**Supplementary Figure Legends**

**Supplementary Figure S1. Timelines for acquired resistance and resensitization.** (A) Parental ALK+ lines were plated initially in low concentrations of either crizotinib or ceritinib and passaged every 3-5 days. When able to proliferate at a given concentration, drug was increased as indicated. “Drug removal” indicates time of passaging required in drug free media for cells to lose inhibitor dependence (required initial plating at ≥106/mL in all cases). (B) Morphology of cells from Fig. 1D on Day 4 (scale bar 200μm).

**Supplementary Figure S2. Assessment of copy number changes in additional subclones.** Copy number assessed as in Fig. 2B. *p<0.01*, \**p<0.05*, NS *p≥*0.05 (t-test).

**Supplementary Figure S3. RS lines behave like original parent cells with return of ALK expression to baseline.** Immunoblotting of resensitized subclones (as Fig. 2E).

**Supplementary Figure S4. Reselection of resensitized cells again selects for up-regulation of NPM-ALK and the resistant-dependent phenotype.** A, Timeline for reacquired resistance appended to the timeline from Supplementary Fig. S1. B, Cell viability in response to ALK inhibition, with original parent lines for comparison. C and D, proliferation (as Fig. 1D) and apoptosis assays (as Fig. 1G). E, copy-number assays (as Fig. 2B). F, increased *NPM-ALK* mRNA expression in reselected subclone (as Fig. 2C). Means of technical quadrupicates (B) or independent triplicates (C-D) or technical triplicates (E-F) ±SEM. For apoptosis assays (D), \**p*=0.05 (Mann-Whitney). For expression data (E) and (F): *p<0.01*, \**p<0.05*, NS *p≥*0.05 (t-test).

**Supplementary Figure S5. Assessing whether an up-front intermittent dosing regimen prolongs tumor control in vivo.** Mean tumor burden of mice injected with 2x106 Karpas-299 cells and treated with vehicle, continuously with ceritinib or intermittently with ceritinib (‘4 weeks on, 2 weeks off’) at the indicated concentrations (n=3 per group). Due to limited amounts of ceritinib, we halted dosing the 50mg/kg cohorts on Day 65.