**Supplementary Materials and Methods**

**Antibodies and Reagents**

MET(8198), pY1349MET(3133), pY1234/1235MET(3077), pERK1/2(4370), ERK1/2(9102), pMEK1/2(9154), MEK1/2(4694) pAKTS473(4060) are purchased from Cell Signaling Technology (Danvers, MA). GAPDH(sc-25778), Redd1(sc-67051), β-actin(sc-47778) are purchased from Santa Cruz Biotechnology (Santa Cruz, CA). α-tubulin (GTX 102078, GeneTex), HSP90 (500494, Origene) and β-catenin (610154, BD Biosciences). Fluorescent secondary antibodies Goat Anti-Mouse IgG(H+L) Dylight 800 Conjugated (35521). Goat Anti-Rabbit IgG(H+L) Dylight 680 Conjugated (35568), Chicken-Anti-Mouse IgG Sencondary antibody, Alexa Fluor 488 conjugate (A21200) and Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 594 conjugate (A11072) are purchased from Thermo Sci., TTF1 (SC-13040, Santa Cruz Biotechnology), ki-67(550609, BD Pharmingen), HGF (100-39, PeproTech, Rocky Hill, NJ).

**Plasmids and Virus**

pCDNA3-*MET* wt-3XFlag was from Dr. Sourav Bandyopadhyay. pBABE-*Met* and pBABE TPR-MET were from Addgene, deposited by ([1](#_ENREF_1)) ([2](#_ENREF_2)). *MET* sequence was amplified from original plasmids and inserted into pENTR using D-TOPO cloning kit according to manual instructions (K2400-20, Life Technologies). pENTR GFP, pENTR RFP are from the PEL-CCP collection, a generous gift from Frederick National Laboratory for Cancer Research. Point mutations and indel mutations including pENTR *MET*Δ14-3XFlag, pENTR *Met*Δ15, pENTR *TPR-MET* ex14wt and pENTR *TPR-MET* ex14Y1003F were made through the In-fusion reaction (In-Fusion HD Cloning Kit, 639648, Clontech). Gateway recombination was used to obtain respective plasmids with pLX302 ([3](#_ENREF_3)) or pHAGE backbone from Dr. Kenneth Scott at Baylor College of Medicine. sgRNA sequence targeting GFP, *MET* exon, intron14 *and Met* exon, intron15 junction were designed using online tool from the Broad Institute (http://www.broadinstitute.org/rnai/public/analysis-tools/sgrna-design) online program. Oligos encoding sgRNA were ligated into pXPR\_001 (addgene#49535) and pSECC ([4](#_ENREF_4)), a generous gift from Dr. Tyler Jacks at MIT. Pseudotyped, replication incompetent lentivirus was produced as described ([5](#_ENREF_5)) by co-transfecting of the backbone, psPAX2 and VSV-G in 4:3:1 ratio in 293 cells with Trans-IT 293 reagent (MIR 2700, Mirus, Madison, WI) according to manufacturer’s instruction. After 48hrs, virus-containing supernatant was collected for direct usage or concentration at UCSF viral core. Functional viral titer was based on Cre recombinase activity at UCSF viral core using 293 LSL-RFP.

**Soft agar assays**

We added 2ml 0.5% agar (SeaPlaque Agarose, 50101, Lonza) containing AALE culture medium without EGF to 6 well plates as a bottom layer, then a middle layer of 25,000 cells suspended in 4ml Lonza SAGM medium without EGF and containing 0.3% agar and 0, 2 or 5ng/ml human HGF, waited for solidification at room temperature, and then added 400ul medium with corresponding concentrations of HGF and no EGF to the top layer, which was changed every 4 days. After 2-3 weeks, we counted the number of colonies from 5 random fields in each well and calculated the average from duplicate or triplicate wells.

**Immunoblotting**

Cell lysates were prepared in RIPA buffer and quantified by the BCA assay (Pierce 23227, ThermoFisher). Samples were then boiled with LDS sample buffer (NP007, Invitrogen) and loaded to 3-8% tris-acetate gel (EA03785BOX, Invitrogen) or 4-12% bis-tris gel (NP0336BOX, Invitrogen). Protein gels were run and transferred to PVDF membrane (10600022, GE Healthcare Life Sciences) according to manufacturer’s instructions. Proteins were detected by specific primary antibody and secondary antibody then visualized using Li-COR Odyssey Infrared Imager (9120, ODY\_0843, Li-COR). Protein band intensity was quantified by the integrated intensity function with background subtraction in the Li-COR software.

***In vivo* mouse tumor analysis**

Serial sections of formalin-fixed paraffin embedded mouse lung tissue were Hematoxylin and Eosin stained and scanned using an Aperio Digital Pathology Slide Scanner. Pathology analysis was performed by a board-certified pathologist (KJ). Immunohistochemistry was performed as described ([8](#_ENREF_8)).

**Preclinical Therapeutic Studies with Micro X-ray Computed Tomography (μCT)**

The experiment is modified from ([9](#_ENREF_9)). Mice (n=6) received intranasal infection of pHAGE lentivirus encoding *MET*Δ14 and CRE. An Inveon microCT system (Siemens Molecular Solutions, Malvern, PA) was used to monitor *in vivo* tumor initiation, progression and to measure tumor volumes from 2-weeks post infection. Mice were assigned to Crizotinib group or vehicle group with matched tumor number and volume at 20 days post-infection. Treatment started from day 21 with a previously established dose (50mg/kg) ([7](#_ENREF_7)) of Crizotinib (PF-02341066, ActiveBiochem) by oral gavage daily with breaks on weekends. During the microCT scans, animals were maintained under anesthesia using 1.5-2% isoflurane while a total of 180 projections were acquired over 220° with an x-ray source at 80kVp and 500μA. The x-ray exposure time at each projection is limited to 225 ms, and the gantry was set to rotate continuously during the scan. The projection data were acquired using a 1024×1024 matrix for 180 projections with a pixel size of 42.8×42.8μm2. A Feldkamp algorithm modified for x-ray conebeam was used for CT reconstruction. The reconstructed volume was a matrix of 512×512×256 matrix with an isotropic voxel size of 85.6×85.6×85.6μm3. The reconstructed CT images were imported to the offline software package Amira (FEI, Hillsboro, OR) for lung tumor volume measurement. In order to ensure consistency, imaging analysis was focused only on clearly discernible tumors greater than 0.2mm3 in size without overlapping regions of pulmonary vasculature. Volumes of interest (VOIs) were manually drawn and then reviewed in all three orthogonal views for consistency, following the same tumor over the course of the study. This process was repeated for all tumors measured and was performed as a blind study. Once the VOIs were finalized, the physical volumes were calculated based on the size of VOIs and the voxel size

**Statistical analysis**

Statistical analyses were performed using R Version 2.15 for Windows and Excel, and data plotted and analyzed using Student’s t-test. \*, \*\*, \*\*\* represent P-values <0.05, 0.01 and 0.001, respectively, unless otherwise noted.

Supplementary References

1. Wrobel, C.N., Debnath, J., Lin, E., Beausoleil, S., Roussel, M.F., and Brugge, J.S. 2004. Autocrine CSF-1R activation promotes Src-dependent disruption of mammary epithelial architecture. *The Journal of cell biology* 165:263-273.

2. Gupta, P.B., Kuperwasser, C., Brunet, J.P., Ramaswamy, S., Kuo, W.L., Gray, J.W., Naber, S.P., and Weinberg, R.A. 2005. The melanocyte differentiation program predisposes to metastasis after neoplastic transformation. *Nature genetics* 37:1047-1054.

3. Yang, X., Boehm, J.S., Salehi-Ashtiani, K., Hao, T., Shen, Y., Lubonja, R., Thomas, S.R., Alkan, O., Bhimdi, T., Green, T.M., et al. 2011. A public genome-scale lentiviral expression library of human ORFs. *Nature methods* 8:659-661.

4. Sanchez-Rivera, F.J., Papagiannakopoulos, T., Romero, R., Tammela, T., Bauer, M.R., Bhutkar, A., Joshi, N.S., Subbaraj, L., Bronson, R.T., Xue, W., et al. 2014. Rapid modelling of cooperating genetic events in cancer through somatic genome editing. *Nature* 516:428-431.

5. Sena-Esteves, M., Tebbets, J.C., Steffens, S., Crombleholme, T., and Flake, A.W. 2004. Optimized large-scale production of high titer lentivirus vector pseudotypes. *Journal of virological methods* 122:131-139.

6. Joffre, C., Barrow, R., Menard, L., Calleja, V., Hart, I.R., and Kermorgant, S. 2011. A direct role for Met endocytosis in tumorigenesis. *Nature cell biology* 13:827-837.

7. Hrustanovic, G., Olivas, V., Pazarentzos, E., Tulpule, A., Asthana, S., Blakely, C.M., Okimoto, R.A., Lin, L., Neel, D.S., Sabnis, A., et al. 2015. RAS-MAPK dependence underlies a rational polytherapy strategy in EML4-ALK-positive lung cancer. *Nature medicine* 21:1038-1047.

8. Roy, N., Malik, S., Villanueva, K.E., Urano, A., Lu, X., Von Figura, G., Seeley, E.S., Dawson, D.W., Collisson, E.A., and Hebrok, M. 2015. Brg1 promotes both tumor-suppressive and oncogenic activities at distinct stages of pancreatic cancer formation. *Genes & development* 29:658-671.

9. Truitt, M.L., Conn, C.S., Shi, Z., Pang, X., Tokuyasu, T., Coady, A.M., Seo, Y., Barna, M., and Ruggero, D. 2015. Differential Requirements for eIF4E Dose in Normal Development and Cancer. *Cell* 162:59-71.