Supplementary Figure 1: Cabozantinib treatment results in significant reduction in prostate tumor FDG-PET uptake and tumor volume in Pb-Cre; PTEN$^{fl/fl}$/p53$^{fl/fl}$ mice. Representative FDG-PET/MRI co-registration images showing the impact of cabozantinib on regression of prostate tumors in Pb-Cre; PTEN$^{fl/fl}$/p53$^{fl/fl}$ mice. Mice with established solid tumors >5mm in diameter were treated with cabozantinib 100 mg/kg by once daily oral gavage for 3 weeks. Left panel shows FDG-PET imaging alone; Middle panel shows co- registration of FDG-PET and MRI images; Right panel shows MRI images alone. Representative imaging from 6 mice are shown.

Supplementary Figure 2: A) Cabozantinib and PF-04217903 both abolish c-MET phosphorylation within PTEN/p53 deficient prostate tumors *in vivo*. Pb-Cre; PTEN/p53 mice were treated with either vehicle, PF-04217903 50 mg/kg or cabozantinib 100 mg/kg for 2 days, and tumor was harvested for phospho-Met IHC (n=3 mice/treatment group). **B) Cabozantinib induces extensive infiltration of granulocytic immune cells into the tumor bed within 48 hours of drug treatment.** Flow cytometry analysis of dissociated tumor show that CD11b^{+} myeloid cells are Ly6G^{hi}Ly6C^{lo}, indicative of granulocytic predominance of tumor-infiltrating immune cells with cabozantinib treatment. In this panel, CD11b^{+} cells were gated prior to Ly6G/Ly6C analysis. Representative data from n=3-4 mice per timepoint.

Supplementary Figure 3: A) Mass spectrometry analysis revealed an intratumoral cabozantinib concentration of 10 μM at 72 hours within PTEN/p53 deficient prostate tumors *in vivo*. Mice were treated with cabozantinib for the indicated times, and tumor metabolites extracted and subjected to mass spectrometry. **B) Phospho-RTK array analysis of PC3 cells reveals that cabozantinib inhibits multiple RTKs, in addition to c-MET, at physiologic concentrations.** PC3 cells were treated with vehicle or 10 μM cabozantinib for the indicated times, and cell lysates were analyzed by phospho-RTK array analysis.

Supplementary Figure 4: A) CXCL12 RNA *in situ* hybridization of tumors from mice acutely treated with cabozantinib for 24 hours revealed increased intratumoral CXCL12 expression. The staining was carried out as described in Figure 4C and the Methods section. Representative staining from n=3 mice per condition. **B) PTEN-wild type, p53 mutant human prostate cancer cells did not exhibit increased HMGB1 release following cabozantinib treatment.** VCaP, 22Rv1, and DU145 cells were treated with vehicle, cabozantinib (10 μM) or doxorubicin (1 μM) for 32 hours. Supernatants were analyzed for HMGB1 by ELISA.

Supplementary Figure 5: Cabozantinib treatment results in an acute increase in myeloid CD86-expressing antigen-presenting cells within prostate tumors. A) Pb-Cre; $PTEN^{fl/fl}/p53^{fl/fl}$ mice with established prostate tumors were treated with cabozantinib for the indicated times. Prostate tumor sections were stained with anti-CD86 antibody by IHC, which revealed increased CD86 staining with acute cabozantinib

treatment (n=3 mice per timepoint). B-C) Mice were treated with either vehicle or cabozantinib for 24 hours, and qRT-PCR on tumor RNA (B, n=3-4 mice per condition) and flow cytometry on intratumoral CD11b+ cells (C, representative data from n=3 experiments) was performed.

Supplementary Figure 6: Cabozantinib-mediated tumor clearance occurs via a T- and NK cell-independent mechanism. A) Acute cabozantinib treatment does not increase T- and NK cell infiltration into PTEN/p53 deficient prostate tumors. Pb-Cre; $PTEN^{fl/fl}/p53^{fl/fl}$ mice were treated with cabozantinib for 24 hours followed by tumor harvest and RNA extraction. qRT-PCR analysis was performed for CD3, CD4, CD8 and NKG2D mRNA (n=3 mice per condition). B) Flow cytometry analysis of splenocytes showing depletion of CD4 and CD8 T and NK cell populations following treatment with depleting antibodies, respectively. Representative data from n=3 mice/condition C) NKG2D qRT-PCR analysis showing complete intratumoral NK cell depletion following anti-sialo GM1 antibody pre-treatment and cabozantinib co-administration (n=3 mice/condition). D) CD4/CD8 and NK depletion, singly and in combination, did not reverse the tumor clearance elicited by cabozantinib. Mice were assigned to the following treatment arms: Panel A: vehicle; Panel B: single-agent cabozantinb treatment; Panel C: CD4 and CD8 depleting-antibody plus cabozantinib treatment; Panel D: NK depleting antibody plus cabozantinib treatment; Panel E: NK, CD4 and CD8 depleting-antibody plus cabozantinib treatment (see methods for details). At the end of the treatment, prostate tumors were stained with H&E. Representative data from n=3 mice/condition.

Supplementary Figure 7: Blockade of neutrophil chemotaxis/infiltration rescues cabozantinib-induced tumor regression. A-B) Pb-Cre $PTEN^{fl/fl}/p53^{fl/fl}$ mice with established solid tumors were enrolled into different treatment arms: vehicle; cabozantinb treatment by daily oral gavage for 2 weeks; Plerixafor (CXCR4 inhibitor) pre-treatment via osmotic pump for 3 days, followed by concomitant plerixafor/cabozantinib treatment for 2 weeks; concomitant 3E8 (HMGB1 neutralization antibody) every other day by intraperitoneal injection /cabozantinib by daily oral gavage for 2 weeks. The tumors were monitored by serial MRI at baseline, 1 week and 2 weeks post-treatment. The percent tumor volumes relative to baseline, were plotted as a function of time, and depicted as an averaged percent tumor volume relative to baseline (A) and Dot Plot (individual data points, B). C) Mice were treated as described in Part A, and H&E was performed on extracted tumors as indicated.

Supplementary Figure 8: **Blockade of neutrophil chemotaxis into the tumor bed attenuates the tumor clearance elicited by cabozantinib.** Pb-Cre $PTEN^{fl/fl}/p53^{fl/fl}$ mice were assigned to the following treatments. A-C: left: untreated control; middle: vehicle pre-treatment for 3 days, followed by cabozantinb treatment (100 mg/kg, daily oral gavage) for an additional 3 days; right: dexamethasone pre-treatment for 3 days (5 mg/kg, daily intraperitoneal injection), followed by concomitant dexamethasone/cabozantinib treatment for an additional 3 days. At the end of the treatment, prostate tumor sections were stained with H&E (n=3 mice per treatment cohort).