

## Supplementary Figure Legends

**Supplementary Figure 1: Effects of REGN910 on endothelial cell proliferation and endothelial cell death.** Colo205 tumors were treated with Fc control protein (25 mg/kg) or REGN910 (15 mg/kg) for 10 days (3 doses of each agent were administered). A) Tumor sections were stained as described in the Supplementary Methods for CD31 to visualize blood vessels (red), TUNEL to visualize apoptotic cells (purple), BrdUrd to visualize proliferating cells (black) and pimonidazole to visualize regions of hypoxia (green). B,C) The bar graphs show the percentage of CD31-positive pixels that were also positive for TUNEL or BrdUrd. D) The bar graph shows the average pimonidazole intensity. Error bars represent SD.

**Supplementary Figure 2: The percentage of blood vessels associated with desmin-positive pericytes increases following REGN910 treatment.** Colo205 tumors were treated with Fc control protein (25 mg/kg) or REGN910 (15 mg/kg) for 10 days (3 doses of each agent were administered). A) Tumor sections were stained for CD31 (blood vessels) and desmin (pericytes) as described in the Supplementary Methods and the percentage of desmin-positive blood vessels was calculated. B) The bar graph depicts the average percentage of desmin-positive vessels in each sample. Error bars represent SD. Values were compared by *t*-test (\*\*\*)  $P < 0.001$

**Supplementary Figure 3: Images of whole tumor sections reveal the dramatic effect of the REGN910 plus aflibercept combination treatment on tumor cell death.** Colo205 tumors were treated with Fc control protein (25 mg/kg), REGN910 (15 mg/kg), aflibercept (25 mg/kg) or the combination of REGN910 plus aflibercept for 72 hours. Whole tumor sections were stained as described in the Supplementary Methods for CD31 to visualize blood vessels (red), TUNEL to visualize apoptotic cells (purple), BrdUrd to visualize proliferating cells (black) and pimonidazole to visualize regions of hypoxia (green). Note the extensive TUNEL-positive area in the combination treated tumor. The scale bars are 1 mm.

**Supplementary Figure 4: Effect of REGN910 plus aflibercept combination treatment on the frequency of dual-positive CD31/TUNEL pixels at 24 hours after treatment.** Colo205 tumors were treated with Fc control protein (25 mg/kg), REGN910 (15 mg/kg), aflibercept (25 mg/kg) or the combination of REGN910 plus aflibercept for 24 hrs. A) Tumor sections were stained for CD31 to visualize blood vessels (green) and TUNEL to visualize apoptotic cells (purple) as described in the Supplementary Methods. The arrows in the image from the REGN910 plus aflibercept treated tumors indicate dual-positive CD31/TUNEL pixels. B) The bar graph shows the percentage of CD31-positive pixels that were also positive for TUNEL. Error bars represent SD. Values were compared by one-way ANOVA with Tukey's multiple comparison test (\*  $P < 0.05$ )