**SuPPLEMENTARY DATA**

**SupplementaRY Figure LEGENDS**

**Supplementary Fig. S1. JNJ-605 blocks MET endocytosis triggered by HGF or DO24. MvDN30 does not induce MET internalization**

(A-C) Endocytosis assays in A549 cells. Cells were incubated with HGF-555 (A), or with antibodies DO24, MvDN30 or Fab unrelated (B) for 1 h at 4°C. In the experiments done with HGF-555 or DO24, cells were incubated in presence or absence of JNJ-605 300nM as indicated on the left. Cells were then shifted at 37°C for 15 min, transferred on ice and subjected to an acid wash, to remove the HGF or the antibodies still bound to the surface, and fixed. Cells were stained with a secondary anti-mouse antibody to reveal the fraction of internalized DO24, MvDN30 or Fab unrelated antibodies (in green), and with anti-EEA1 antibody (in red), DAPI is in blue in merge. Confocal images were acquired. HGF-555 was pseudo coloured in green and EEA1 in red to be consistent with Fig.1 and Fig.2 of the main text. Co-localization, detected in cells treated with HGF-555 or DO24, was abrogated by JNJ-605 treatment. No internalization was seen in the cells stimulated with MvDN30 or with Fab unrelated antibodies. Magnifications of the endosomal compartment, boxed in merge, are shown on the right. C) Quantification of the percentage of co-localization between HGF-555 (bar graph on the left) and antibodies (bar graph on the right) and EEA1. Means ± s.e.m. are shown, n=8. Bar, here and in the following figures otherwise specified, is 10 m.

**Supplementary Fig. S2. JNJ-605 does not inhibit EGFR endocytosis**

(A) EGFR endocytosis assays in A549 and H1993 cells. Cells were mock treated (CTR) or treated with EGF (100 ng/ml) for 1 h at 4°C in serum free medium in presence or absence of JNJ-605 300 nM as indicated on top. Cells were then shifted at 37°C for 15 min to allow EGFR endocytosis, fixed and stained with anti-EGFR (green) and anti-EEA1 antibodies (red) and DAPI (blue). Magnifications, boxed in merge, are shown below. B) Quantification of the percentage of co-localization between EGFR and EEA1. Means ± s.e.m. are shown, n=8.

**Supplementary Fig. S3. Interfering with receptor dimerization by mean of decoy MET severely affects receptor endocytosis**

(A) MET endocytosis assays in A549 and H1993 cells. In A549 cells endocytosis has been triggered by ligand stimulation. A549 were mock treated (CTR) or treated with HGF (50 ng/ml) for 1 h at 4°C in serum free medium in presence or absence of JNJ-605 300 nM or decoy MET 2 M as indicated on top. In H1993 cells, constitutive MET endocytosis has been evaluated. H1993 cells were mock treated or treated with JNJ-605 300 nM or decoy MET 2 M for 1 h at 4°C in serum free medium. Cells were then shifted at 37°C for 15 min to allow MET endocytosis, subjected to acid wash, fixed and stained with anti-MET (green), anti phospho-MET (red), anti-EEA1 (magenta) antibodies and DAPI (blue). Insets show magnification of the endosomal compartment. B) Quantification of the percentage of co-localization between MET and EEA1 in the two cell lines (indicated in the legend) normalized over control of A549. Means ± s.e.m. are shown, n=8.

**Supplementary Fig. S4. Rebound S phase entry mainly relies on MET**

A)EBC-1cells were treated with 500 nM JNJ-605 overnight. CTR are control untreated cells. Cells were then released from the inhibition for 24h in presence or absence of EGF (100 ng/ml), PDGF (50 ng/ml) or NRG1-1 (50 ng/ml). JNJ-605 sample was treated overnight with the inhibitor and not released; w/o untreated are cells that were released from JNJ-605 inhibition without addition of growth factors. The bar graph shows percentage of S-phase cells treated as indicated on bottom (means ± ranges). B-C) H1993 cells were treated or not with JNJ-605 overnight. Samples were subjected to the washout procedure and treated with EGF (50 ng/ml) (B) or with NRG1-1 (50 ng/ml) (C) for the time indicated on top. CTR: cells that were not treated with JNJ-605; JNJ-605: cells that were not released; w/o untreated: JNJ-605-treated cells that underwent the washout in absence of stimulation. Cells were lysed and total cellular lysates were immunoblotted as indicated on the left.

**Supplementary Fig. S5. MvDN30 causes MET shedding under the experimental conditions employed in this study**

EBC-1 cells were treated as in Fig.6. Briefly, after overnight incubation with 500 nM JNJ-605, cells were released or not (JNJ-605) through inhibitor washout. Monovalent antibodies MvDN30 or Fab unrelated [57.4 g/ml] were added to the media and, 24 hours later, culture media were collected and cells lysed. Top: 50 l of surnatant culture media from the indicated samples blotted with the anti-MET antibody to reveal the MET extracellular domain. Bottom: total cellular lysates (20 g) blotted with anti-MET and anti--tubulin antibodies. MvDN30 induces MET shedding as shown by the increased amount of MET extracellular domain present in the medium and by the severe reduction of MET protein levels in the total lysates.

**Supplementary Fig. S6. *In vivo* rebound MET activation**

A) Scheme of the experimental protocol. Control mice (CTR), mice treated with JNJ-605 and mice in which the JNJ-605 treatment was suspended for 24 hours were sacrificed at day 21. Mice in which the JNJ-605 treatment was discontinued for 3 days or for 5 days were sacrificed at day 23 and 25, respectively. B) Mice bearing the experimental tumors were injected with EdU 24 hours before tumor excision. Tumor sections were reacted with Alexa555-azide to stain the cells that had incorporated EdU. Confocal images are representative sections of tumors showing the nuclei (stained with DAPI) in blue, and the EdU-positive cells in red. No EdU correspond to a tumor that did not receive the EdU. CTR is a tumor that was not treated with JNJ-605, JNJ-605 is a tumor that was not released. 1d, 3d and 5d, are sections of tumors from mice in which treatment with JNJ-605 was interrupted for one, three or five days. Bar is 50 m. The bar graph on the right reports the ratio between the % of EdU-positive area and the % of DAPI staining. Values are the mean ± s.e.m, 8 images per tumor were evaluated (5 mice per group). C) Tumor sections were analyzed by immunohistochemistry with anti phospho-MET (top panel) and anti phospho-ERK (bottom panel) antibodies. In the phospho-MET panel, a region has been boxed and magnified to highlight the localization of the phosphorylated form of the receptor to the plasma membrane. Representative images from tumors treated as indicated on top are shown. Bar is 50 m.