**Supplemental Methods**

**MSK-Ampliseq**

An amplicon-capture based next generation sequencing assay, was used to identify specific mutations in 98 genes. The specific mutations are detected by amplifying genomic DNA with the MSK-AmpliSeq custom panel and sequencing on the Personal Genome Machine (PGM) system.

**Gene Analyses**

Genes were queried for enrichment among the pre and post-treatment groups. Unless otherwise noted, analysis included previously described oncogenic/likely oncogenic variants and variants of unknown significance. Cancer cell fractions (CCF) were determined using the FACETS algorithm1 (version 0.5.6). Tumor purity- and ploidy-adjusted allelic copy number estimates were calculated with the following parameters; cval = 50, min.nhet = 15, ndepth = 25, snp.nbhd = 250, seed = 100. Based on these allelic copy number estimates, we used the PyClone Bayesian statistical framework2 to elucidate clonal population structure, where somatic mutations are grouped into clonal clusters based on CCF using default parameters.

**Material.** The PC9 cell line was obtained from RIKEN Bioresource Center (Japan). HCC827 was obtained from American Type Culture Collection (Manassas, VA). All cell lines were routinely tested for mycoplasma and identify verified. Media, phosphate-buffered saline and antibiotics for cell culture were obtained from the MSK Media preparation Core Facility. Phospho-specific and total antibodies were obtained from Cell Signaling Technology (CST, Danvers, MA). All PCR primers were obtained from Integrated DNA Technologies (Coralville, Iowa). Molecular biology and Western blotting reagents were obtained from ThermoFisher Scientific. All kinase inhibitors were obtained from Selleckchem (Houston, TX), dissolved in dimethyl sulfoxide and stored at 10 mM stock concentration at -20 oC for up to 6 months. All plasmids were obtained from Addgene (Boston, MA).

**Cell culture and growth inhibition assays.** Cells were grown in RPMI-1640 supplemented with 1% antibiotics and 10% FBS, in a humidified incubator at 37oC with 5% CO2 and 95% air. For viability studies cells were plated directly into the desired concentration of drugs, at a density of 5,000 cells per well of 96-well plates, and viability determined 96 h later using alamarBlue. Fluorescence (Ex: 530 nm, Em: 570 nm) was measured using a SpectraMax M2 micro-plate reader (Molecular Devices). There were 3 replicates of each condition in each experiment. Results are the mean± SD/SE of 2-3 independent experiments. Viability data was analyzed by nonlinear regression using GraphPad Prism.

**Western blotting**. Protein expression levels were examined by Western blotting. Total cellular proteins were extracted using RIPA buffer supplemented with protease and phosphatase inhibitors and subjected to SDS-PAGE. Separated proteins were transferred onto PVDF membranes, and incubated with primary antibodies overnight as follows: (#8198, 1:1000 dilution), phospho-MET (#3077, 1:1000 dilution), EGFR (#4267, 1:1000 dilution), phospho-EGFR (#2234, 1:1000 dilution, CST), MTOR (#2972, 1:1000 dilution), phospho-MTOR (#2971, 1:1000 dilution), ERK (#9102, 1:1000 dilution), phospho-ERK (#9101, 1:1000 dilution), AKT (#9272, 1:1000 dilution), phospho-AKT (#4060, 1:1000 dilution) S6 ribosomal protein (#2217, 1:1000 dilution), phospho-S6 (#5364, 1:1000 dilution), p70 S6 kinase (#2708, 1:1000 dilution), phosphor-p70 S6 kinase (#9208, 1:1000 dilution), 4E-BP1 (#9644, 1:1000 dilution), phospho-4E-BP1 (#2855, 1:1000 dilution), and bands detected using enhanced chemiluminescence.

**Construction of expression plasmids**. Full-length wild-type human MET in pDONR223 (Plasmid #23889) and all MET mutants were cloned into pLX303 (plasmid#25897) by LR reaction (Thermo Fisher). Full-length wild-type human EGFR in pDONR223 (Plasmid #23935) and EGFR L858R mutation were cloned into pLenti CMV Blast DEST (plasmid#17451) by LR reaction. Full-length wild-type human mTOR in R777-E137 (Plasmid #70421) and mTOR A1098S mutation were cloned into pLenti PGK Hygro DEST (#19066) by LR reaction.

MET mutants (H1094Y, H1094R, and K1110A), EGFR-SV768IL and mTOR-A1098S were generated by PCR amplification using QuickChange Lightning (Agilent) according to manufacturer’s protocol. Primer sequences are listed in Supplemental Table 2.

**Production and transduction of lentiviruses**. High titer lentiviruses were generated by transient co-transfection of HEK-293T cells with a three-plasmid combination. 1 x 107 HEK-293T cells was transfected using FuGENE (Promega) with 10 µg lentiviral vector, 8 µg psPAX2 (Plasmid #12260, Addgene), and 2 µg VSVG (Plasmid #14888, Addgene). Supernatants were collected every 24 hours from 48 to 96 hours after transfection, filtered through 0.45 μm filter (Millipore, Bedford, MA). For lentiviral Transduction, 1x105 cells/well were seeded in 6 well plates and infected with lentiviruses. Infections were performed for 24 h in the presence of 10 µg/ml polybrene. The transfected cells were selected for 7 days with 20 µg/ul of blasticidin or 250 µg/ml hygromycin.

**Caspase assay**. Caspase 3/7 enzymatic activity was measured in cell homogenates using the ApoOne Homogenous Caspase assay kit from Promega according to manufacturer’s protocol. Cells were seeded in 96 well plates at a density of 30,000 cells per well and incubated for 72 h. Reagent were added to wells and incubated 1 h at room temperature. There were 3 replicates of each condition in each experiment. Results are the mean± SD/SE of 2-3 independent experiments. Results were analyzed by t-test for statistical significance.

References

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