**Supplementary Materials and Methods**

**Analysis of cell viability**

 EBC1 and NCI-H358 cell lines were obtained from ATCC and authenticated by short tandem repeat profiling (IDEXX Bioresearch). Normal Human Bronchial Epithelial cells (NHBE) were obtained from Lonza BioReasearch. Relative cell growth in monolayer following various treatments was determined by measuring the reduction of the indicator dye alamarBlue (Invitrogen, DAL1100) according to manufacturer’s instructions.

For detection of apoptosis, EBC1 cells were stained with Annexin V-conjugated to fluorescein isothiocyanate (FITC) and propidium iodide (PI) using the FITC Annexin V/Dead Cell apoptosis kit (Invitrogen V13242) according to the manufacturer's instructions. Immediately after staining, the cells were analyzed on a flow cytometer using 488-nm excitation and a 525-nm band pass filter for FITC and a 620-nm filter for PI detection. At least 10,000 cells were acquired in an Accuri C6 flow cytometer. Percentages of cells undergoing apoptosis were determined by dual-color analysis.

**Kinetics of MET antibody trafficking to lysosomes**

MET antibodies were conjugated with fluorophore Alexa Fluor 647 according to manufacturer’s instructions and incubated with EBC1 cells for 15 minutes. Noninternalized primary antibodies on the cell surface were detected with Alexa Fuor 488-conjugated goat anti-human IgG Fab Fragment (Jackson ImmunoResearch Laboratories). Lysosomes and endosomes were labeled by incubating cells with 1 mg/ml Fluorescein-3kDa-dextran and 5 g/ml AF568-labeled recombinant human transferrin (Sigma), respectively. Images were acquired using Zeiss Spinning disk confocal microscope. Six fields per condition were acquired and the colocalization between MET antibodies and either dextran or transferrin was quantified.

**Epitope Mapping by Hydrogen Deuterium Exchange (HDX)**

HDX was used to map the binding epitopes of the biparatopic MET antibody and the parental antibodies on human MET. The recombinant extracellular domain of human MET with a C-terminal myc-myc-hexahistidine tag (hMET.mmH) was utilized. The antibodies were individually covalently attached to NHS-activated Sepharose 4 Fast Flow beads (GE Healthcare). We applied two methods, ‘On-Antigen’ and ‘On-Complex’, to confirm the binding epitopes of the antibodies. In the ‘On-Antigen’ experimental condition, the antigen hMET.mmh was deuterated for 5 or 10 minutes in PBS buffer prepared with deuterium oxide (D2O). The deuterated antigen was then bound to MET antibody-coated beads and subsequently eluted with low pH quench buffer. The eluted sample was loaded on Waters SYNAPT G2-Si H/DX-MS system consisting of integrated online peptide digestion, trapping, 9 minute liquid chromatography separation and data acquisition. In the ‘On-Complex’ experimental condition, the hMET.mmh was first bound to MET antibody-coated beads and then deuterated for 5 or 10 minutes via incubation in PBS buffer prepared with D2O. The deuterated MET ligand was eluted and analyzed by Waters SYNAPT G2-Si H/DX-MS system as described above.

For the identification of the peptic peptides from hMET.mmH, LC-MSE data from an un-deuterated sample were processed and searched against hMET.mmH using Waters ProteinLynx Global Server (PLGS) software. The identified peptides were imported to DynamX 3.0 software and filtered by the following two criteria: the minimum products per amino acid is 0.3 and the replication file threshold is 3.0. DynamX 3.0 software automatically calculated the deuterium uptake difference of each identified peptide between ‘On-Antigen’ and ‘On-Complex” across both 5 and 10 minute deuteration time points. The individual isotopic peak of each peptide picked up by DynamX 3.0 software for the centroid value calculation was also manually examined to ensure the accuracy of the deuterium uptake calculation. In general, delta values for deuteration above 0.2 were used as the cut-off for determining a specific binding epitope.

**Surface plasmon resonance**

*Determination of the kinetics binding parameters for the interaction of METxMET and parental antibodies with recombinant human MET protein under neutral conditions:* Using SPR-Biacore, METxMET and parental antibodies binding kinetics were determined on a Biacore T200 instrument using a dextran-coated (CM5) chip at 25°C. The running buffer was HBS-ET (10 mmol/L Hepes, 150 mmo/L NaCl, 3.4 mmol/L EDTA, 0.05% polysorbate 20, pH 7.4). A capture sensor surface was prepared by covalently immobilizing goat anti-human Fcγ antibody (Regeneron) to the chip surface using (1¬Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride)/N-hydroxysuccinimide (EDC/NHS) coupling chemistry. METxMET and parental antibodies were captured through their Fc regions by an anti-human Fc antibody immobilized on the sensor chips and were tested for binding to the extracellular domains of monomeric and dimeric MET proteins (with C-terminal MycMycHis or mouse Fc tags) prepared at a concentration range of 250 nmol/L to 0.79 nmol/L and individually injected over captured surfaces for 2 minutes followed by 1-15 minutes dissociation phase. All capture surfaces were regenerated with one 15 second pulse of 10 mmol/L glycine-HCl, pH 1.5 (pH 1.5, (GE Healthcare). Kinetic parameters were obtained by globally fitting the data to a 1:1 binding with mass transport limitation or heterogeneous ligand binding model using Biacore T200 Evaluation Software. The equilibrium dissociation constant (KD) was calculated by dividing the dissociation rate constant (kd) by the association rate constant (ka).

*Binding competition assay (****Table S2****):* Determination of the ability of each Fab arm of METxMET biparatopic antibody to bind non-overlapping epitopes of recombinant monomeric human MET. Using SPR-Biacore, antibody competition studies were performed on a Biacore T200 instrument using a dextran-coated (CM5) chip at 25°C. The running buffer was HBS-ET (10 mmol/L Hepes, 150 mmo/L NaCl, 3.4 mmol/L EDTA, 0.05% polysorbate 20, pH 7.4). A capture sensor surface was prepared by covalently immobilizing goat anti-his antibody (GE Healthcare) to the chip surface using (1¬Ethyl-3-[3 dimethylaminopropyl]carbodiimide hydrochloride)/N-hydroxysuccinimide (EDC/NHS) coupling chemistry. Human MET was captured by surface-coupled anti-His until a signal of 120 resonance units (RU) was reached. METxMET, control antibody, parental Ab1 or parental Ab2 were pre-bound to hMET.mmH immobilized on the sensor surface, followed by injections of either METxMET, control antibody, parental Ab1 or parental Ab2 (second antibody injection). Antibodies were injected at a concentration of 3 μmol/L. The first antibody (pre-bound) was injected at a flow rate of 15 μL/minute for 5 minutes and the second antibody was injected for 5 minutes immediately after the injection of the first antibody. Binding of the antibodies to the hMET.mmH -sensor surface was analyzed using Scrubber 2.0c. The binding signals of the pre-bound and second antibody were measured 30 seconds after the respective injection.

**Luciferase Reporter Assay (Table S1)**

Antibodies at concentrations ranging from 1.7 pmol/L–100 nmol/L were added to triplicate wells of HEK293 cells engineered to express luciferase under the control of a serum response element and incubated at 37°C for 6 hours. ONE-Glo luciferase substrate was added to each well and relative light units (RLU) were measured on a VICTOR X5 multilabel plate reader.

**Supplementary Figure Legends**

**Figure S1**. **Biparatopic MET antibody (METxMET) specifically inhibits growth of MET-amplified cancer cells.** (**A**) SNU5 cells were incubated with IgG4 control, METxMET antibody, parental Ab1 or parental Ab2 at 1 g/ml or a combination of the parental antibodies at 0.5 g/ml each for 5 days and cell growth was determined. The bar graph depicts the relative cell growth in each treatment group (mean ± SD). \*\*P < 0.01, \*\*\*\*P < 0.0001, versus IgG4 control. ++P < 0.01, parental antibodies versus METxMET antibody, one-way ANOVA with Tukey’s post hoc test for multiple comparisons. (**B**) Flow cytometric analysis of Annexin V-FITC and PI staining for the determination of apoptosis in EBC1 cells following treatment with IgG4 control, METxMET or parental antibodies at 5g/ml for 72 hours. (**C,D**) EBC1 or NCI-H358 cells were incubated with increasing concentrations of IgG4 control, METxMET or parental antibodies (0.1 – 100 nmol/L) for 5 days and cell viability was measured. The line graphs depict the relative cell viability in each treatment group (mean ± SD). (**E**) Normal human bronchial epithelial cells were incubated with either control antibody (10 g/ml; 68 nmol/L), METxMET antibody (5 or 10 g/ml; 34 or 68 nmol/L) or the MET TKI capmatinib (10 nmol/L) for 72 hours and cell growth was determined. The bar graph depicts the relative cell growth in each treatment group (mean ± SD). (**F**) SNU5 tumor cells were treated with IgG4 control, METxMET antibody, parental Ab1 or parental Ab2 (5 g/ml) or the combination of parental antibodies (2.5 g/ml each) for 18 hours. Cell lysates were prepared from duplicate wells and subjected to western blot analysis with antibodies against MET or Tubulin.

**Figure. S2. Ligand binding properties of biparatopic MET antibody.** Sensorgrams of binding kinetics of biparatopic MET antibody (METxMET) binding to monomeric and dimeric human MET proteins. METxMET antibody was captured on an anti-human Fc coupled chip surface. The association phase of human MET was monitored at 50 μl/minute for 2 minutes over each of the captured surfaces. Representative sensorgrams of (**A**) METxMET antibody binding to monomeric MET (hMET.mmh), concentration range 25 nmol/L to 0.79 nmol/L and (**B**) METxMET antibody binding to dimeric MET (hMET.mFc), concentration range 12.5 nmol/L to 0.40 nmol/L are shown as black lines. The data were globally fit to a 1:1 or heterogeneous ligand binding interaction model using T200 evaluation software 2.0. Kinetic fits from the analyses are overlaid on the binding data in red.

**Figure S3. Ligand binding properties of MET parental antibodies.** Sensorgram of binding kinetics of parental antibodies binding to monomeric human MET protein. Parental antibodies was captured on an anti-human Fc coupled chip surface. The association phase of human MET was monitored at 50 μl/minute for 2 minutes over each of the captured surfaces. Representative sensorgrams of (**A**) Parental Ab1 binding to monomeric MET (hMET.mmh), concentration range 250 nmol/L to 7.9 nmol/L and (**B**) Parental Ab2 binding to monomeric MET (hMET.mmh), concentration range 250 nmol/L to 7.9 nmol/L are shown as black lines. The data were globally fit to a 1:1 binding interaction model using T200 evaluation software 2.0. Kinetic fits from the analyses are overlaid on the binding data in red.

**Figure S4**. **Biparatopic MET antibody accelerates the rate of MET degradation.** EBC1 cells were incubated with cycloheximide (50 g/ml) and IgG4 control, biparatopic MET antibody (METxMET), parental Ab1 or parental Ab2 at 5 g/ml for the indicated times. Cell lysates were prepared from duplicate wells and MET protein levels were assessed by western blot analysis and quantified using ImageJ64. The line graph depicts the average MET protein level as a function of time.

**Figure S5. Biparatopic MET antibody traffics rapidly to lysosomes.** Alexa Fluor 647-labeled MET antibodies were bound to EBC1 cells at 4°C. Cells were then switched to 37°C in the presence of 5 g/ml AF568-labeled recombinant human transferrin and 1 mg/ml Fluorescein-3kDa-dextran to label endosomes or lysosomes, respectively. After 15 or 60 minutes, cells were fixed with 4% paraformaldehyde and imaged using Zeiss Spinning disk confocal microscope. Six fields per condition were acquired and the colocalization between internalized MET antibodies and either dextran or transferrin was quantified. The bar graph shows the percent colocalization of each MET antibody with labeled dextran (lysosomes) at 15 minutes. \*\*\*\*P < 0.0001, versus METxMET.

**Figure S6. Mapping of epitopes for biparatopic and parental MET antibodies on human MET using Hydrogen Deuterium Exchange.** Peptides corresponding to amino acid residues 192-228, 296-349 and 421-455 were found to have significantly reduced deuterium uptake upon binding of the biparatopic MET antibody and were defined as the binding epitopes. The regions corresponding to residues 305-315 and residues 421-455 were defined as the binding epitope for parental Ab1. The region corresponding to residues 192-210 was defined as the binding epitope for parental Ab2.