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Adjuvant aromatase inhibitors in patients with PIK3CA mutation early breast cancer

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Introduction:

- Phosphatidylinositide-3-kinase (PI3K) regulates proliferation and apoptosis and somatic *PIK3CA*-mutations may activate these processes.
- There is a multidirectional interplay between PI3K/AKT-signaling pathway and the ER-signaling pathway implicating a potential inter-action with the effect of endocrine therapy.
- Thus, activation of PI3K/AKT may result in endocrine resistance.

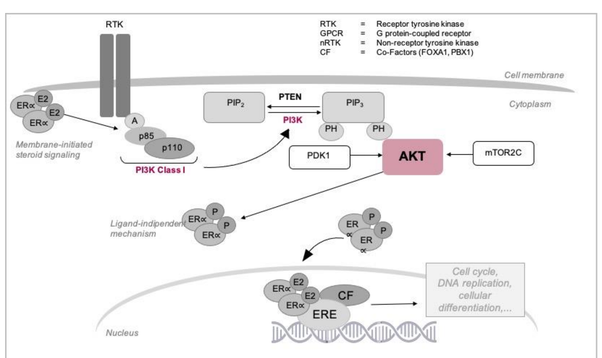

Fig. 1: Crosstalk between PI3K/Akt signaling pathway and ER pathway[2]

In a retrospective analysis of a prospective cohort study of early breast cancer (eBC) patients, we observed resistance to aromatase inhibitor (AI) therapy [1] in case of somatic *PIK3CA*-mutation.

Background:

We observed that patients with HR-positive HER2-negative tumours who were treated with aromatase inhibitors only (n = 208), had a

- significant, 4.39 times higher occurrence of RFI events if they harboured a *PIK3CA*-mutation (n = 68) compared to those with PIK3CA-wildtype
  (n = 140; adjusted HR 4.39, 95% CI 1.385–13.920, p = 0.012)
- significantly impaired OS if *PIK3CA* mutated
  (adjusted HR 2.12, 95% CI 1.021–4.404, p = 0.044)
- In contrast, no association between *PIK3CA* mutation status and RFI or OS was observed in patients with luminal-like tumours who were treated with tamoxifen only.

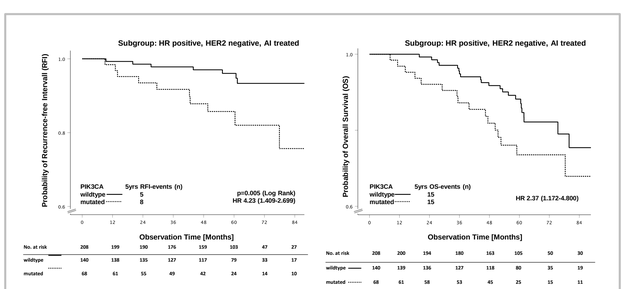

Fig. 2: Survival estimates for RFI and OS stratified by detection of *PIK3CA*-mutations in HR-positive and HER2-negative tumours, Aromatase Inhibitors (AI) treated (n = 208).[1]

The study presented here is aimed at validating these findings in a second cohort.

Methods:

We studied a single centre cohort of 262 patients with steroid hormone receptor-positive, HER2-negative eBC, who were assigned to endocrine adjuvant therapy only: aromatase inhibitor (AI, n=183), tamoxifen (TAM, n=69), AI and TAM (n=9), or fulvestrant (n=1). In these patients, we tested the three most common somatic PIK3CA gene mutations (H1047R, E545K, E542K) by qPCR.
The primary endpoint was recurrence-free survival (RFS), secondary endpoint overall survival (OS). Median follow up was 62 months.

Tab.1: Patients' characteristics and histopathological parameters of the tumours in relation to the *PIK3CA* mutation status

	n=262	Wildtype n=152	(%)	Mutated n=110	(%)	OR	95% CI	*p-value*
Grading								
G1	90	47	(30.9)	43	(39.1)	2.745	0.275 – 27.394	*0.39*
G2	168	102	(67.1)	66	(60.0)	1.941	0.198 – 19.059	*0.57*
G3	4	3	(2.0)	1	(0.9)	1		
Tumour size								
≤ 2cm	166	94	(61.8)	72	(65.5)	1.169	0.701 – 1.950	*0.55*
> 2cm	96	58	(38.2)	38	(34.5)	1		
Nodal status								
negative	215	128	(85.9)	87	(79.1)	1.611	0.840 – 3.091	*0.15*
positive	44	21	(14.1)	23	(20.9)	1		
Endocrine therapy								
AI	183	108	(71.1)	75	(68.2)	1.440	0.403 – 5.149	*0.58*
Tamoxifen	69	39	(25.7)	30	(27.3)	1.108	0.633 – 1.939	*0.72*
AI + Tamoxifen	10	5	(3.2)	5	(4.5)	1		

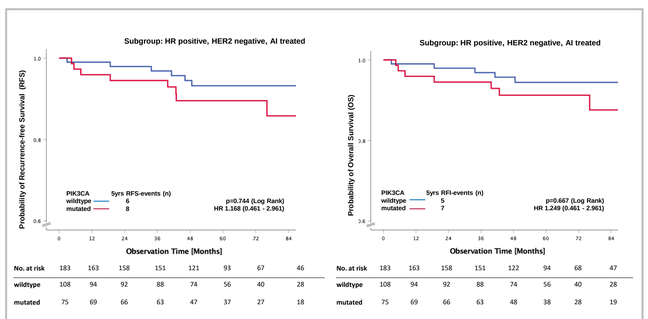

Fig. 3: Survival estimates for RFS and OS stratified by presence of *PIK3CA*-mutations in HR-positive and HER2-negative tumours, Aromatase Inhibitors (AI) treated (n = 183).

Results:

We observed that patients with HR-positive HER2-negative tumours who were treated with aromatase inhibitors only (n = 183) did not have a higher occurrence of RFS or RFI events if they harboured a *PIK3CA*-mutation (n = 75) compared to those with *PIK3CA*-wildtype (n = 108; HR 1.168, 95% CI 0.461 – 2.961) and higher mortality (HR 1.249, 95% CI 0.461– 2.961). There was also no association between *PIK3CA* mutation status and RFS or OS in patients with luminal-like tumours who were treated with tamoxifen only.

Conclusion:

Although we observed a trend that AIs would be less effective in patients with *PIK3CA* mutated tumours, formal validation of our former results is lacking. Further data including prospective studies are required.

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References

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[2]Brufsky, A. M., & Dickler, M. N. (2018). Estrogen Receptor-Positive Breast Cancer: Exploiting Signaling Pathways Implicated in Endocrine Resistance. The Oncologist, 23(5), 528–539. https://doi.org/10.1634/theoncologist.2017-0423