Figure S1. Drug sensitivity of HER2 or KRAS mutations in soft agar colony formation assay.

A, IMCE expressed either HER2 WT or mutants were seeded in soft agar in duplicates, treated in the presence or absence of trastuzumab (100ug/ml) or neratinib (500nM). Colonies allowed to grow for 12 days and then stained with crystal violet.

B, IMCE-KRAS, IMCE-HER2 WT and IMCE-HER2 V842I cells were treated with the indicated doses of neratinib and allowed to grow for 12 days. The effect of neratinib on colony formation was quantified and graphed.
Figure S2. Tumor growth curves in mice injected with NCI-H508 cells and treated with the indicated drugs.
Drug treatment was started on day 0 and n = 5 for each treatment arm. Error bars represent the standard errors of the mean (SEM).
Figure S3. Neratinib sensitivity of KRAS WT and KRAS mutant colorectal cancer lines.
DIFI and NCI-H508 cells are KRAS WT. SW480 cells have a KRAS G12V mutation and HCT116 cells have a KRAS G13D mutation. Neratinib was added at the indicated doses and cell growth was measured after 5 days by Alamar blue.
Figure S4. HER2 mutant PDX’s are cetuximab resistant.
PDX’s are treated with cetuximab 20mg/kg twice weekly or placebo. Drug treatment was started on day 0 and n = 6 for each treatment arm. Error bars represent the SEM.
Figure S5. Hematoxylin-and-eosin (H&E) staining and immunohistochemistry on PDX M122 at the end of treatment.
NER, neratinib; LAP, lapatinib; TRAS, trastuzumab.
Figure S6. Hematoxylin-and-eosin (H&E) staining and immunohistochemistry on PDX M051 at the end of treatment.
NER, neratinib; TRAS, trastuzumab.
Figure S7. HER2 L866M is an activating mutation that confers resistance to cetuximab, and is sensitive to neratinib. 
A, IMCE HER2 WT or L866M cells were serum starved for 6 hours. Cell lysates were prepared and analyzed by western blot. B-C, DIFI cells transduced with HER2 WT, V842I, or L866M were treated with panitumumab (B) or neratinib (C) for 5 days and cell growth was measured by Alamar blue.
Figure S8. HER2 S310F is more sensitive to trastuzumab than HER2 L866M.
NCI-H508 cells expressing HER2 WT, S310F, L866M cells were treated with trastuzumab for 5 days and cell growth was measured by Alamar blue.