strong></td>
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<td>• PFS, ORR, and CBR with confirmed response (based on local radiology assessments and using RECIST 1.1 criteria)</td>
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<tr>
<td>• Safety and tolerability of study treatment</td>
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<tr>
<td><strong>Exploratory</strong></td>
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<tr>
<td>Molecular analysis of ctDNA samples collected on C1D1, C3D8, and at EOT, and its correlation with clinical efficacy</td>
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</tbody>
</table>

ABC, advanced breast cancer; ALP, alpelisib; C, cycle; CBR, clinical benefit ratio; ctDNA, circulating tumor deoxyribonucleic acid; D, day; DAPA, dapagliflozin; EOT, end of treatment; ET, endocrine therapy; FUL, fulvestrant; HER2–, human epidermal growth factor receptor-2–negative; HG, hyperglycemia; HR+, hormone receptor–positive; MET, metformin; ORR, overall response rate; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria In Solid Tumors; XR, extended release.
Methods (1 of 5)

Study Design

• EPIK-B4 is a phase 2, multicenter, randomized, open-label, active-controlled study to assess the safety and efficacy of DAPA + MET XR versus MET XR during treatment with ALP in combination with FUL in participants with HR+, HER2– ABC with a PIK3CA mutation following progression on/after ET (Figure 2)

• The study will enroll participants who have at least one of the following baseline risk factors for the development of severe HG:
  – Diabetes (fasting plasma glucose (FPG) ≥126 mg/dL or ≥7.0 mmol/L and/or HbA1c ≥6.5%)
  – Prediabetes (FPG ≥100 mg/dL to <126 mg/dL or 5.6 to <7.0 mmol/L and/or HbA1c 5.7 to <6.5%)
  – Obesity (body mass index [BMI] ≥30)
  – Age ≥75 years

• Eligible participants will be randomized in a 1:1 ratio (~66 participants in each arm) to receive DAPA + MET XR or MET XR alone starting on cycle 1 day 1 during treatment with ALP plus FUL
Figure 2. EPIK-B4 study design

Patient population (N=132)
- Men or postmenopausal women with ER+/PR+, HER2−, PIK3CA-mut ABC
- At least one baseline risk factor for developing severe HG based on glycemic status, BMI, and age
- ECOG PS 0 or 1
- Prior ET (in metastatic setting)
- Prior CDK4/6i (adjuvant or metastatic setting)
- ≥1 measurable lesion per RECIST v1.1 or, if no measurable disease is present, then at least one predominantly lytic bone lesion must be present
- Not more than 1 line of prior treatment in the metastatic setting
- No prior CT (except for neoadjuvant/adjuvant CT), PI3Ki, mTORi, or AKTi

Arm A (n=66)
ALP (300 mg PO QD starting on C1D8) +
FUL (500 mg IM on C1D1, C1D15, and on
D1 of each subsequent 28-day cycle) +
DAPA (5 mg PO QD) +
MET XR (500 mg PO QD)*

Arm B (n=66)
ALP (300 mg PO QD starting on C1D8) +
FUL (500 mg IM on C1D1, C1D15, and on
D1 of each subsequent 28-day cycle +
MET XR (500 mg PO QD)**

Primary endpoints
Occurrence of severe HG (grade ≥3) over first 8 weeks of treatment with ALP + FUL (C1D8 to C3D8)

Secondary endpoints
- PFS
- ORR
- CBR
- Safety and tolerability

Exploratory endpoints
Molecular analysis of ctDNA samples and its correlation with clinical efficacy

Stratification criteria: Diabetic status at baseline, ie, normal vs prediabetic/diabetic (based on fasting plasma glucose and/or HbA1c laboratory values)

*On a continuous dosing schedule starting at C1D1, with dose titration up to 10 mg for DAPA + 2000 mg MET XR PO QD. **On a continuous dosing schedule starting at C1D1, with dose titration up to 2000 mg MET XR PO QD.

ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; ALP, alpelisib; BMI, body mass index; C, cycle; CBR, clinical benefit ratio; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CT, chemotherapy; ctDNA, circulating tumor deoxyribonucleic acid; D, day; DAPA, dapagliflozin; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor–positive; ET, endocrine therapy; FUL, fulvestrant; HbA1c, glycated hemoglobin; HER2−, human epidermal growth factor receptor−2–negative; HG, hyperglycemia; IM, intramuscular; MET, metformin; mTORi, mammalian target of rapamycin inhibitor; mut, mutated; ORR, overall response rate; PFS, progression-free survival; PI3Ki, phosphoinositide 3-kinase inhibitor; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; PR+, progesterone receptor–positive; QD, once daily; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; XR, extended release.
Methods (3 of 5)

Assessments

- **Efficacy**: Tumor response will be assessed locally using RECIST 1.1. Imaging assessments for response evaluation will be performed every 8 weeks (+/- 7 days) until disease progression, death, withdrawal of consent/opposition to use data/biological samples, or lost to follow-up.

- **Safety**: Safety will be monitored via physical examinations, vital signs, height, weight, abdominal girth, ECOG PS, cardiac imaging and electrocardiogram, laboratory evaluations (including hematology, biochemistry, coagulation, and urinalysis), and collection of AE information.

- **Biomarkers**: This study will explore the concept of using ctDNA as a surrogate approach for monitoring early detection of resistance to treatment by assessing changes of PIK3CA mutation fraction and the emerging new mutations of other genes.
Methods (4 of 5)

Statistical Analysis

• The primary analysis will assess the difference in the percentage of participants with severe HG (grade ≥3, based on glucose laboratory values) between the two treatment arms with a stratified Cochran-Mantel-Haenszel test (stratified by baseline diabetic status) at an overall one-sided 5% level of significance.

• The secondary endpoint, PFS will be analyzed using the Kaplan-Meier method, and the median PFS and PFS rates along with their 95% confidence intervals will be presented for each treatment group.

HG, hyperglycemia; PFS, progression-free survival.
Methods (5 of 5)

**Trial Status**

- EPIK-B4 is recruiting; the first patient first visit occurred in April 2022
- Approximately 132 pts are expected to be randomized at 56 sites in 8 countries (Figure 3)
- The estimated primary completion date is anticipated in October 2023
- The estimated study completion date is anticipated in October 2024

*On hold due to geopolitical situation*
Conclusions

• Based on the results from SOLAR-1 and BYLieve, the use of ALP in combination with FUL is recommended in HR+, HER2– PIK3CA-mut ABC

• There remains an unmet need for management strategies that offer earlier and more sustained improvement of ALP-induced HG

• The purpose of the EPIK-B4 study is to determine whether the combination of DAPA plus MET XR, when given prophylactically to participants considered at high risk for the development of HG, leads to a greater reduction in severe HG events compared with the prophylactic use of MET XR alone

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References

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