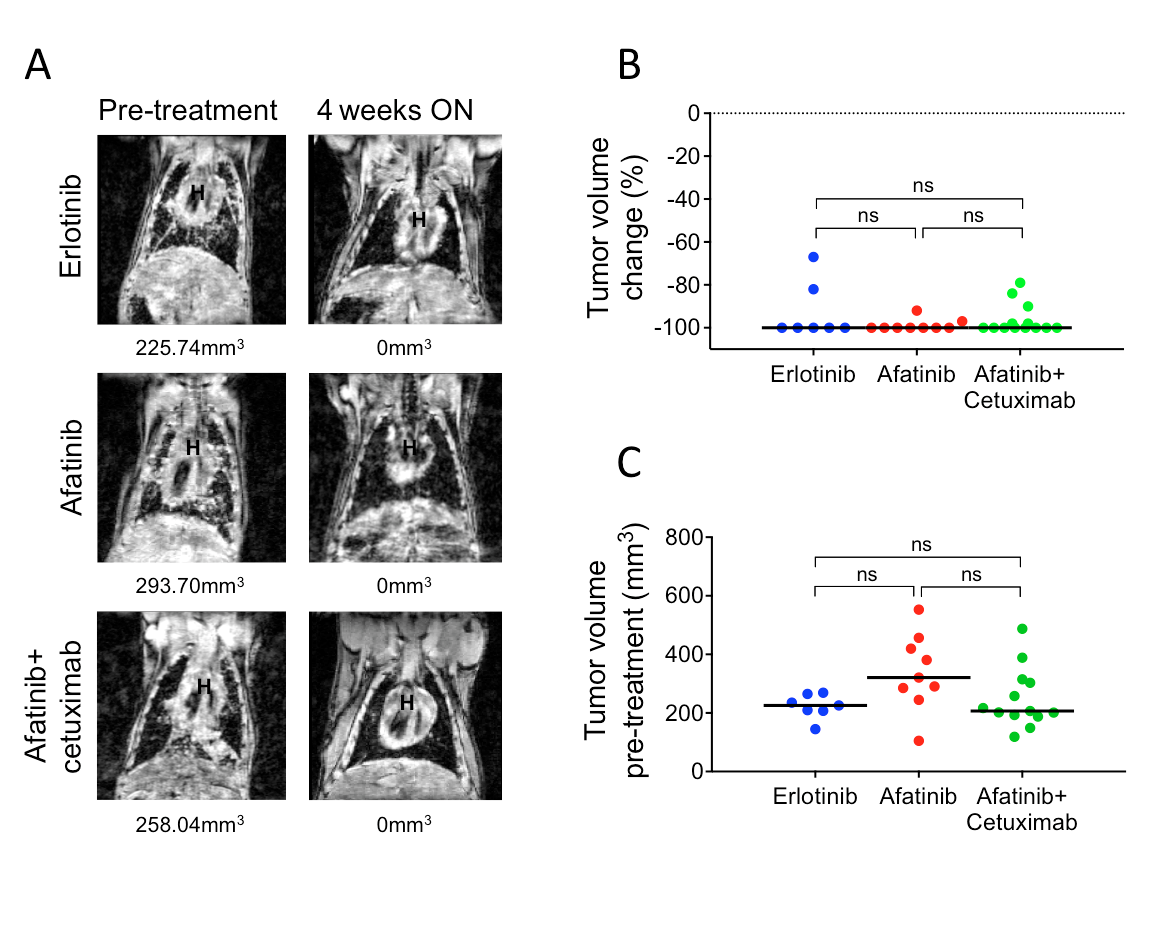
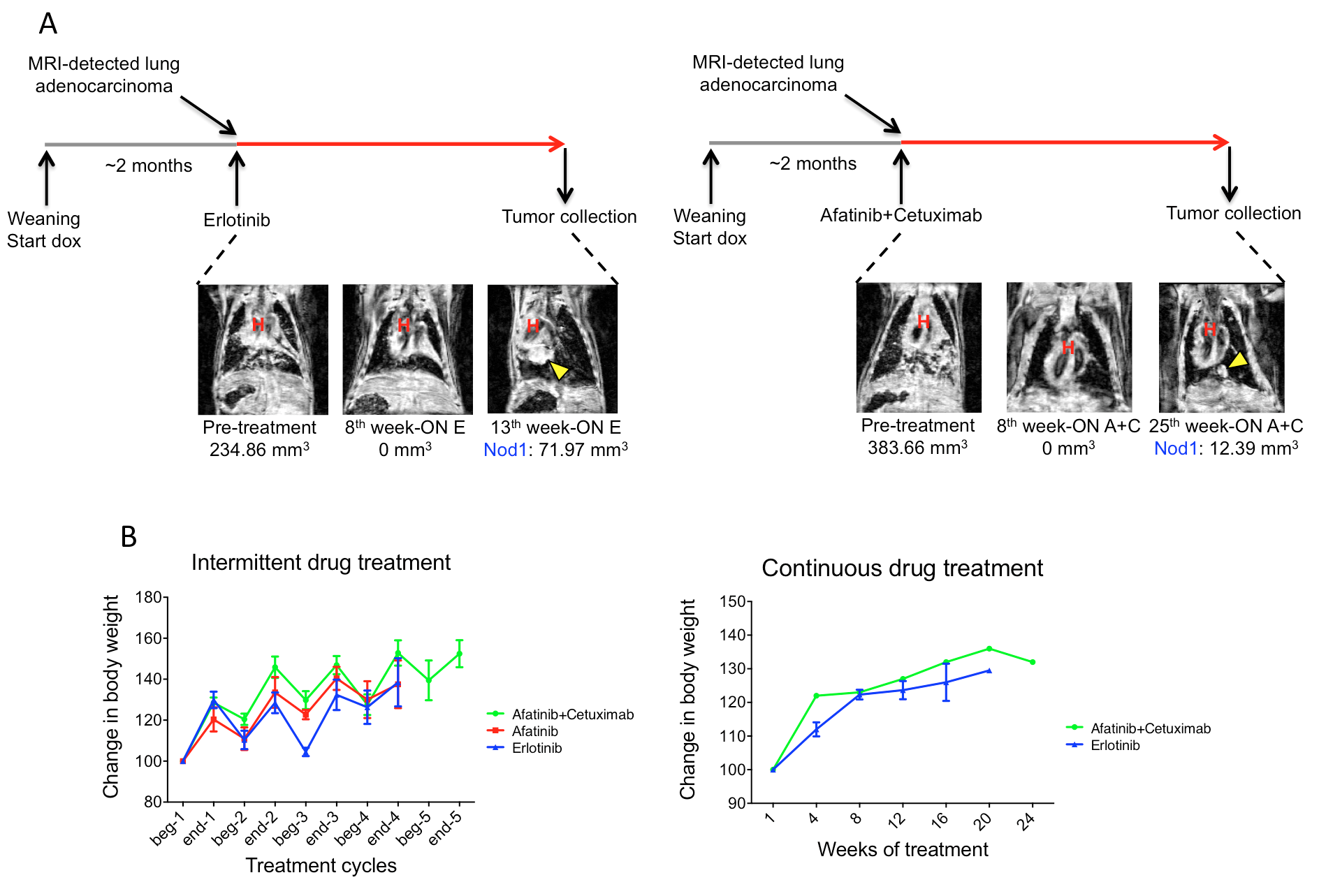
**SUPPLEMENTARY FIGURES**

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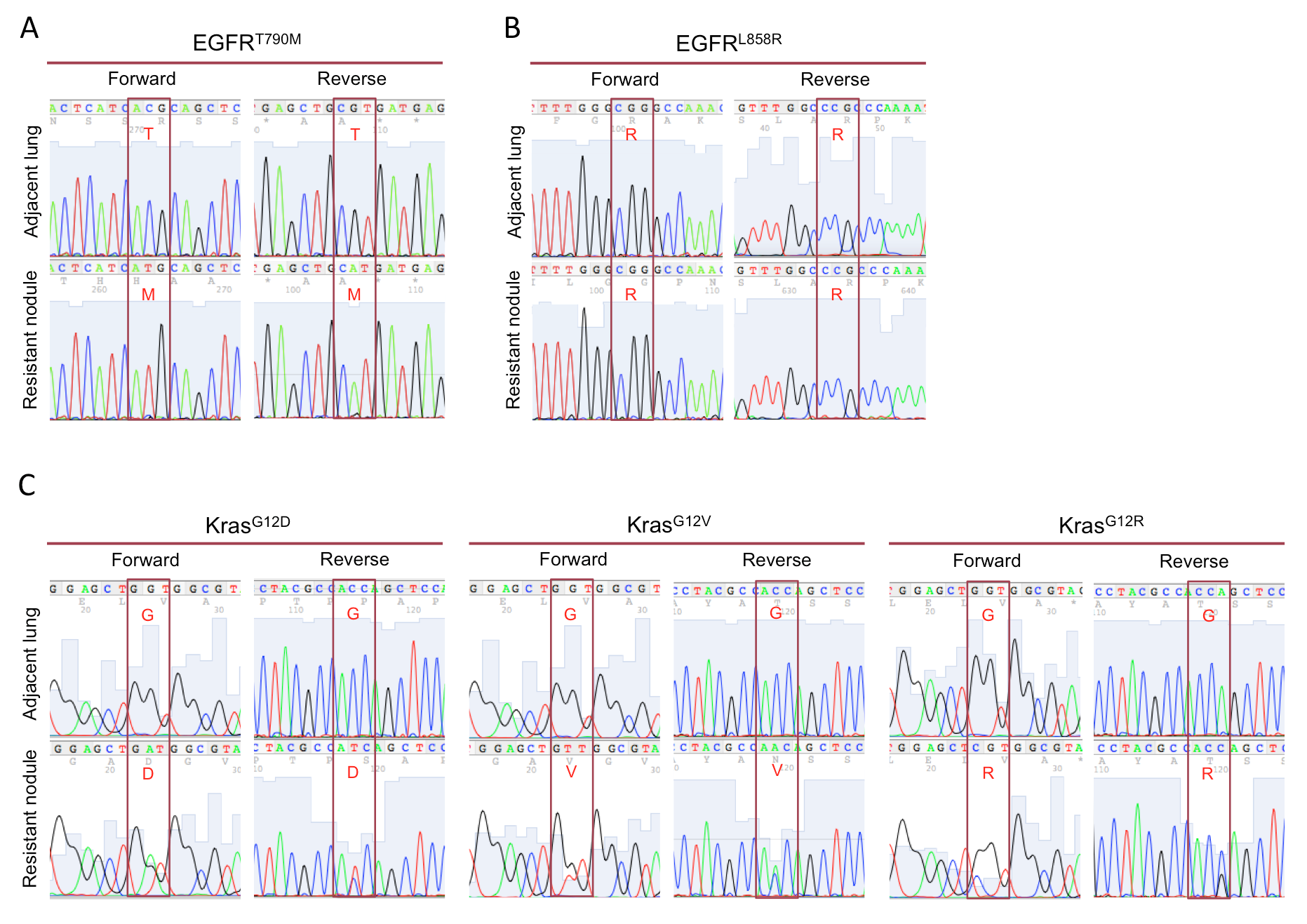
**Supplementary Figure S1**

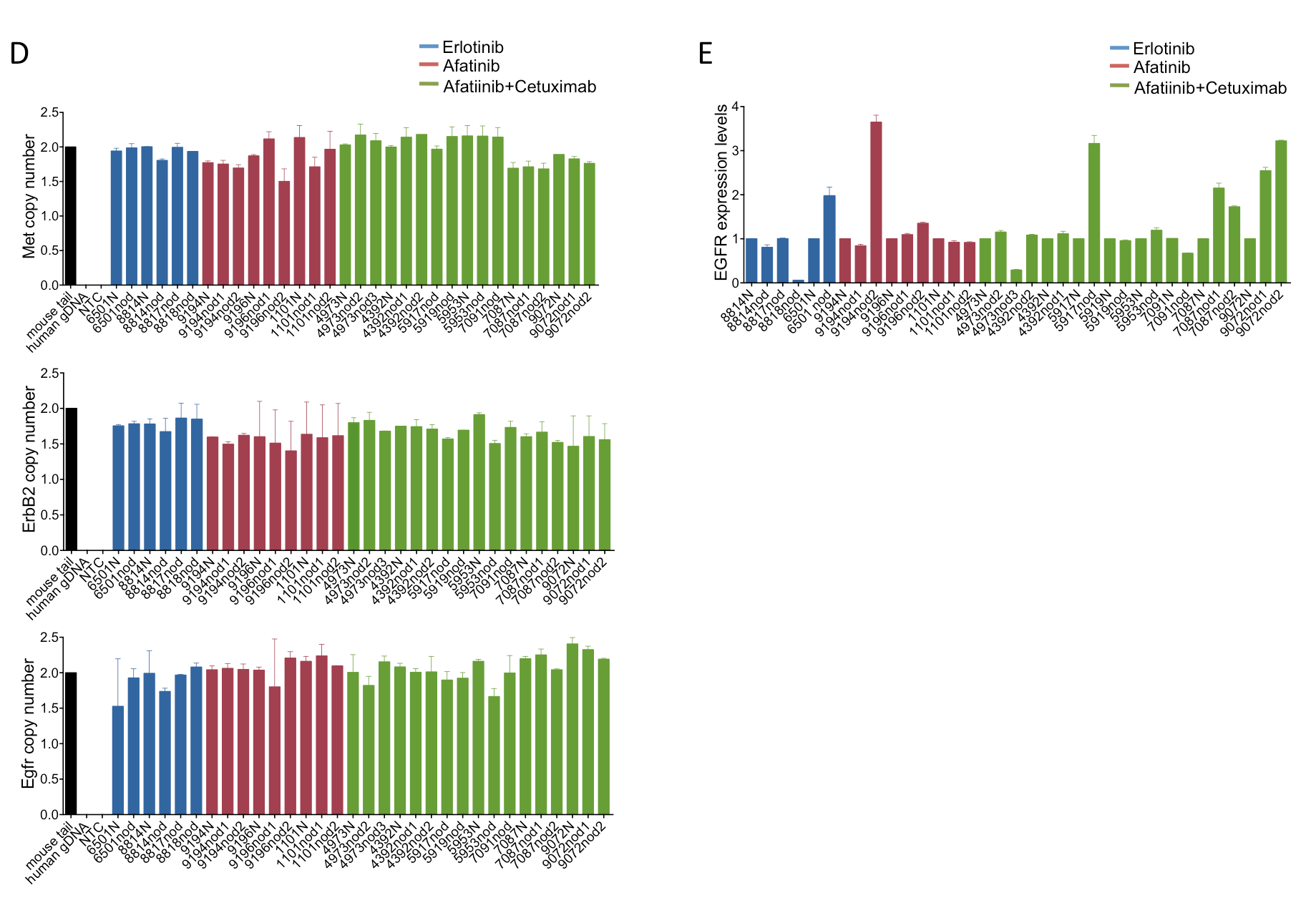
**A.** Coronal MR images of *CCSP-rtTA*; *TetO-EGFRL858R*mice pre-treatment and after 4 weeks of treatment with erlotinib, afatinib or afatinib plus cetuximab. Tumor volumes are shown at the bottom of the images. H= heart. **B.** Scatter plot showing the percent tumor shrinkage after 4 weeks of treatment on erlotinib, afatinib or afatinib plus cetuximab. One-way ANOVA Bonferroni multiple comparison test shows no statistical difference among the groups (p=ns). **C.** Scatter plot showing the initial tumor volumes in *CCSP-rtTA*; *TetO-EGFRL858R*mice used to study tumor recurrence after erlotinib, afatinib or afatinib plus cetuximab treatment. One-way ANOVA Bonferroni multiple comparison test shows no statistical difference among the groups (p=ns).



**Supplementary Figure S2**

**A.** Change in body weight during intermittent dosing. Values are plotted as the percentage of the pre-treatment mouse weight.

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**Supplementary Figure S3**

**Secondary mutations in EGFR in drug-resistant tumors. A.** DNA sequencing chromatograms showing the presence of the T790M mutation in a drug resistant nodule from a mouse treated with afatinib plus cetuximab. The mutation is not present in the normal adjacent lung. **B.** RepresentativeDNA sequencing chromatograms showing the presence of L858R in afatinib plus cetuximab resistant nodules. **C.** DNA sequencing chromatograms showing 3 *Kras* mutations found in the afatinib plus cetuximab-resistant nodules 5953, 7091 and 7087nod1 (G12D), 5917 (G12V) and 4392nod1 (G12R). The mutations are not present in the normal adjacent lung. **D.** Copy number assay for *Egfr*, *Her2* and *Met* in lung adenocarcinomas from *CCSP-rtTA*; *TetO-EGFRL858R* mice. Erlotinib resistant tumors are shown in blue, afatinib-resistant tumors are shown in red and afatibib+cetuximab-resistant tumors are shown in green. In black, genomic DNA from the tail of a C57BL/6J mouse used as “calibrator”. Two assays have been run for *ErbB2* and *Egfr*. The mean and standard error are shown for each sample. N= normal, nod= nodule, NTC= no template control. **E.** Expression levels of the *EGFR* transgene in the erlotinib-resistant (blue), afatinib-resistant (red) and afatinib plus cetuximab-resistant (green) tumors. Data are normalized to normal adjacent lung or tail of the same mouse. N= normal, nod= nodule.