NOVARTIS

CBYL719CIN02 Study Results Abstract for Public Disclosure

Title

SPEAR (Study of *PIK3CA* mutations and Effectiveness and tolerability outcomes of Alpelisib in Real world)

A descriptive study of *PIK3CA* mutations and outcomes with Alpelisib in patients with HR-positive and HER2-negative advanced breast cancer (ABC)/metastatic breast cancer (MBC) in India

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Non-PASS

Keywords

PIK3CA mutations, HER2-negative advanced breast cancer, HER2-negative metastatic breast cancer, TNM staging

Rationale and background

Breast cancer (BC) is the most prevalent cancer among women globally, constituting one in four female cancer cases, according to GLOBOCAN 2022. In recent years, BC treatment outcomes have significantly improved with the advent of targeted therapies, including those targeting the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene. Alpelisib, a PI3K inhibitor, received approval in India in 2020 for hormone receptor-positive (HR-positive), human epidermal growth factor 2-negative (HER2-negative), *PIK3CA*-mutated advanced BC (ABC)/metastatic BC (MBC) patients. This study aimed to address the knowledge gap regarding *PIK3CA* mutation prevalence and assess the real-world efficacy and tolerability of Alpelisib plus fulvestrant among this patient population.

Part B data are not included in this clinical study report.

Despite collective efforts, there were significant challenges in recruitment, particularly in Part B of the study. A few key obstacles encountered included:

- Low PIK3CA positivity rate among Indian patients with ABC or MBC.
- Poor quality of tissue sample blocks, leading to frequent quality control (QC) failures.
- High screen failure rates among potential PIK3CA-positive patients.
- Limited eligible cases where Alpelisib could be recommended, as it is indicated only after progression on a prior endocrine-based therapy.

Only 5 patients were identified for Part B of the study between October 2021 and February 2025, and the data was not suitable for analysis. No adverse event or safety observation was recorded. Given these challenges and the limited feasibility of achieving the study objectives, Part B of the study was closed.

However, both parts of the study were independent of each other.

Research question and objectives

Objectives	Endpoints
Part A	
Primary	
To evaluate the frequency of *PIK3CA* mutations in men, premenopausal women with ovarian ablation (as per physician decision), or postmenopausal women with HR-positive and HER2-negative ABC/MBC among the Indian population	Percentage of patients with tumors harboring a *PIK3CA* mutation (specifying each hotspot mutation)
Secondary	
To describe demographic characteristics of HR-positive, HER2-negative ABC/MBC patients	Age at early-stage (initial) disease, and advanced/metastatic disease diagnosis and gender
To describe the clinical characteristics of HR-positive, HER2-negative ABC/MBC patients during early (initial) disease stage and advanced / metastatic disease stage	Clinical characteristics of the disease at early (initial) stage of diagnosis by Tumor, Node, and Metastasis (TNM) staging and receptor expression (estrogen receptor [ER], progesterone receptor [PgR], and HER2). Clinical characteristics of advanced / metastatic disease stage by disease-free interval (DFI), number and location of metastases, and receptor expression (ER, PgR, and HER2)
To characterize treatment patterns (prior lines of therapy [LoTs]) among HR-positive, HER2-negative ABC/MBC patients	Prior therapies received by HR-positive, HER-negative ABC/MBC patients by number of LoT(s), treatment type (hormone alone, hormone with targeted therapy [TT], or chemotherapy), and sequence in these. Also, time to subsequent treatment during prior LoTs

Study design

The SPEAR study was a non-interventional, observational, prospective, multicenter study designed to be conducted across approximately 30–40 sites in India, targeting HR-positive, HER2-negative ABC/MBC patients.

In Part A, males, postmenopausal women, or premenopausal women undergoing ovarian ablation, were enrolled. The study collected *PIK3CA* mutation status for those who signed an informed consent form (ICF).

Setting

Part A

Inclusion Criteria

1. Males (≥18 years of age), postmenopausal* females or premenopausal** females with ovarian ablation (as per physician decision).
2. Patients with a confirmed diagnosis of ABC/MBC (locoregionally recurrent, not amenable to curative therapy, or metastatic)

3. Subject with histologically and/or cytologically confirmed diagnosis of HR-positive (ER+ and/or PgR+), as well as HER2-negative BC by a local laboratory (HER2- by immunohistochemistry [IHC] for borderline2+ fluorescence in situ hybridization [FISH])
4. A separate signed subject ICF for Part A of the study must be obtained prior to any data collection and sample shipment to the central designated laboratory
5. Patient's tumor tissue (archival or fresh) was available to send to a central laboratory for *PIK3CA* testing. In case a tissue sample (archival or fresh) was not available or feasible, or quality control (QC) criteria failed as per the central laboratory report, liquid biopsy was allowed.

Exclusion criteria

1. Prior or current enrolment in any interventional clinical trial for ABC/MBC.

Approximately 1,200 patients were planned, and 595 were enrolled in Part A of this study.

Variables and data sources

Variables

Part A: Key endpoint variables

1. Primary endpoint variable:

- *PIK3CA* mutation status

2. Secondary endpoint variables:

- Demographic and baseline characteristics
- Clinical characteristics of the disease
- Treatment pattern (prior therapy)

Data sources

The study used primary data collected from medical records at the investigational site and from the designated lab.

Statistical methods

Considering the observational design of the study and the objectives, all statistical analyses were descriptive in nature.

Analysis data sets:

Full Analysis Set (FAS): Included all patients enrolled in the study.

Results

A total of 595 patients were included in the analysis, predominantly female (98.7%), with most patients aged 50–64 years (49.2%). The most frequent comorbidities observed were hypertension (17.1%), type 2 diabetes (12.9%), and hypothyroidism (5.4%). Regarding treatment history, chemotherapy was the most frequent prior therapy (51.1%), followed by hormone therapy alone (28.9%) and hormone therapy with targeted agents (27.2%). The most common metastatic sites were bone (42.7%), lymph nodes (32.9%), and lungs (25.2%). Among all samples analyzed (plasma n=99; tissue n=496), PIK3CA hotspot mutations were identified in 191 tissue samples (38.5%) and 20 plasma samples (20.2%). Across all subgroups, H1047R emerged as the most prevalent mutation. Furthermore, the median disease-free

interval (DFI) among early-stage patients was 78.2 months. DFI was longer in PIK3CA negative patients (130.6 months) compared with PIK3CA positive patients (50.7 months). Use of CDK4/6 inhibitors (Palbociclib, Ribociclib) was more frequent in PIK3CA negative patients. Across therapy types and PIK3CA mutation groups, disease progression was the primary reason for therapy discontinuation. Among patients with advanced disease, chemotherapy produced complete response in 7.1% and partial mutation in 30.1% of patients. Additionally, the median time between successive treatments was 29 days.

Discussion

PIK3CA mutations were detected in 35.5% of patients, with H1047R as the predominant hotspot, reflecting patterns typical of HR positive, HER2 negative breast cancer. Mutation distribution was consistent across menopausal status, disease stage, prior therapies, and metastatic burden. The cohort mainly included postmenopausal women aged 50–64 years. The median DFI was 78.2 months; although longer in PIK3CA negative patients (130 days). Chemotherapy was the most common first line treatment.

Conclusion

The current study demonstrated that PIK3CA mutations are common among Indian patients with HR positive, HER2 negative ABC/MBC, with H1047R as the predominant hotspot across all clinical subgroups. Mutation patterns were similar across demographic, clinical, or treatment characteristics. The study provides detailed information on PIK3CA mutation frequency and distribution, while assessment of prognostic or predictive associations was not within the scope of this analysis.

List of abbreviations

ABC	Advanced Breast Cancer
AE	Adverse Event
BC	Breast Cancer
CDSCO	Central Drugs Standard Control Organization
CI	Confidence Interval
CBR	Clinical Benefit Rate
CGP	Comprehensive Genomic Profiling
CR	Complete Response
DFI	Disease Free Interval
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ER	Estrogen Receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FSH	Follicular-Stimulating Hormone
GCLP	Good Clinical Laboratory Practice
GPP	Good Pharmacoepidemiology Practices
HER2	Human Epidermal Growth Factor Receptor 2
HIC	High Income Countries
HR	Hormone Receptor
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LMIC	Low- and Middle-Income Countries
LoT	Line of Therapy
MAH	Marketing Authorization Holder
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NIS	Non-Interventional Study
NVS	Novartis

PgR	Progesterone Receptor
PI	Principal Investigator
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PR	Partial Response
QC	Quality Control
RT	Radiotherpay
SIV	Site Initiation Visit
SOC	System Organ Class
SPEAR	**S**tudy of ***PIK3CA*** mutations and **E**ffectiveness and tolerability outcomes of **A**lpelisib in **R**eal-world
TNM	Tumor, Node and Metastasis
TT	Targeted Therapy
WHO	World Health Organization