PI3K MUTATION IS ASSOCIATED WITH REDUCED SENSITIVITY TO CDK4/6 INHIBITORS IN METASTATIC BREAST CANCER

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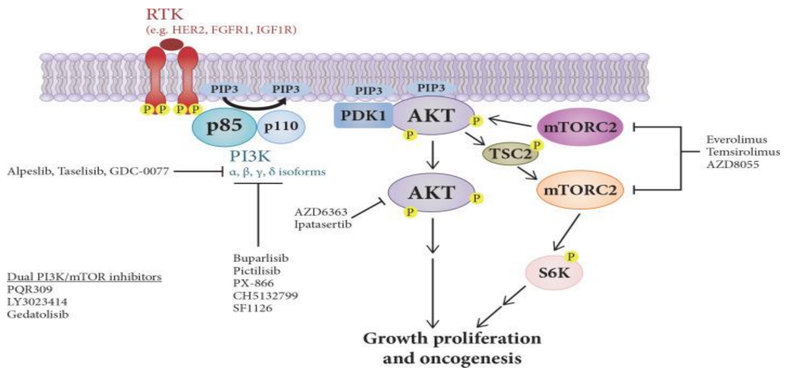
BACKGROUND

The PI3K pathway is the most frequently enhanced oncogenic pathway in breast cancer. Among mechanisms of PI3K enhancement, *PIK3CA* mutations are most frequently (~30%) observed, along with protein loss of PTEN.
In particular, breast cancer tumorigenesis is believed to depend on the PI3K pathway. This is based on the fact that the majority of cases of this disease harbor at least one molecular mechanism that potentially enhances the pathway. These PI3K-enhancing mechanisms include mutations of the *PI3K* gene, more specifically *PIK3CA* gene mutations. First discovered in 2004 in various solid tumors, including breast cancer, these mutations have the potential to become a clinically useful biomarker, because they 1) are gain-of-function mutations of molecules located on an important signaling pathway, 2) are found at high frequency, and 3) are easy to measure (present or absent).

Many retrospective studies, including a large meta-analysis of >10 000 patients with early-stage BC, have proposed that *PIK3CA* mutations are prognostic markers for improved relapse-free survival on univariate analysis.

AIM

PI3K mutations contribute to endocrine resistance. *PIK3CA* mutation may be present de novo at the time of diagnosis or may be acquired later. The present study evaluated the incidence and distribution of de novo *PIK3CA* mutations in hormone receptor-positive / HER2-negative metastatic breast cancer (MBC) and its impact on clinical outcomes of patients treated with CDK4 inhibitors.



Signaling by the phosphatidylinositol-3-kinase (PI3K)-AKT- mammalian target of rapamycin (mTOR) pathway.

MATERIALS AND METHODS

This was a retrospective study. All patients with MBC on endocrine therapy with CDK4/6 inhibitors whose initial tissue - formalin-fixed, paraffin-embedded (FFPE) blocks were available were enrolled in this study. The genomic DNA was extracted and analysed using Therascreen® PIK3CA RGQ PCR Kit.
The Therascreen PIK3CA RGQ PCR Kit is a real-time qualitative PCR test for the detection of 11 mutations in the phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) gene (Exon 7: C420R; Exon 9: E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R; and Exon 20: H1047L, H1047R, H1047Y) using genomic DNA (gDNA) extracted from FFPE breast tumor tissue or circulating tumor DNA (ctDNA) from plasma derived from K2EDTA anticoagulated peripheral whole blood taken from patients with breast cancer.

RESULTS

- 36 patients were included in this study.
- The median age was 59 years (range 34-81).
- 21 (58.6%) patients were on palbociclib and 15 (41.4%) on ribociclib along with endocrine therapy.
- Of the 36 patients 17 (47.2%) were *PIK3CA* mutant (12 patients- exon 20 (70.5%); 5 had exon 9 (29.4%) mutation). The common amino acid substitutions in exon 9 were at codon 542 and 545 and exon 20 at 1047R.
- One patient had a double mutation on both exons 9 and 20. This patient had progression within 6 months of initiation of therapy.
- At 12 months, the overall response rate (ORR) in the non-mutant group was 26% (2 CR and 3 PR); 3 (15.7%%) had stable disease whereas 11 patients (57.89%) had progressive disease (PD), of which 3 patients died in less than 1 year.
- Among the 17 patients with *PIK3CA* mutation, there were no complete or partial responders; only 1 patient had stable disease. The remaining 16 (94.1%) patients had PD, of which 5 patients succumbed to the disease in less than 12 months.
- *PIK3CA* mutation was associated with shorter progression-free survival (PFS) compared to *PIK3CA* wild type (18 versus 32.2 months, p-value 0.004) and shorter overall survival (OS) (41.7 versus 45 months, p value=0.772).
- The mean PFS was better in the exon 9 than exon 20 (22.2 versus 11.2 months, p-value 0.4).

RESULTS

Characteristics		P value
Median age	59 years (range 34-81)	
CDK4/6 inhibitor Palbociclib Ribociclib	 21 (58.6%) 15 (41.4%)	
PIK3CA mutation +ve	17 (47.2%)	
PFS in non mutant group	32.2 months	p-value 0.004
PFS in mutant group	18 months	
12 months overall response rate in non mutated group	Complete response- 2 (10.5%) Partial response - 3 (15.7%) Stable disease- 3 (15.7%%) Progressive disease-11 (57.89%)	
12 months overall response rate in mutated group	Complete response- 0 (0%) Partial response - 0 (0%) Stable disease- 1 (5.88%) Progressive disease-16 (94.1%)	

Conclusions

The incidence and type of *PIK3CA* mutation are similar to the data reported previously. The presence of de novo PI3K mutation confers a worse clinical outcome in HR-positive / HER2 negative metastatic breast cancer patients despite the use of CDK4/6 inhibitors.

REFERENCES

Del Re M, Crucitta S, Lorenzini G, et al. PI3K mutations detected in liquid biopsy are associated to reduced sensitivity to CDK4/6 inhibitors in metastatic breast cancer patients. *Pharmacol Res*. 2021;163:105241. doi:10.1016/j.phrs.2020.105241

DISCLOSURE

All the authors declare that there is no conflict of interest.