**Supplemental FIGURE legends**

**Figure S1. Additional data from high content screening. A)** Representative image acquisition by ImageXpress microscope of a well (four images) from 384 well plates. Left, negative control well. Right, epirubicin treatment. Blue, yellow and red dots represent separated nuclei from cells identified by cell profiler software. **B-F)** Survival assays in FA cells (FA primary fibroblasts, and three different FA HNSCC cell lines) for AEE788 (B), vandetanib (C), AZD9291 (D), CO1686 (E) and ceritinib (F). Graphs show mean +/- SEM of at least three independent experiments with similar results. Cell line legend shown in the upper right. G) Survival assay in cells treated with cetuximab (10 µg/ml). Graph shows mean +/- SEM of at least three independent experiments. H) Survival assay in non-FA HNSCC cell lines treated with afatinib. Graph shows mean +/- SD of two independent experiments.

**Figure S2. Additional data on gefitinib and afatinib *in vivo* mouse xenograft experiments. Weight control. A-D)** Body weight (upper panel) and percentage body weight (lower panel). A-B) Gefitinib treatment. C-D) Afatinib treatment. A, C) FA HNSCC 1604 cell line. B, D) FA HNSCC 1131 cell line. **E-L)** Tumor weight mean at end-point (E, G, I, K) and percentage of tumor volume change at baseline (start of treatment) (F, H, J, L) for individual tumors (from Figures 4A-B and 5A-B). E-H) Gefitinib treatment. I-L) Afatinib treatment. E, F, I, J) FA HNSCC 1604 cell line. (G, H, K, L) FA HNSCC 1131 cell line. The arrows indicate the start of the treatment. Dashed lines indicate transitions between RECIST categories. Dashed lines in F, H, J and L represent 20 % volume above and - 30 % below the X axis. All graphs show mean +/- SEM. Student’s T-test: \* p<0.05, \*\* p<0.01, \*\*\* p<0.001, \*\*\*\* p<0.0001.

**Figure S3. Additional immunohistochemistry images from tumor xenografts.** Immunohistochemistry of phospho-ERK activation in representative FFPE tumors from xenografts treated with vehicles or gefitinib (left) and afatinib (right) in 1604 (A) or 1131 (B) FA HNSCCs.

**Figure S4. Additional data on toxicity experiments in *Fanca*-deficient mice.** White blood cells (A, E), hemoglobin (B, F), hematocrit (C, G) at 0 and 14 days of vehicle, gefitinib or afatinib treatment. D) Percentage body weight from day 7 after reducing afatinib dosage. Dashed blue lines show physiologic range of white blood cells, hemoglobin or hematocrit. Graphs show data for individual mouse (green dots, wild type, red dots, *Fanca*-deficient) and mean +/- SEM. Student’s T-test: ns: not significant, \* p<0.05, \*\* p<0.01.

**Figure S5. FACS gating strategy to analyze white blood cell population in WT and *Fanca*-deficient mice.** Cells were gated (upper left dot plot) from FSC (forward scatter, cell size) and SSC (side scatter, cell complexity). Life cells were gated by DAPI exclusion (upper right dot plot). CD4+ and CD8+ T cells (medium left dot plot) were gated from CD3+ cells (medium right dot plot). Monocytes (MAC1+ GR1+) and granulocytes (MAC1- GR1+), in lower left dot plot, were gated from CD3- B220- cells (myeloid cells, medium right dot plot).

**Figure S6. Additional data on gefitinib and afatinib toxicity analysis in WT and *Fanca*-deficient mice.** **A-B)** B cells (B220+). **C-D)** T cells (CD3+). **E-F)** CD4+ T cells. **G-H)** CD8+ T cells. Cells were from blood of WT and *Fanca*-deficient mice, counted at 0 and 14 days of vehicle, gefitinib (A, C, E, G) or afatinib (B, D, F, H) treatments. Graphs show data for individual mouse (green dots, wild type, red dots, *Fanca*-deficient) and mean +/- SEM.

**Figure S7. Additional data on gefitinib and afatinib toxicity analysis in WT and *Fanca*-deficient mice. A-B)** Myeloid cells (CD3- and B220-). **C-D)** Monocytes (CD3- B220- GR1- MAC1+). **E-F)** Granulocytes (CD3- B220- GR1+ MAC1+). Cells were from blood of WT and *Fanca*-deficient mice, counted at 0 and 14 days of vehicle, gefitinib (A, C, E) or afatinib (B, D, F) treatments. Graphs show data for individual mouse (green dots, wild type, red dots, *Fanca*-deficient) and mean +/- SEM. Student’s T-test: \* p<0.05, \*\* p<0.01.

**Figure S8. Additional data on genotoxicity in blood samples from WT or *Fanca*-deficient mice, by gefitinib and afatinib treatment. A-B)** Percentage of reticulocytes (A) and reticulocytes with MN (B) in WT *vs* *Fanca*-deficient mice. **C-F)** Percentage of reticulocytes (C-D), and reticulocytes with MN (E-F) in WT and *Fanca*-deficient mice treated with vehicle, gefitinib or afatinib. Graphs show data for individual mouse (green dots, wild type, red dots, *Fanca*-deficient) and mean +/- SEM. Student’s T-test: ns: not significant, \* p<0.05, \*\*\*p<0.001.