

**Association of vorinostat with decrease in gene expression of proliferation-related genes in tumors from women with newly diagnosed breast cancer.**

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**Background:** Epigenetic modifications contribute to breast cancer initiation and progression and may be reversible. In preclinical breast cancer models, the histone deacetylase vorinostat induces cell cycle arrest, apoptosis, and differentiation. We evaluated biomarker modulation in breast cancer tissues obtained from women who received vorinostat and from untreated controls.

**Methods:** Women with a newly diagnosed invasive breast cancer received vorinostat 300 mg PO BID x 6 doses, the last dose 2 hours prior to surgery or biopsy. Pre- and post-vorinostat tumor specimens were analyzed for gene methylation (QM-MSP) and expression (RT-PCR using the Oncotype DX 21-gene assay and IHC for Ki67 and cleaved caspase 3). Tissues were also collected from untreated controls. We performed Wilcoxon nonparametric tests to compare changes in quantitative gene expression levels pre- and post-vorinostat with changes in expression in untreated patients, and changes between pre- and post-vorinostat methylation.

**Results:** Samples were collected from 25 vorinostat-treated and from 25 untreated women. Evaluable samples and key results are shown in the Table. For 25 evaluable matched sample sets for both IHC and RT-PCR, 76% had ER+ tumors by both assays (100% concordance). In the vorinostat group, we observed statistically significant decreases in Ki-67 and STK15 by RT-PCR but not in Ki-67 by IHC. Differences between treatments in pre- to post-changes were statistically significant for Ki-67 (p=0.008) and STK15 (p=0.012). No significant changes were observed for ER or in gene methylation.

**Conclusions:** Short-term vorinostat is associated with decreases in expression of proliferation-associated genes. The results will be used to design future studies in which vorinostat will be combined with other therapies.

**P values associated with change in gene expression and number of patients with paired samples**

Assay (evaluatable: treated/untreated)	P value	
	Treated	Untreated
<b>IHC</b>		
<b>Ki67 (22,15)</b>	0.51	0.44
<b>Cleaved caspase-3 (19,0)</b>	0.36	-
<b>RT-PCR (14,11)</b>		
<b>STK15</b>	0.004	0.44
<b>Ki-67</b>	0.038	0.85
<b>MYBL2</b>	0.061	0.28
<b>Cyclin B1</b>	0.10	0.74
<b>Survivin</b>	0.12	0.80
<b>ER</b>	0.45	0.80