Triple negative breast cancer (TNBC) accounts for 15-20% of total invasive breast cancer. These tumors are more aggressive and have a worse prognosis relative to other types of breast cancer, partially due to the lack of FDA-approved targeted therapy. Utilizing the RNA-seq data for invasive breast cancer specimens deposited in the Cancer Genome Atlas (TCGA), we found that the mRNA expression of receptor tyrosine kinase-like orphan receptor 1 (ROR1) decreased in the luminal A (n=231), luminal B (n=128) and Her2+ (n=58) subtypes relative to their corresponding normal controls. In contrast, ROR1 expression increased in all the pathologic stages of TNBC samples relative to normal specimens and ROR1 expression correlates positively with progression of TNBC (n=78). ROR1 is a receptor tyrosine kinase that is involved in embryonic patterning, but lacks expression in adult tissues. We undertook a series of mechanistic studies to understand the role of ROR1 in TNBC and evaluate ROR1 as a potential target for TNBC therapy. Using complex bioinformatics analysis, we found that ROR1 expression correlates with signature genes of TNBC, cancer stem cells, and TGFβ/SMAD pathways, which, in addition to recent observation of potential crosstalk between WNT5A/ROR1 signaling with TGFβ/SMAD, prompted us to examine if this crosstalk contributes to progression TNBC. Indeed, we found that WNT5a promotes SMAD2/3 activation in a ROR1- and TGFβR1-dependent manner. Inhibiting ROR1 by neutralizing antibody shifted cancer stem cells of TNBC to a more luminal-type, indicating a critical of ROR1 in self-renewal of cancer stem cells. SNAI1/2, master regulators of epithelial to mesenchymal transition (EMT), are potentially involved in the WNT5a/ROR1-mediated self-renewal of cancer stem cells. In agreement with these findings, TNBC cell lines with the highest surface expression of ROR1 had a greater cancer stem cell (CSC) population (CD24CD44^high). In collaboration with Speed Biosystems LLC, we developed an anti-ROR1 immunotoxin that specifically kills ROR1-high TNBC cells but not ROR1-low breast cancer cells or normal epithelial cells. Our findings suggest a role of WNT5a/ROR1 signaling in the progression of TNBC, through its role in potentiating TGFβ/SMAD/SNAI2 pathway thus promoting EMT and stem-like phenotype. ROR1 represents a novel therapeutic target for TNBC, especially for late-stage diseases.