PIK3CA Mutation in the ShortHER Randomized Adjuvant Trial for Patients with Early HER2+ Breast Cancer: Association with Prognosis and Integration with PAM50 Subtype

Valentina Guarneri[1,2], Maria Vittoria Dieci[3,2], Giancarlo Bisagni[4], Alba A Brandes[5], Antonio Frassoldati[6], Luigi Cavanna[7], Antonino Musolino[8,9], Francesco Giotta[10], Anita Rimanti[11], Ornella Garrone[12], Elena Bertone[13], Katia Cagossi[14], Oriana Nanni[15], Federico Piacentini[16], Enrico Orvieto[17], Gaia Griguolo[1,2], Matteo Curtarello[18], Loredana Urso[1], Laia Paré[19], Nuria Chic[20,21], Roberto D'Amico[22,23], Aleix Prat[19,20,21], Pierfranco Conte[1,2]
Affiliations expand

- PMID: 32843527

- DOI: 10.1158/1078-0432.CCR-20-1731

Abstract

Purpose: We explored the prognostic effect of *PIK3CA* mutation in HER2+ patients enrolled in the ShortHER trial.

Patients and methods: The ShortHER trial randomized 1,253 patients with HER2+ breast cancer to 9 weeks or 1 year of adjuvant trastuzumab combined with chemotherapy. *PIK3CA* hotspot mutations in exon 9 and 20 were analyzed by pyrosequencing. Expression of 60 genes, including PAM50 genes was measured using the nCounter platform.

Results: A mutation of the *PIK3CA* gene was detected in 21.7% of the 803 genotyped tumors. At a median follow-up of 7.7 years, 5-year disease-free survival (DFS) rates were 90.6% for *PIK3CA* mutated and 86.2% for *PIK3CA* wild-type tumors [HR, 0.84; 95% confidence interval (CI), 0.56-1.27; $P = 0.417$]. *PIK3CA* mutation showed a favorable prognostic impact in the PAM50 HER2-enriched subtype ($n = 232$): 5-year DFS 91.8% versus 76.1% (log-rank $P = 0.049$; HR, 0.46; 95% CI, 0.21-1.02). HER2-enriched/*PIK3CA* mutated versus wild-type tumors showed numerically higher tumor-infiltrating lymphocytes (TIL) and significant upregulation of immune-related genes (including *CD8A, CD274, PDCD1,* and *MYBL2*, a proliferation gene involved in immune processes). High TILs as well as the upregulation of *PDCD1* and *MYBL2* were associated with a significant DFS improvement within the HER2-enriched subtype (HR, 0.82; 95% CI,

0.68-0.99; *P* = 0.039 for 10% TILs increment; HR, 0.81; 95% CI, 0.65-0.99; *P* = 0.049 for *PDCD1* expression; HR, 0.72; 95% CI, 0.53-0.99; *P* = 0.042 for *MYBL2* expression).

Conclusions: *PIK3CA* mutation showed no prognostic impact in the ShortHER trial. Within the HER2-enriched molecular subtype, patients with *PIK3CA* mutated tumors showed better DFS versus *PIK3CA* wild-type, which may be partly explained by upregulation of immune-related genes.