IMPACT OF SOMATIC *PIK3CA* MUTATIONS ON CLINICAL OUTCOMES IN HER2-POSITIVE BREAST CANCER

Nickolas Stabellini[1,2,3,4], Sonia D. de Oliveira[3], Takae Mizukami[3], Alberto J. Montero[1,3]

AACR GENIE Authors: Shawn M. Sweeney, Nikolaus Schultz, Ken Kehl, Gregory Riely, Katherine Panageas, Deborah Schrag, Philippe Bedard, Christine Micheel, Xindi Guo

1. Case Western Reserve University School of Medicine, Case Western Reserve University, Cleveland, OH, United States; 2. Immunomonitoring Lab (IML), Center for Immunotherapy & Precision Immuno-Oncology (CITI), Cleveland Clinic, Cleveland, OH, United States ; 3. Department of Hematology-Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH, United States; 4. Division of Cardiology, Department of Medicine, Medical College of Georgia at Augusta University, Augusta, GA, United States.

INTRODUCTION

- **HER2-positive (HER2+)** breast cancer accounts for **~15–20% of all breast cancer diagnoses**, identifying patients who benefit from HER2-targeted treatments.
- The phosphatidylinositol-3-kinase (PI3K) pathway, driven by the ***PIK3CA* gene**, plays a critical role in **tumor initiation, growth, proliferation, and therapy resistance**.
- After the TP53 tumor suppressor gene, the *PIK3CA* oncogene is the most frequently mutated gene in breast cancer. In **HER2+ breast cancer**, these **mutations are found in approximately 25–30% of cases**.
- *PIK3CA* mutations (***PIK3CAm***) have been reported to be associated with **shorter survival times** in **metastatic breast cancer**, **reduced effectiveness of HER2-targeted therapies**, and **resistance to endocrine therapy**.
- In the recently presented phase 3 **Destiny Breast09 trial**, the presence of a ***PIK3CAm*** was identified as a **marker of early progression in HER2+ metastatic breast cancer receiving first-line therapy** with trastuzumab/pertuzumab monoclonal antibodies.
- The precise prognostic significance of *PIK3CAm* across various lines of therapy and disease stages in HER2+ breast cancer is not fully understood.

OBJECTIVE

Evaluate the impact of *PIK3CAm* status on clinical outcomes in HER2+ breast cancer patients.

METHODS

Breast Cancer cohort (version 1.2)

Population

HER2+ patients who had received at least one line of therapy

Outcomes

- Overall survival (OS)
- Distant Recurrence-Free Survival (DRFS; calculated for early-stage patients)
- Progression-free survival (PFS; calculated for those with Stage IV disease)

Descriptive analysis

Survival analysis

Subgroup

- TNM Stage (early stage [TNM I-III] vs. metastatic breast cancer [TNM IV])
- Estrogen Receptor (ER) status (positive vs. negative)

RESULTS

Table 1. Overall patient characteristics of HER2+ patient cohort and by *PIK3CAm* Status

Patients with *PIK3CA* alterations had statistically significant higher rates of ER positivity and hormone therapy receipt, as well as lower rates of HER2-targeted therapy receipt. The kinase domain was mutated in 41% of cases.

Characteristic	Overall N = 212[1]	*PIK3CA* Not Altered N = 154[1]	*PIK3CA* Altered N = 58[1]	p-value[2]
Age at Diagnosis	43 (37, 48)	42 (37, 48)	43 (37, 46)	0.8
Race				0.8
White	163 (77%)	117 (76%)	46 (79%)	
Black	16 (7.5%)	12 (7.8%)	4 (6.9%)	
Other	12 (5.7%)	8 (5.2%)	4 (6.9%)	
Unknown/Other	21 (9.9%)	17 (11%)	4 (6.9%)	
Ethnicity				0.9
Hispanic	7 (3.3%)	6 (3.9%)	1 (1.7%)	
Non-Hispanic	201 (95%)	145 (94%)	56 (97%)	
Unknown	4 (1.9%)	3 (1.9%)	1 (1.7%)	
Stage at Diagnosis				0.5
Stage I-III	150 (71%)	107 (69%)	43 (74%)	
Stage IV	62 (29%)	47 (31%)	15 (26%)	
Histology				0.7
Invasive ductal carcinoma	204 (96%)	148 (96%)	56 (97%)	
Invasive lobular carcinoma	6 (2.8%)	5 (3.2%)	1 (1.7%)	
Other histology	2 (0.9%)	1 (0.6%)	1 (1.7%)	
ER Status				**0.007**
Negative	80 (38%)	67 (44%)	13 (22%)	
Positive	132 (62%)	87 (56%)	45 (78%)	
PR Status				0.063
Negative	90 (42%)	72 (47%)	18 (31%)	
Positive	121 (57%)	81 (53%)	40 (69%)	
Unknown/Not Tested	1 (0.5%)	1 (0.6%)	0 (0%)	
***PIK3CA* mutation type**				**<0.001**
Kinase Domain (H1047)	24 (11%)	0 (0%)	24 (41%)	
Helical Domain (E545)	7 (3.3%)	0 (0%)	7 (12%)	
Other *PIK3CA* Mutation	26 (12%)	0 (0%)	26 (45%)	
Received Chemotherapy	207 (98%)	152 (99%)	55 (95%)	0.13
Received Hormone Therapy	142 (67%)	97 (63%)	45 (78%)	**0.05**
Received Immunotherapy	19 (9.0%)	14 (9.1%)	5 (8.6%)	>0.9
Received HER2 Therapy	194 (92%)	145 (94%)	49 (84%)	**0.049**
Received CDK4/6 Inhibitors	29 (14%)	17 (11%)	12 (21%)	0.076
Received PI3K/mTOR Inhibitors	19 (9.0%)	11 (7.1%)	8 (14%)	0.2

[1]Median (Q1, Q3); n (%)

PIK3CA altered vs. not

- The time from initial diagnosis to distant metastasis was significantly ↑ for patients with *PIK3CAm* (median: 38 months [IQR: 23-73] vs. 22 months [IQR: 10-43], p=0.01).
- Patients with PIK3CAm had ↑ rates of altered PI3K pathway (100% vs. 21%, p<0.001).
- Patients with PIK3CAm had significantly ↓ rates of Hippo pathway alteration (0% vs. 11%, p=0.01).

Impact of *PIK3CAm* on survival outcomes

OS

- Median OS from initial breast cancer diagnosis = 124.4 months (95% CI 98.4-157.2).
- Univariable COX PH analysis = *PIK3CAm* is not significantly associated with worse OS outcomes from breast cancer diagnosis (HR=1.06, 95% CI 0.68-1.66).
- LASSO did not select *PIK3CAm* for the set of covariates in multivariable COX PH analysis (from diagnosis).
- Median OS from initial breast cancer treatment = 125.1 months (95% CI, 98.3–155.3) for the overall cohort: 131.2 months (95% CI, 98.3–160.6) for early-stage patients, and 112.1 months (95% CI, 80.8–NA) for those with stage IV disease.
- Univariable COX PH analysis = *PIK3CAm* was not associated with OS from breast cancer treatment (HR=1.11, 95% CI 0.70-1.75).
- LASSO did not select *PIK3CAm* for the set of covariates in multivariable COX PH analysis (from treatment).

DRFS

- Median DRFS from initial breast cancer diagnosis = 26.3 months (95% CI, 21.8–35.5).
- Univariable COX PH analysis = *PIK3CAm* is not associated with a higher risk of distant recurrence from breast cancer diagnosis (HR=0.67, 95% CI 0.44-1.01).
- LASSO did not select *PIK3CAm* for the set of covariates in multivariable COX PH analysis (from diagnosis).
- Median DRFS from initial breast cancer treatment = 26.9 months (95% CI 21.9-35.6).
- Univariable COX PH analysis = *PIK3CAm* was not associated with distant recurrence from treatment (HR = 0.7, 95% CI 0.44-1.01).
- LASSO did not select *PIK3CAm* for the set of covariates in multivariable COX PH analysis (from treatment).

PFS

- Median PFS from initial breast cancer diagnosis = 11.6 months (95% CI, 7.1–18.5).
- Univariable COX PH analysis = *PIK3CAm* is not associated with a higher risk of progression from breast cancer diagnosis (HR=1.44, 95% CI 0.79-2.63).
- LASSO did not select *PIK3CAm* for the set of covariates in multivariable COX PH analysis (from diagnosis).
- Median PFS from initial breast cancer treatment = 14.2 months (95% CI 6.9-55.6).
- Univariable COX PH analysis = *PIK3CAm* was not associated with progression from treatment (HR=0.95, 95% CI 0.38-2.36).
- LASSO did not select *PIK3CAm* for the set of covariates in multivariable COX PH analysis (from treatment).

Impact of *PIK3CAm* on survival outcomes

OS

- Median OS from initial breast cancer diagnosis = 126 months (95% CI 98.8-NA) for those with *PIK3CAm*.
- Median OS from initial breast cancer treatment = 125.1 months (95% CI 98.3-NA) for those with *PIK3CAm*.

DRFS

- Median DRFS from initial breast cancer diagnosis = 37.7 months (95% CI 30.2-57.1) for those with *PIK3CAm*.
- Median DRFS from initial breast cancer treatment = 36.9 months (95% CI 29.1-55.2) for those with *PIK3CAm*.

PFS

- Median PFS from initial breast cancer diagnosis = 3.9 months (95% CI 1.6-7.8) for those with *PIK3CAm*.
- There were not enough patients and/or follow-up to obtain PFS from treatment on patients with *PIK3CAm*.

CONCLUSIONS

***PIK3CAm* was not significantly associated with worse OS, PFS, or distant-recurrence risk, according to COX PH regressions. However, among Stage IV HER2+ patients, those with *PIK3CAm* had a significantly shorter PFS with first-line therapy compared to those with wild-type *PIK3CA* (median PFS from diagnosis: 5.5 months vs. 14.9 months, p = 0.04). These findings suggest that *PIK3CAm* may serve as a predictive biomarker for identifying HER2+ Stage IV patients at higher risk of disease progression.**

The authors would like to acknowledge the American Association for Cancer Research and its financial and material support in the development of the AACR Project GENIE registry as well as members of the AACR Project GENIE consortium for their commitment to data sharing. Interpretations are the responsibility of study authors.

Contact: nickolas@case.edu

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