Supplementary Figure S1: Expression Profiles of Markers of Proliferation and Invasion. mRNA levels of (A) Wnt5A, (B) MITF, (C) GP100, (D) DCT, and (E) MART1 in multiple microarray databases of melanoma patient samples divided into a more proliferative, less metastatic cohort (Cohort A), an intermediate cohort (Cohort B) and a highly metastatic cohort (Cohort C)(***p<0.001).

Supplementary Figure S2: ROR1 Degradation does not Occur Through Lysosomes. (A) Immunofluorescent analysis of ROR1 (green) and LAMP2 (red) following treatment with rWnt5A over time in G361 cells. (B) Immunofluorescent analysis of ROR1 (green) and LAMP2 (red) following pre-treatment with the lysosomal inhibitors Lys05 (5 μM, 2 hours) and BAF1 (50 nm, 2 hours) and subsequent treatment +/- rWnt5A (10 minutes) in G361 cells.

Supplementary Figure S3: ROR1 Degradation is PKC-dependent. (A) Immunofluorescent analysis of ROR1 (green) and Wnt5A (red) in UACC903 cells following treatment with the PKC inhibitor GO6983 (1 μM, 17 hours). (B) Immunofluorescent analysis of ROR1 (green) and Wnt5A (red) protein expression in poorly invasive G361 cells following pre-treatment with the PKC inhibitor GO6983 (1 μM, 16 hours) and subsequent treatment with rWnt5A (200 ng/ml, 16 hours) +/- GO6983 (1 μM, 16 hours).

Supplementary Figure S4: ROR1 and ROR2 Regulate Expression of One Another and Knockdown of ROR1 Decreases Proliferation *in vivo*. (A) Real-time PCR analysis of ROR1 and ROR2 mRNA levels following knockdown of ROR2 by siRNA at 24 hours and 48 hours in UACC903 cells (*p<0.05, **p<0.01, ***p<0.001; error bars=STDEV). (B) Tumor growth assays (*in vivo*) in athymic nude mice following injection of WM35 cells after transfection with CTRL or ROR1 siRNA (2 different ROR1 siRNAs). (D) Tumor growth assays (*in vivo*) in athymic nude

mice following injection of WM983B cells after transfection with CTRL or ROR1 siRNA (2 different ROR1 siRNAs).

Supplementary Figure S5: Wnt5A regulates HIF1a in highly invasive cells and regulates β-catenin expression through Siah2. (A) Validation of 2 different HIF1α siRNAs, showing changes in Wnt5A expression by Western analysis. (B) Knockdown of Wnt5A in poorly invasive cells does not affect levels of HIF1α or ROR2 (C) Expression of β-catenin following Wnt5A treatment (200 ng/ml, 16 hours) analyzed by immunofluorescence. (D) Real-time PCR analysis of Siah2 mRNA levels in G361 and UACC1273 cells following Siah2 knockdown by siRNA (48 hours and 72 hours) (*$p<0.01$, ***$p<0.001$; error bars=STDEV). (E) Expression of β-catenin in untreated and in rWnt5A-treated G361 melanoma cells following transfection with CTRL or Siah2 siRNA, visualized by immunofluorescence.

Supplementary Figure S6: Additional ROR2 Knockdown Studies. (A) Expression of ROR2 protein in 1205LU, FS4, and UACC62 cells following transfection with CTRL or ROR2 siRNA at 20 nM (72 hours and 144 hours) analyzed by Western blot. (B) PLX-resistant UACC62 and (C) FS4 melanoma cells were transfected with CTRL or ROR2 siRNA and treated with increasing doses of PLX4720. Proliferation was analyzed by an MTS assay. (D) ROR2 protein expression (green) in CTRL or ROR2 siRNA treated 1205LU tumors was examined by immunofluorescence following excision. (E) Tumor volume analysis in athymic nude mice injected with WM983B cells transfected with CTRL or ROR1 siRNA (2 different siRNAs). Once tumor formation had occurred, mice were fed AIN-76A chow containing 417 mg/kg PLX4720 and tumors were tracked for 17 days. The fold change in tumor volume was recorded.

Supplementary Table 1: Wnt5A Expression May Predict Response to Therapy. Wnt5A expression in patients before treatment with BRAF/MEK inhibitors and percent response to therapy. * Indicates removal from treatment due to adverse effects. Li= liver, sc= subcutaneous, n=nodule, br=brain. Brafi= vemurafenib or dabrefanib, Meki= trametinib. Expression of Wnt5A in non-responders is significant to p=0.002.

Supplementary Table 2: Wnt5A Expression Increases in Patients Who Acquire Resistance to MAPK Inhibition. Change in Wnt5A positivity (%) in patients both pre- and post-treatment with BRAF/MEK inhibitors (Vemurafenib/ Trematenib / Dabrefanib / PLX4032). Increase in Wnt5A during resistance is significant to p=0.018.