**Materials.** HCC-95 was obtained from Dr. John Minna (University of Texas Southwestern, Dallas, TX). All other cell lines were obtained from ATCC (Manassas, VA). TaqMan real-time PCR probes, cell culture media, plastic wares and puromycin were obtained from ThermoFisher Scientific (Waltham, MA). Receptor tyrosine kinase and phospho-kinase profiling arrays were obtained from R&D Systems Inc (Minneapolis, MN). Antibodies to AKT (9272S), pAKT S473 (4060S), p*ERBB3* Y1289 (4791S) and *ERBB3* (12708S) were obtained from Cell Signaling Technologies (Beverly, MA). Alpha-tubulin antibody (T9026) and all other chemicals were purchased from Sigma-Aldrich (St. Louis, MO). Primers for RT-PCR were obtained from Integrated DNA Technologies (Coralville, IA). Apo-ONE homogenous caspase 3/7 activity assay kit and CellTiter-Glo Luminescent Cell Viability Assay were purchased from Promega (Madison, WI). Complete protease inhibitor cocktail and PhosSTOP phosphatase inhibitors were from Roche (Germany). RIPA lysis buffer was obtained from Teknova (Hollister, CA). Fetal bovine serum (FBS) was obtained from Atlanta Biologicals (Flowery Branch, GA). Afatinib, erlotinib, and neratinib (HKI-272) were purchased from Selleckchem (Houston, TX).

**Molecular Profiling.** To detect somatic structural aberrations using MSK-IMPACT, a framework was developed that first aligns raw reads to the reference human genome (hg19) using the Burrows-Wheeler Alignment tool. Duplicates are then filtered using the Picard-tools java package (samtools) and searched for candidate structural rearrangements using DELLY. All candidate somatic structural aberrations were filtered, annotated using in-house tools, and manually reviewed using the Integrative Genomics Viewer (IGV).

To identify a lung cancer cell line with aberrant expression of *NRG1*, 67 lung cancer cell lines were screened using microarray expression data (GEO, accession number series GSE32989), thus identifying HCC-95 as overexpressing *NRG1*. Analysis of copy number alterations of the genome of HCC-95 (BC Cancer Agency Sub-Megabase Resolution Tiling Path Array) revealed that *NRG1* resides in an area of amplification in chromosome 8 (Figure 2B).

**RT-PCR.** We used forward primers targeting *DOC4* exon 11-12 junction and reverse primers targeting *NRG1* exon 3 to detect the presence of the *DOC4-NRG1* fusion: TGGATTCAGGAATCTGGCACTTGG (*DOC4* exon11-12 forward) and CTGATCACTTTGCACATATACTC (*NRG* exon 3 reverse).

**shRNA infection, proliferation and caspase 3/7 activity assay.** To generate growth curves for cells treated with GSK2849330 or control IgG, MDA-MB-175-VII (500 cells/well), HCC-95 (200 cells/well), NCI-H292 (200 cells/well) and MCF7 (300 cells/well) were plated in 96-well plate (Nunc 136102) in triplicate. One day after plating, the cells were treated with a final concentration of 10 µg/mL GSK2849330 or Epo-Fix AccretamAb IgG (control IgG). Cell proliferation was measured using CellTiter-Glo Luminescent Cell Viability Assay (Promega) on days 0, 3, 6, 8, 10, and 13 following manufacturer’s instructions. For shRNA infection, 250,000 cells were plated in 6-well plates and then infected 24h later with viral supernatant (MOI=5) containing 10 µg/mL polybrene. Infected cells were selected with 5 µg/mL puromycin then replated at a density of 10,000 cells per well (6-well plates) and counted after 7 days of growth. For caspase 3/7 activation assay, 25,000 of puromycin-selected cells were plated in white clear bottom 96-well plates and then caspase 3/7 enzymatic activity measured the APO-ONE homogenous caspase 3/7 activity assay kit (Promega). There were 3 replicates of each condition.

**Protein isolation and western blot.** One million cells were seeded in 10 cm dishes. One day after plating cells were treated with 10 µg/mL GSK2849330 or Epo-Fix AccretamAb IgG. Some of the dishes were treated with 20 ng/mL heregulin 30 min following antibody addition. Thirty minute after heregulin treatment (or 1 h after antibody addition) the cells were scraped and transferred to a 15 mL Falcon tube and pelleted by centrifugation (1000 x g for 5 min). Cell pellets were washed in ice cold PBS twice and lysed in 80 µL RIPA buffer (Teknova R3792) supplemented with Complete protease inhibitor cocktail (Roche 04693124001) and PhosSTOP (Roche 04906837001). The lysates were sonicated then centrifuged at 14000 xg, 4oC for 5 min. Protein concentration in the supernatants were estimated using BCA assay (Thermo scientific). Twenty micrograms of the protein was resolved on 4-12 % Bis-Tris mini gels (Nupage) by SDS-PAGE and transferred electrophoretically to nitrocellulose membrane using iBlot. Blots were blocked in Odyssey blocking Buffer (Li-Cor, N2381) then incubated with primary antibody overnight. Membranes were incubated with IRDye 680RD goat anti-mouse or IRDye 800CW Goat anti-rabbit secondary antibodies and scanned using Odyssey-Li-Cor, Infrared Imager. Images were analyzed using the Odyssey software.

**Patient-derived xenograft generation and treatment.** The ovarian PDX model OV-10-0050 was originally established from a surgically resected clinical sample. Each mouse was implanted subcutaneously at the right flank with the OV-10-0050 P4 tumor slices (~30 mm3) for tumor development. The treatments were started on day 35 after tumor implantation when the average tumor size reached approximately 163 mm3. All the procedures related to animal handling, care and the treatment in the study were performed according to the guidelines approved by the Institutional Animal Care and Use Committee (IACUC). Mice were treated with vehicle, an IgG control, or the anti-*ERBB3* monoclonal antibody GSK2849330 at 25 mg/kg. Tumor size was measured twice weekly in two dimensions. The volume was expressed in mm3 using the formula: V = 0.5 *a* x *b*2 where *a* and *b* are the long and short diameters of the tumor, respectively. The tumor size was then used for calculations of both T-C and T/C values. T-C was calculated with T as the median time (in days) required for the treatment group tumors to reach a predetermined size (e.g., 1,000 mm3), and C as the median time (in days) for the control group tumors to reach the same size. The T/C value (in percent) is an indication of antitumor effectiveness; T and C are the mean volumes of the treated and control groups, respectively, on a given day. TGI was calculated for each group using the formula: TGI (%) = [1-(Ti-T0)/ (Vi-V0)] ×100; Ti is the average tumor volume of a treatment group on a given day, T0 is the average tumor volume of the treatment group on the day of treatment start, Vi is the average tumor volume of the vehicle control group on the same day with Ti, and V0 is the average tumor volume of the vehicle group on the day of treatment start. The mean tumor size of the vehicle treated control mice reached 1,092 mm3 at day 35 after treatment.

**Fusion gene analysis for TCGA samples**. A total of 8,984 cancer samples from 33 different cancer types in TCGA were analyzed using the MediSapiens FusionSCOUT fusion gene detection pipeline. Fastq files were used whenever available for a sample, with use of BAM files, converted back into fastq, otherwise. Briefly, sequences were aligned against all human transcripts in Ensembl database version 75 using the Bowtie2 aligner. Discordantly aligning read pairs were filtered by alignment against the human genome and passing read pairs used to identify candidate fusion gene-gene pairs. Candidate fusion genes were filtered based on gene-gene distance, sequence homology, either partner being annotated as a pseudogene and presence of the fusion in RNA-seq data from ~600 normal tissue samples from the TCGA project. The exact exon-exon fusion junctions were identified by constructing all possible exon-exon combinations between each pair of genes, followed by alignment of unmapped reads against the synthetic junctions. Only junction reads for which the pair aligned to one of the two partner genes in the expected orientation were accepted. As a final filtering step, reads were filtered based on the pattern of alignment start positions of the junction spanning reads. Reading frame status for fusions was predicted based on the end and start phases of junction exons. *NRG1* expression by cancer type was drawn using the RSEM scaled estimate expression values from Broad Institute GDAC Firehose pipeline run 2015/11/01.

**Expression and copy number analysis of non-small cell lung cancer cell lines.**  Gene expression microarray data (Illumina HumanWG-6 v2.0) for 67 NSCLC cell lines was downloaded from the Gene Expression Omnibus (GEO, Accession number Series GSE32989). Log2 intensity values for *NRG1* were subsequently normalized across all cell lines and the resulting values plotted using Graphpad Prism software. Copy number data (BC Cancer Agency Sub-Megabase Resolution Tiling Path Array) for HCC-95 was downloaded from GEO (GSE2922) and each array element was mapped to genomic position (NCBI 36). Normalized log2 intensity values were subsequently plotted according to genomic position and circular representations were generated using Circos.