Supplementary Figure S3. Validation experiments in preclinical models of acquired resistance to targeted agents *A, Proliferation assays of cell line models of acquired resistance*

*and parental counterparts in response to targeted therapies. Data are average ± SD of three technical replicates and are representative of three independent experiments. **B**, siRNA-mediated depletion of WRN was verified by Western blot (images are representative of two independent experiments). siRNA non-targeting controls (siNTC), siRNA targeting WRN (siWRN). Tubulin is a loading control. **C**, Reduction in WRN protein levels with two independent WRN-targeting sgRNAs confirmed by Western blot (images are representative of two independent experiments). **D**, Sequenom sequencing spectrum of VACO432 C+D+T cell model revealing an acquired KRAS G13D mutation in addition to the BRAF V600E mutation shared with the parental counterpart. **E**, Schematic representation of a patient-derived NTRK1-rearranged in vivo model of acquired resistance to entrectinib. **F**, Proliferation assays of IRCC-1-XL and IRCC1-XL-ENT-R cell lines treated with entrectinib. Data are average ± SD of three technical replicates and are representative of three independent experiments. **G**, Representative images of IRCC-1-XL-ENT-R line after 96h from transduction with non-essential gene targeting sgRNA (sgNon). Metaphases were karyotyped based on DAPI-banding patterns and visualized by microscopy. No alterations were detected.*