Supplemental Figure S1. (A) Schema for ALK+ NSCLC patients included in this study of crizotinib-resistance. (B) PET/CT Imaging of patient #7 demonstrating a left adrenal gland metastasis prior to crizotinib (left), complete response by PET after 41 days of crizotinib (center), followed by regrowth after 197 days of crizotinib therapy at which time the adrenal gland was resected.

Supplemental Figure S2. DNA sequence analysis of ALK, EGFR, and KRAS mutations. (A) Forward (top) and reverse (middle) chromatograms from direct sequencing of *ALK* exon 25 amplified from genomic DNA (gDNA) demonstrating at GGA→GCA mutation (G1269A) in patient #7. Direct sequencing of the EML4-ALK (E6;A19) RT-PCR product is also shown (bottom). (B) Chromatogram from direct sequencing of *EGFR* exon 21 amplified from gDNA demonstrating a CTG→CGG mutation (L858R) in patient #9a. (C) Chromatogram from direct sequencing of *KRAS* exon 2 demonstrating at GGT→TGT mutation (G12C) in the cell line CUTO-1 derived from patient #10 (left). Chromatogram from direct sequencing of *KRAS* exon 2 demonstrating at GGT→TGT mutation (G12C) in pre-crizotinib biopsy from patient #10 (right). (D) Chromatogram from direct sequencing of *KRAS* exon 2 demonstrating at GGT→GTT mutation (G12V) in patient #11.

Supplemental Figure S3. A novel ALK gene rearrangement. (A) Chromatogram from direct sequencing of an RT-PCR reaction demonstrating exon 6 of *EML4* fused to exon 19 of *ALK* from patient #7. (B) Chromatogram from direct sequencing of an RT-PCR reaction demonstrating exon 6 of *EML4* fused to exon 20 of *ALK* from patient #6 for comparison.

Supplemental Figure S4. Soft agar colony formation by NIH3T3 cells expressing *EML4-ALK* (E6;A20) with non-mutated *ALK*, G1269A, L1196M, or C1156Y in the presence of increasing doses of crizotinib. Photographs of soft agar plates are displayed in (A). Colony counts are plotted against crizotinib dose in (B).

Supplemental Figure S5. FISH analysis of patient #10 before crizotinib treatment (A) and after progression on crizotinib treatment (B) demonstrating a similar pattern of split green (5') and red (3') *ALK* signals in tumor cells.