Supplementary 1. Responding and non-responding MMTV/HER2 tumor-bearing mice stratified by tumor burden. Tumor regression occurred concomitantly with serial Tz in therapy in responding MMTV/HER2 tumor-bearing mice (A). Alternately, significant tumor growth was observed in similarly treated non-responding mice (B).

Supplementary 2. BT474 human breast cancer xenografts regress when treated with Tz. Two weeks of Tz treatment induced significant tumor regression (A), which was not observed in PBS-treated animals (B).

Supplementary 3. Quantitative analysis of NIR700-Annexin-V accumulation in MMTV/HER2 tumor-bearing mice. Quantitative NIR700-Annexin-V clearance profiles for MMTV/HER2 tumor and reference muscle prior to treatment and following each week of Tz treatment for three weeks were generated based on each imaging session. Shown are representative profiles from responding (A) and non-responding (B) mice. Significant accumulation of NIR700-Annexin-V was observed in tumors when compared to reference muscle following two weeks of treatment and beyond in responding tumors (A), while no significant NIR700-Annexin-V accumulation is observed in the non-

responding tumors (B). Ratio of area under the curves (AUC) for tumor and muscle is used for quantitative analysis; Δ in R* = the change in ratio of T/M AUC compared to baseline.

Supplementary 4. Trastuzumab treatment upregulates cleaved caspase-3 in MMTV/HER2 tumors. (A) MMTV/HER2 tumors harvested from mice before or after one, two, or three weeks of Tz treatment were immunostained for cleaved caspase-3. Representative images from each time point are shown (100x mag.). (B) The numbers of positively stained cells were counted from five randomly selected fields of viable tumor tissue. Percentage of cleaved caspase-3-positive cells is shown. Paired t-test shows statistically significant increase after Tz treatment (§$p < 0.05$).

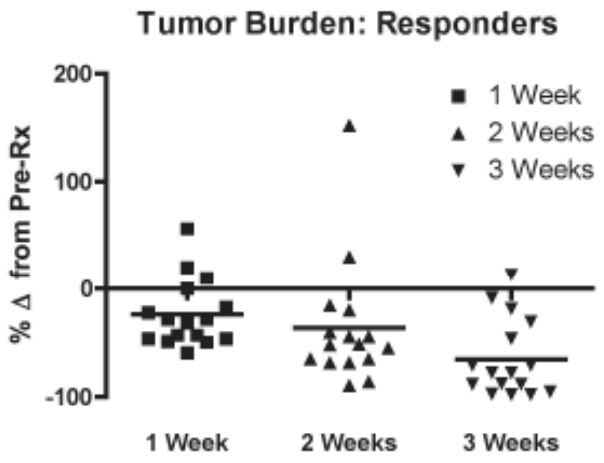
Supplementary 5. [^{18}F]FLT uptake does not exceed background levels and is unchanged by Tz treatment in MMTV/HER2 tumors. (A) Uptake of [^{18}F]FLT is not significantly higher than background tissues both before and after Tz therapy. (B) Serial Tz treatments do not significantly alter MMTV/HER2 tumor uptake of [^{18}F]FLT.

Supplementary 6. *In situ* markers of drug action correlate with non-invasive imaging biomarkers in BT474 xenografts. Compared to vehicle treated controls (characterized at both 1 and 2 weeks of treatment), significantly elevated cleaved caspase-3 staining was observed in Tz-treated BT474 tumor tissues. Ki67 immunoreactivity of BT474 tumor tissues was significantly decreased following treatment with Tz at both 1 and 2 weeks of therapy. Similar levels of nuclear and

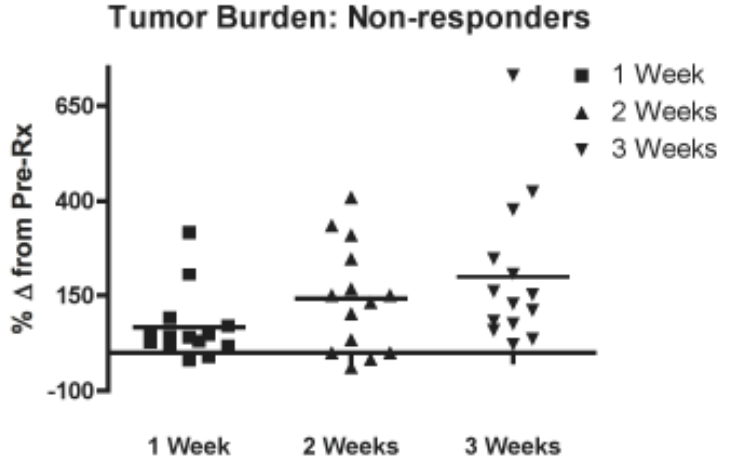
cytoplasmic p-AKT immunoreactivity was observed in both vehicle-treated control and Tz-treated BT474 tumors tissues at all time points.

Supplementary 7. Histological scoring of BT474 tumor tissues following 1 or 2 weeks of vehicle or Tz treatment. The numbers of positively stained cells were counted from three randomly selected fields of viable tumor tissue per mouse (n = 3 mice). The percentage of Ki67-positve (A) or the percentage of cleaved caspase-3-positive cells (B) are shown. Paired t-test shows statistically significant results compared to baseline values (*, P value shown).

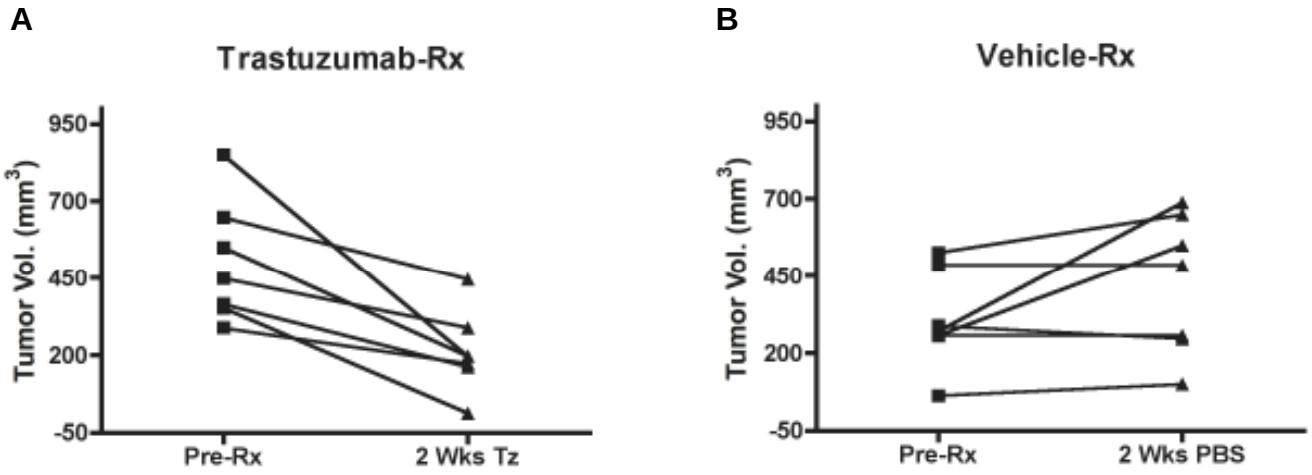
A



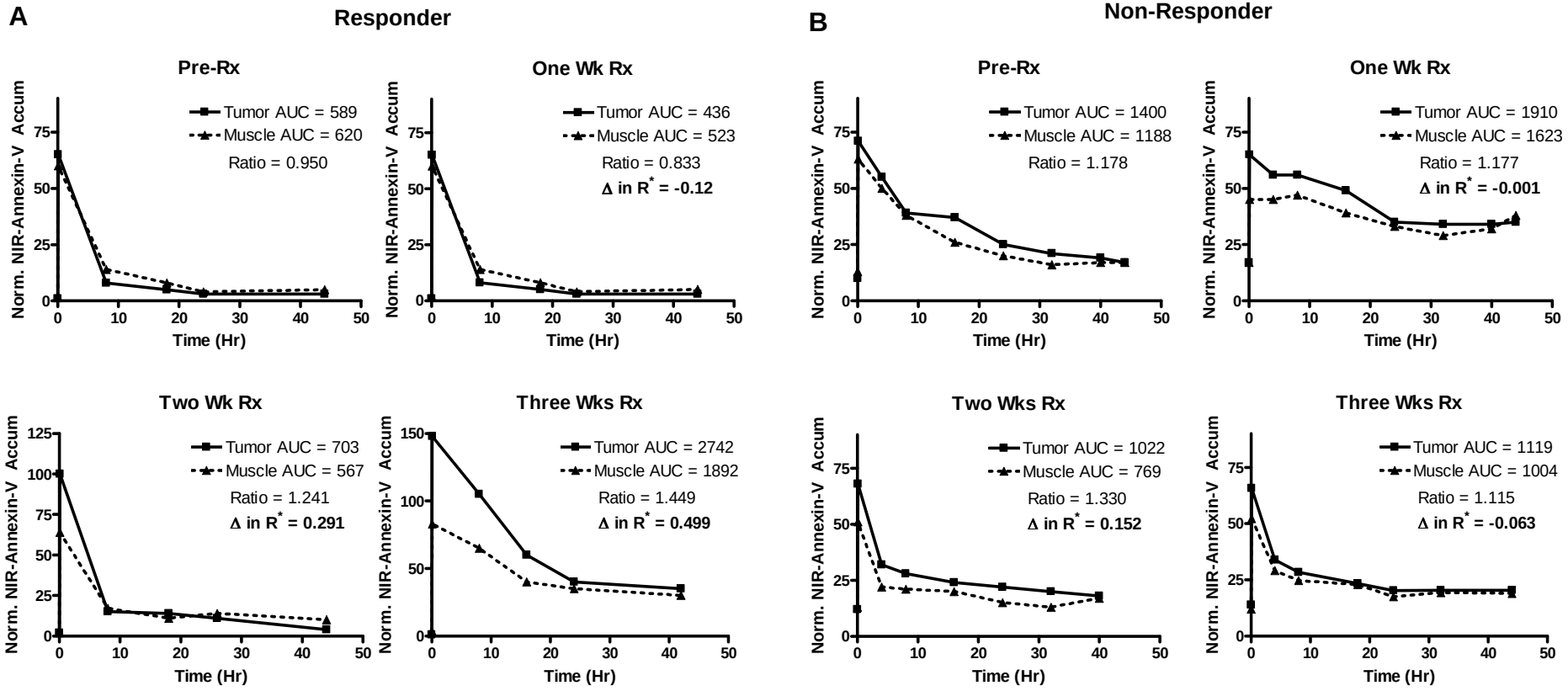
B



Supplement 1

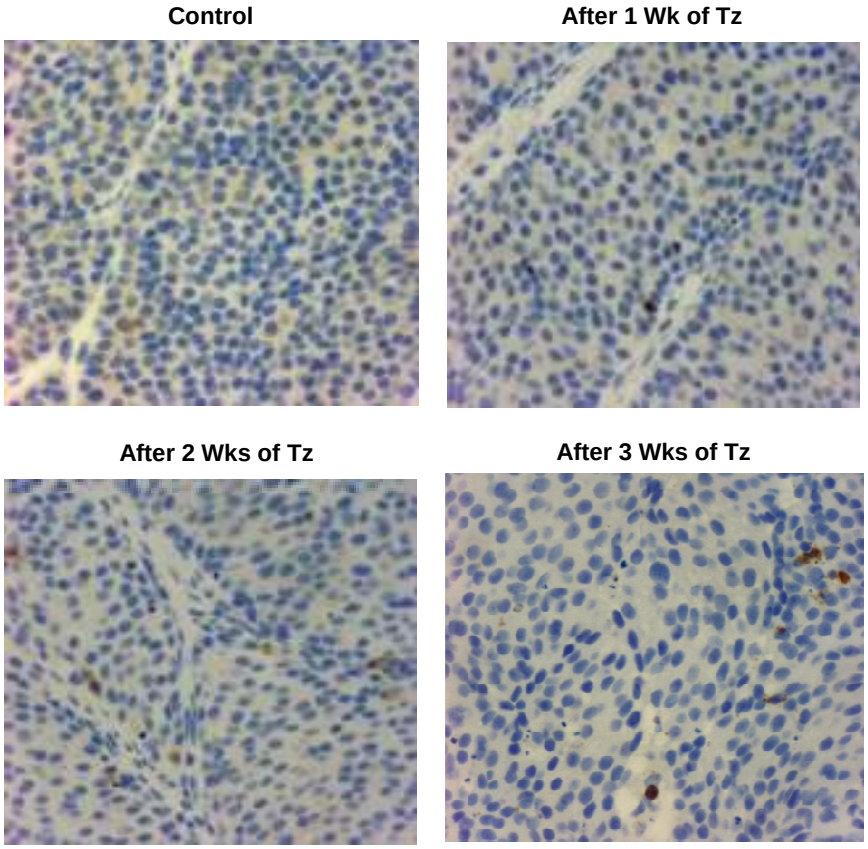


Supplement 2

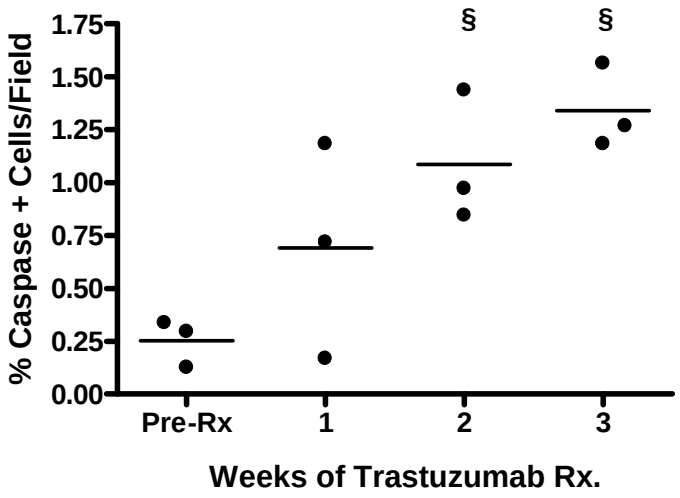


Supplement 3

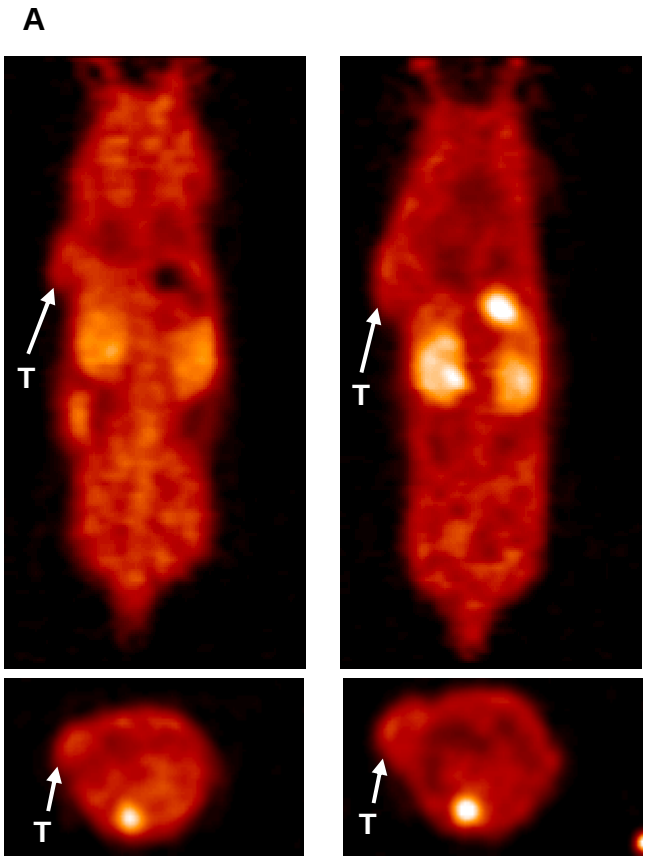
A

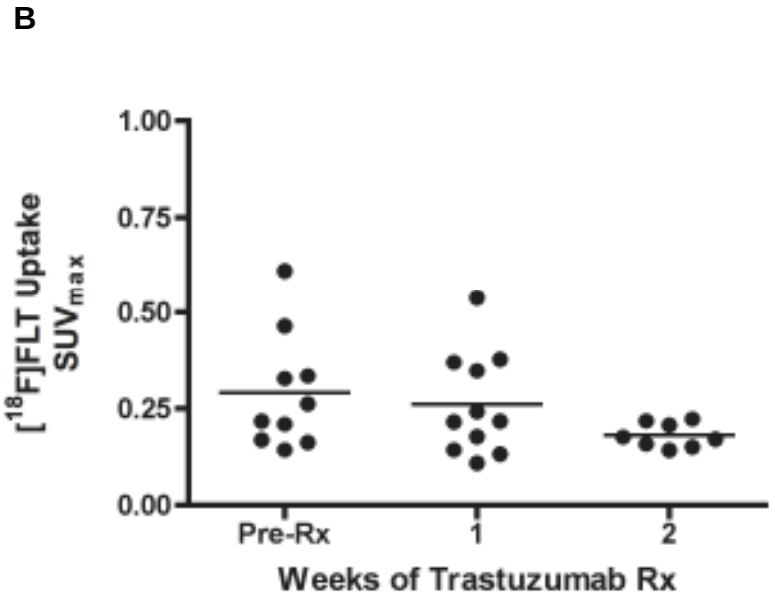


B

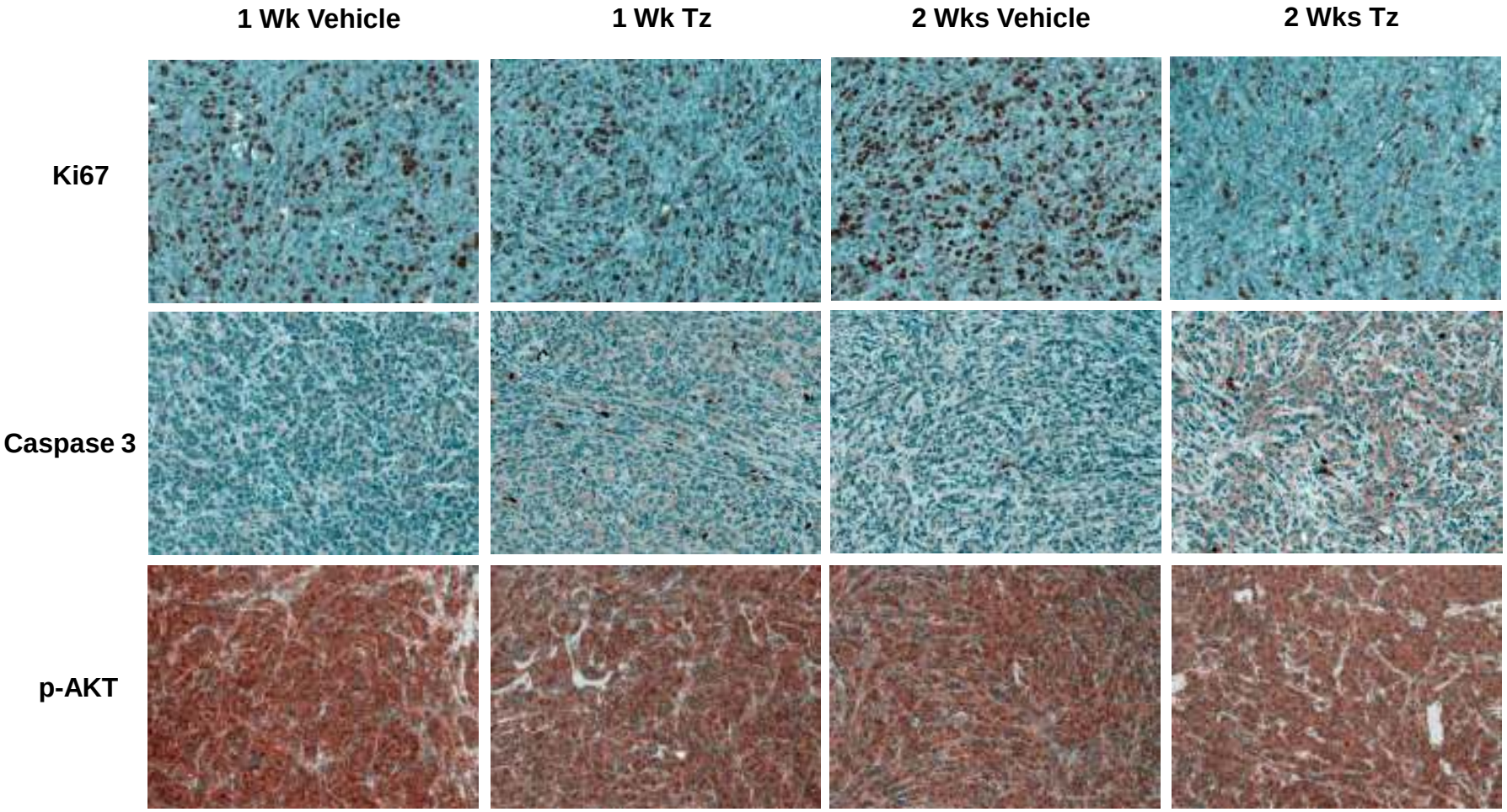


Supplement 4

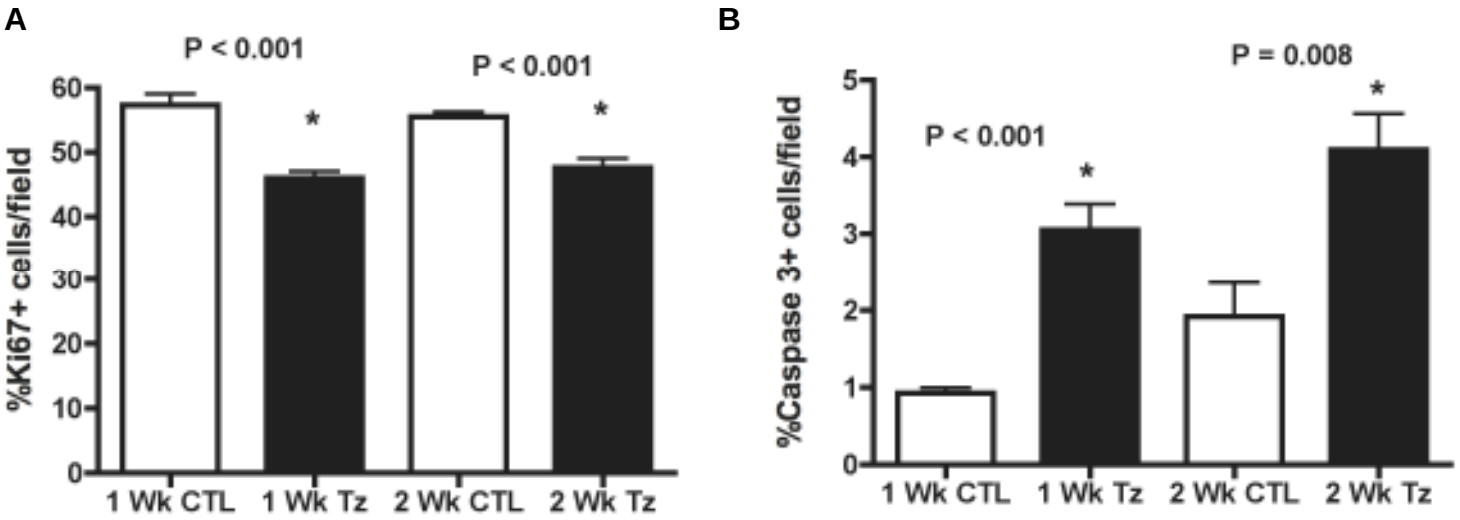




Supplement 5



Supplement 6



Supplement 7