Endocrine resistance is a major contributor to treatment failure in breast cancer. A close examination of the signaling mechanisms by which cells may impart their resistance presents an attractive strategy for the development of viable treatment options. Sphingosine kinase (SK), and its product, Sphingosine-1-phosphate (S1P) have been increasingly implicated in many disease states and SK/S1P signaling is a known regulator of apoptosis and cell survival. Furthermore, inhibition of sphingosine kinase has been shown to be anti-proliferative as useful method to reset the cell signaling aberrations which lead to endocrine resistance, and may contribute to overall greater efficacy of current therapeutic interventions by re-sensitizing cells to the endocrine therapy. Well apoptotic in a multitude of human cancer cell lines. In this study, we investigated the biological activity of the sphingosine kinase inhibitor, SKI-II (4-[4-(4-Chlorophenyl)-2-thiazolyl]amino)phenol) and its ability to disrupt cell signaling in estrogen-dependent and endocrine-resistant breast cancer. SKI-II blocked both viability and survival at low micromolar IC$_{50}$ concentrations in the endocrine therapy-resistant MDA-MB-231, MDA-MB-468 and MDA-MB-361 cells in addition to endocrine therapy-sensitive MCF-7 breast cancer lines. Additionally, treatment with SKI-II significantly (p<0.05) decreased proliferation, as seen in Ki-67 immunostaining. The potent biological activity of this inhibitor led us to characterize the precise molecular mechanisms in which SKI-II imparts its effects. Sphingosine kinase is known to affect various signaling cascades, and its effect on the MAPK and PI3K/Akt pathways are cell line dependent. Growth factor signals such as MAPK can cross-talk with estrogen receptor and confer hormone therapy resistance. Therefore, we chose to investigate several signaling cascades to determine if SK inhibition mediates its effect through disruption of signaling. SKI-II diminished phosphorylation of ERK1/2 in both a time-dependent and dose-dependent manner. Treatment with SKI-II also inhibited phosphorylation of p38/MAPK at similar concentrations. This blockade of MAPK signaling may contribute to SKI-II’s dual anti-cancer effect, which can target ER activation in an estrogen-dependent and an estrogen-independent manner. Targeting the production of sphingosine-1-phosphate through pharmacological inhibition presents a potentially useful method to reset the cell signaling aberrations which lead to endocrine resistance, and may contribute to overall greater efficacy of current therapeutic interventions by re-sensitizing cells to the endocrine therapy.