William J. Gradishar | w-gradishar@northwestern.edu

EPIK-B4: A Phase 2, Randomized Study 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)

William J. Gradishar,[1] Azeez Farooki,[2] Karthik V. Giridhar,[3] Heather Moore,[4] Abigail M. Johnston,[5] Michelle Miller,[6] Craig Wang,[7] Albert Reising,[6] Joyce A. O'Shaughnessy[8]

[1]Northwestern University Feinberg School of Medicine, Chicago, IL, United States; [2]Memorial Sloan Kettering Cancer Center, New York, NY, United States; [3]Mayo Clinic, Rochester, MN, United States; [4]Duke University Medical Center, Durham, NC, United States; [5]Connect IV Legal Services, Inc., Miami, FL, United States; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; [7]Novartis Pharma AG, Basel, Switzerland; [8]Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology, Dallas, TX, United States

Scan to obtain:
- Poster

https://bit.ly/Gradishar1

CONCLUSIONS

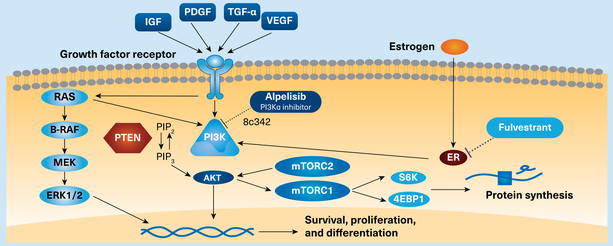
- Based on the results from SOLAR-1 and BYLieve, the use of ALP in combination with FUL is recommended in HR+, HER2– *PIK3CA*-mut ABC
- There remains an unmet need for management strategies that offer earlier and more sustained improvement of ALP-induced HG
- The purpose of the EPIK-B4 study is to determine 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

This study is sponsored by Novartis Pharmaceuticals Corporation
JADPRO Live 2022, Aurora, Colorado, USA, October 20-23, 2022

INTRODUCTION

- Mutations of the *PIK3CA* gene, inducing hyperactivation of the alpha isoform (p110α) of phosphatidylinositol 3-kinase (PI3K) occur in 28% to 46% of pts with HR+, HER2– ABC[1]
- 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 challenge[2]
- ALP (an α-selective PI3K inhibitor and degrader, **Figure 1**)[3-5] 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 regimen[2,6,7]
- In the pivotal SOLAR-1 trial, among ALP-treated pts, 65% developed HG of any grade and 37% developed severe (grade ≥3) HG[1]. Among these severe hyperglycemic pts, 87% developed the events within the first two cycles of treatment[8]
- 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[9-11]
- 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[10,12]

Figure 1. Alpelisib (BYL719): Oral PI3Kα inhibitor



4EBP1, eukaryotic initiation factor 4E-binding protein 1; AKT, protein kinase B; 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; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PDGF, platelet-derived growth factor; PTEN, phosphatase and tensin homolog; 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

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

ALP, alpelisib; C, cycle; CBR, clinical benefit rate; ctDNA, circulating tumor deoxyribonucleic acid; D, day; EOT, end of treatment; FUL, fulvestrant; HG, hyperglycemia; ORR, overall response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.

METHODS

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

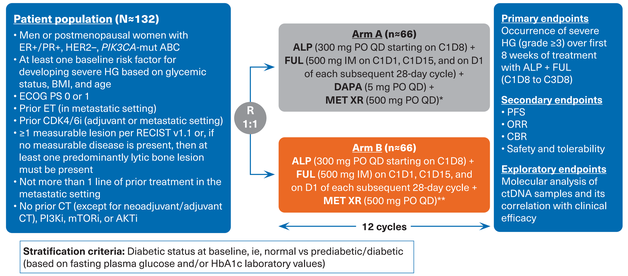
Assessments

- **Efficacy:** Tumor response will be assessed locally using Response Evaluation in Solid Tumors (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, Eastern Cooperative Oncology Group performance status (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 circulating tumor deoxyribonuncleic acid (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

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

Figure 2. EPIK-B4 study design

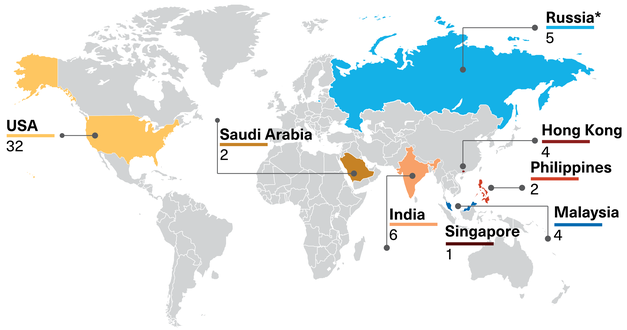


*On a continuous dosing schedule starting at C1D1, with dose titration up to 10 mg for DAPA + 2000 mg MET XR PO QD.
**On a continuous dosing schedule starting at C1D1, with dose titration up to 2000 mg MET XR PO QD.
ABC, advanced breast cancer; AKTi, protein kinase B inhibitor; ALP, alpelisib; BMI, body mass index; C, cycle; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 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, phosphatidylinositol 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.

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

Figure 3. Countries participating in EPIK-B4



*On hold due to geopolitical situation

Acknowledgments

The authors thank the patients who have enrolled in this study and their families, as well as all the participating investigators and their site teams. Medical editorial assistance was provided by Sarah A. Hutchinson, PhD, of Healthcare Consultancy Group, LLC.

References

1. Andre F, et al. *Ann Oncol*. 2021;32(2):208-217
2. Turner S, et al. *Oncologist*. 2021;26(7):e1133-e1142
3. Fritsch CM, et al. AACR 2012:abst 3748
4. Juric D, et al. SABCS 2012:abst CT-01
5. Fritsch C, et al. AACR 2018;abst 3934
6. Andre F, et al. *N Engl J Med*. 2019;380(20):1929-1940
7. Piqray [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp.
8. Data on file. Novartis Pharmaceuticals Corp. 2021
9. Paddock MN, et al. *J Lipid Res*. 2019;60(4):747-752
10. Hopkins BD, et al. *Nature*. 2018;563(7731):E24
11. Rugo HS, et al. *Ann Oncol*. 2020;31(8):1001-1010
12. Schnell C, et al. AACR 2021:abst P137