**SUPPLEMENTARY MATERIAL**

**MATERIALS AND METHODS**

**Tumor Cell Lines and PBMCs**

NCI-H1975 (H1975) cells and SNU5 cells were obtained from the American Type Culture Collection (ATCC) and cultured in RPMI (Invitrogen, Cat#72400-047) supplemented with 10% Hi FBS, 1X NEAA, 1X Sodium Pyruvate or in IMDM (Invitrogen, Cat#12440-061) supplemented with 20% Hi FBS, 1X NEAA, 1X Sodium Pyruvate, respectively. Both cell lines were maintained free of mycoplasma contamination and authenticated on a regular basis by karyotype and short tandem repeat analysis at Janssen R&D facility. The Peripheral Blood Mononuclear Cells (PBMCs) and isolated immune cells (NK cells and Monocytes) were purchased from Hemacare. The PBMCs were isolated from leukopaks collected in HemaCare’s FDA-registered collection centers following cGMP and cGTP collection guidelines from IRB consented healthy human donors. PBMCs were purified by a density gradient centrifugation. NK cells were isolated using CD56 negative selection and Monocytes were isolated using CD14 negative selection from the same donor leukopak. The isolated cells were purchased from Hemacare in cryopreserved format and stored in liquid nitrogen until use.

**ADCC Assay**

PBMCs were thawed one day prior to assay in X-VIVO 10 media (Lonza, Cat#04-380Q) supplemented with 10% heat inactivated FBS (GIBCO, Cat#16140) and rested overnight under standard incubation conditions (370C, 5% CO2, 95% humidity). On the day of assay, H1975 target cells were loaded with DELFIA BATDA reagent (PerkinElmer Inc., Cat#C136-100) for 30 minutes, washed 3 times, and resuspended in RPMI media. PBMCs and BATDA-loaded target cells were added to 96-well U-bottom plates at an effector to target cell (E:T) ratio of 25:1 along with increasing concentrations of test antibodies. RPMI media or RPMI media containing 2% Triton X-100 (EMD Millipore, Cat#648463) was added to control wells for measurement of spontaneous and maximal TDA release respectively. Plates were incubated for 2 hours, after which 20uL of supernatant was removed and combined with 200uL of DELPHIA Europium solution (Perkin Elmer, Cat#C135-100). After incubation at RT for 15 mins, Relative Fluorescence Units (RFU) were measured using an EnVision 2104 Multilabel Plate Reader (PerkinElmer, Cat#2104-0010). Percent lysis was calculated as (Experimental release – Spontaneous release)/(Maximal release – Spontaneous release) X 100.

**C1q binding Assay**

Purified C1q protein (US Biologics, Cat#C0010A) was conjugated with MSD GOLD SULFO-TAG NHS-Ester (MSD, Cat# R91AO-1) using the Conjugation pack (MSD, Cat#R31AA-2) and purified as per manufacturer’s instructions. MSD multi-array 96 well high bind plates (MSD, Cat#L15XB) were coated with the test antibodies overnight at 40C. The coated plate was washed thrice with MSD Tris wash buffer, blocked with 150μL/well of blocking solution (prepared from MSD Blocker-A kit) and incubated for 1 hour with shaking at room temperature. The plate was washed thrice with MSD Tris wash buffer, tagged C1q protein was added and incubated at RT with shaking for 1 hour. The plate was washed, 2X READ buffer was added, and the plate was read on the MSD Sector imager to obtain the Relative Luminescence Units (RLU) values.

**CDC Assay**

Target cells were dissociated with cell dissociation buffer and plated at a cell density of 50,000 cell per well in 80ul media. Test antibodies were added to the plate at 10X concentration, followed by 5% Baby rabbit complement (CedarLane, Cat#CL3441-S) at 10X concentration. The plates were spun at 1000rpm for 2 mins and incubated for 2 hours at 370C. 45 mins prior to harvesting the assay, 10ul of 10x Lysis Buffer provided with the CytoTox Non-Radioactive Cytotoxicity Assay kit (Promega, Cat#G1780) was added as max-lysis control. Post incubation, LDH release was measured using the CytoTox Non-Radioactive Cytotoxicity Assay kit (Promega, Cat#G1780) as per the manufacturer’s instructions. Briefly, 50µL of supernatant was mixed with 50 µL of working Cytotox Reagent and incubated for 30 minutes in the dark at RT. After adding 50 µL of stop solution to each well, the absorbance was measured at 490 nm using the SpectraMax Plate reader. % CDC mediated target cell lysis was calculated using the following formula: [(Experimental O.D – Avg O.D from Media alone cnt)/ O.D of Max lysis] x 100.

**MSD Multi-plex assay and statistical analysis**

For PBMC, NK cells and monocytes experiments, NCI-H1975 cells were plated into 96-well plates and allowed to incubate overnight at 37◦C and 5% CO2. The next day, PBMC, monocytes or NK cells were added at a ratio of 10:1, 5:1 and 5:1 respectively. For macrophage experiments, the monocytes were differentiated as previously described, dissociated using StemPro Accutase (Gibco, Cat#A11105-01) and plated into 96-well plates and allowed to incubate overnight at 37◦C and 5% CO2. The next day, H1975 cells were added at an E:T ratio of 5:1. The cells were treated with therapeutic antibodies at varying concentrations and incubated at 37◦C and 5% CO2 for 4 or 72 hrs. At the designated time, the plates were spun at 1200 rpms for 10 min at room temperature. The supernatant was removed and evaluated using MesoScale Discovery (MSD) U-plex and V-plex formats for the respective cytokine assays as per manufacturer’s instructions. Briefly, for the U-plex plates, on the day before the assay, the plates were coated with the antibody and linkers according to manufacturer’s protocol and incubated on an orbital shaker at 4◦C overnight. On the day of the experiment, the U-plex or V-plex plates were washed 3X with MSD wash buffer and supernatants, standards and calibrators were added to the plates and run according to manufacturer’s protocol. Plates were read on an MSD Sector instrument and analyzed using Spotfire to obtain the Calculated levels (in pg/ml) for each cytokine using the standard curve.

From the calculated concentrations, area under the curve (AUC) was calculated by the trapezoidal method for each treatment, cell type, and incubation time in order to compare magnitude of response. Response data was excluded if the observed value was below the lower limit of detection, and AUC was calculated only where there were at least 6 valid observations out of the 8 dose concentrations. A heatmap was then generated to illustrate data availability (no data, not enough data, or calculable AUC data) across all cytokines and conditions. Heatmaps of log-transformed AUC were then produced by incubation time and limited to cytokines with at least one measurable AUC in the H1975+PBMC cell type. All heatmaps were produced using package heatmap.2 in the statistical software R version 3.5.0 (R Core Team 2018; R: A language and environment for statistical computing; http://www.R-project.org/). Finally, relative change of amivantamab and IgG2σ treatment compared to isotype was calculated for each condition and bar graphs were generated using Graphpad Prism.

**Flow cytometry-based determination of immune cell composition**

The PBMCs (purchased from Hemacare) were thawed in X-VIVO-15 media with 10% FBS and counted. After counting, ~300,000 to 400,000 cells/well were plated (in triplicates) and the plate was spun at 40C at 1500 rpms for 3min and washed with 150ul/well of DPBS. Cells were stained with Near IR- Live/Dead stain (Life Technologies, Cat#L10119) in PBS and incubated in dark at RT for 30 min. The cells were washed with FACS/Stain buffer (BD Biosciences, Cat#554657). The cells were then stained with the antibody cocktail: CD19 (FITC), CD56 (BV711), CD14 (PE-cy7), CD3 (BV605), CD4 (BV785), CD8 (PerCP-cy5.5), CD16 (BUV395), CD32 (PE) and CD64 (APC) and incubated for 30 min at RT in dark. A compensation plate was prepared using compensation beads and the single channel antibodies from the panel above as per calculations and incubated for 30mins in dark at RT. All plates were spun at 1500rpm for 5 min at 4°C and washed twice with FACS Buffer. The plates were run on the Fortessa where the compensation was set using the single channel controls from the compensation bead plate. The assay plate was then run at flow rate of 1.5ul/sec with the compensation applied. The data was analyzed in FLOWJo, where appropriate gating was done to obtain the percentage of the each of the individual immune cell populations within the PBMCs and the expression of Fcγ receptors.

**Depletion of NK cells and monocytes from PBMCs**

Depletion of NK cells were performed using the EasySep Human CD56 Positive Selection kit II (STEMCell Technologies, Cat#17855) and depletion of Monocytes was performed using the EasySep Human CD14 Positive Selection kit II (STEMCell Technologies, Cat#17858). 10 million PBMCs were resuspended in the EasySep buffer at the desired conc (100 million cells/mL) and the depletion of the NK cells or monocytes was performed as per the manufacturer’s protocol. Briefly, 50ul of the respective antibody selection cocktail was added and incubated at RT for 10 mins. 50ul of the magnetic particles were added to the PBMCs + antibody cocktail and incubated for 3 mins at RT. The tubes were then placed into the EasySep Magnet (STEMCell Technologies, Cat#18000) and supernatant was carefully transferred to a new tube. The magnetic separation step was repeated twice to obtain NK cell depleted or Monocyte depleted PBMCs. The depletion was verified using flow cytometry and then utilized for the Simple Western assays.

**Differentiation of Monocytes into M1, M2a and M2c macrophages**

Monocytes (Hemacare) were thawed in the XVIVO-15 media and differentiated with 50ng/mL M-CSF (R&D systems; Cat#216-MC-025/CF) for 6 days to obtain M0 macrophages. To obtain M1 macrophages, on day 5, M0 macrophages were polarized with 50ng/mL M-CSF and 100ng/mL IFN-g (R&D systems; Cat#285-IF-100/CF) for 48 hrs. To obtain M2 macrophages, on day 5, M0 macrophages were polarized with 20ng/mL IL-4 (R&D systems; Cat#204-IL-020/CF) and IL-13 (R&D systems; Cat#213-ILB-025/CF) for M2a or 20ng/mL IL-10 (R&D systems; Cat#217-IL-025/CF) for M2c macrophages for 48 hrs. After polarization, M1, M2a and M2c macrophages were thoroughly rinsed with fresh media before use in the assays.

**Western blot analysis of *in vivo* tumors**

SNU5 tumors were harvested, flash frozen in liquid nitrogen, and lysed in ice-cold 4X lysis buffer - RIPA (Thermo Scientific) containing 2× HALT/EDTA protease and phosphatase inhibitor cocktail (Thermo Fisher Scientific), 50 mmol/L NaF, 2 mmol/L sodium orthovanadate (activated), and 1 mmol/L PMSF. The lysates were transferred into a 1.5 ml tube, sonicated on ice (water-bath sonicator) for 20mins and spun at 13000rpm for 30mins at 4C to remove tissue debris. Protein concentrations was determined by BCA Protein Assay (Pierce). Protein samples were resolved by SDS-PAGE and transferred to nitrocellulose membranes. Membranes were blocked in Odyssey blocking buffer (LI-COR) for 1 hour at room temperature and incubated with the appropriate primary antibodies overnight at 4°C: anti-EGFR (Cell Signaling Technology, Cat#2239) at 1:1000, anti-Met (Cell Signaling Technology, Cat#3138) at 1:1000, anti-pEGFR (Cell Signaling Technology, Cat#3777) at 1:1000, anti-pMet (Cell Signaling Technology, Cat#3077) at 1:1000, and anti-GAPDH (Kangchen Biotech, Cat#KC-5G4) at 1:10,000. Bands were detected with anti-mouse IRDye680 (LI-COR) or anti-rabbit IRDye800 (LI-COR) and imaged using an Odyssey Infrared Imaging System (LI-COR). Average total protein quantitated from Western blots, relative to loading control (GAPDH), was graphed and statistical analysis performed using GraphPad Prism.

**Flow cytometry-based determination of tumor associated macrophages**

Tumors were excised from mice, weighed, sectioned into 2-4mm pieces, placed into C-tubes (Miltenyi, Cat#130-093-237) containing 2.5mL of RPMI and maintained on ice. According to manufacturer’s instruction, the lyophilized enzymes contained in a Human Tumor Dissociation Kit (Miltenyi, Cat#130-095-929) were reconstituted and a 2x enzyme cocktail was prepared and tumors were dissociated on a GentleMACS Octo Dissociator (Miltenyi, Cat#130-095-937) using manufacture protocol “h\_tumor\_01” followed by two rounds of incubation at 37°C for 30 minutes. Dissociated cells were washed twice in FACS Stain Buffer (BD Pharmingen, Cat#554657) and passed through a Falcon 40µm cell strainer (Corning, Cat#352340). Cells were incubated in GolgiPlug (BD, Cat#555029) diluted 1:1000 in FACS buffer and incubated for 3 hours at 37°C, washed twice, and resuspended in 100µL of antibody staining cocktail. The antibody cocktail consisted of anti-CD45 (Cat#103138), anti-F4/80 (Cat#123137), anti-Ly6G (Cat#127639), anti-MHCII (Cat#107612), anti-EpCAM (Cat#324214), anti-PD1 (Cat#135231), anti-PD-L1 (Cat#393606), anti-CD206 (Cat#141729) from BioLegend, anti-CD11b (Cat#563553) and anti-Ly6C (Cat#561237) from Becton-Dickinson, anti-iNOS (Cat#25-5920-82) and Fixable Live/Dead stain (Cat#L10119) from Invitrogen. Cells were incubated with external cell surface marker antibodies for 30 minutes at 4°C protected from light, washed twice with PBS, and resuspended in PBS containing Fixable Live/Dead stain, incubated for 30 minutes at 4°C, and washed twice with FACS buffer (BD Pharmingen; Cat#554657). Cells were fixed/permeabilized according to manufacturer’s instructions (Invitrogen, Cat#88-8824-00), incubated with internal target antibodies for 30 minutes at 4°C, washed 2x with FACS buffer, and resuspended in 200 µL for analysis on BD LSR Fortessa. Compensation was performed using UltraComp eBeads (for antibodies; Invitrogen, Cat#01-2222-42) and ArC Amine Reactive beads (for Fixable Live/Dead, Invitrogen, Cat#A10346). FMO controls were performed for all markers. To determine tumor associated macrophage depletion, macrophages were defined as CD45+ CD11b+ Ly6C- Ly6G- F4/80+.

**SUPPLEMENTARY FIGURE LEGENDS**

**Supplementary Figure S1. Amivantamab Fc interaction with immune cells is required for tumor cell growth inhibition: A)** Time course of H1975 cell proliferation upon treatment with amivantamab in the absence (left) or presence (right) of PBMCs (Donor #6) at an E:T ratio of 10:1. **B)** Representative images showing dose-dependent effect on proliferation of NucLight Red labeled H1975 cells upon treatment with increasing concentrations of isotype control, amivantamab or EGFR/cMet-IgG2σ in the presence or absence of PBMCs (Donor #6) at an E:T ratio of 10:1 for 72 hours. **C)** Dose-response curves measuring proliferation (AUC of Total NucRed area/well) of H1975 cells upon treatment with isotype control or amivantamab, in the presence or absence of PBMCs from Donor #6 at an E:T ratio of 10:1 for the indicated time points.

**Supplementary Figure S2. Amivantamab Fc interaction with immune cells is crucial for anti-tumor effect in H975 and SNU5 cells *in vitro*: A)** Representative images showing dose-dependent effect on proliferation of NucLight Red labeled H1975 cells upon treatment with increasing concentrations of isotype control, amivantamab or EGFR/cMet-IgG2σ in the presence or absence of PBMCs from a donor #3 at an E:T ratio of 10:1 for 72 hours. **B)** Dose-response curves measuring cell proliferation post 72 hours (AUC of Total NucRed area/well) and apoptosis post 48 hours (AUC of Total Annexin+ NucRed area/well) upon treatment with isotype control, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) antibodies, in presence or absence of PBMCs from Donor #3 at an E:T ratio of 10:1. **C)** Representative images showing does-dependent effect on proliferation of NucLight Red labeled SNU-5 cells upon treatment with increasing concentrations of Isotype control, amivantamab or EGFR/cMet-IgG2σ in the presence or absence of PBMCs (Donor #3) at an E:T ratio of 10:1 for 72 hours.

**Supplementary Figure S3. Amivantamab Fc interaction induces ADCC, C1q binding and ADCR but not CDC in NSCLC: A)** BATDA-loaded H1975 cells were treated for 2 hours with isotype, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) in presence of PBMCs from donor #7 at an E:T ratio of 25:1 and ADCC lysis measured by Europium release. **B)** BATDA-loaded H1975 cells were treated for 2 hours with multiple concentrations of amivantamab in presence of PBMCs, NK cells or monocytes isolated from donor #4 at E:T ratios of 25:1, 5:1, and 5:1, respectively and ADCC lysis measured by Europium release. **C)** Dose response measuring the binding of labeled C1q protein onto the indicated concentrations of isotype control, cetuximab, rituximab, amivantamab or EGFR/cMet-IgG2σ (IgG2σ). **D)** Dose response of CDC lysis measured by LDH (Lactate dehydrogenase) levels from H292 target cells after 2 hours of treatment with amivantamab or EGFR/cMet-IgG2σ (IgG2σ) in presence of 5% baby rabbit serum. **E)** Heat map showing data availability (no data, not enough data, or calculable data) of area under the curve (AUC) measurements from 71-plex MSD of PBMCs alone, H1975 cells in the presence or absence of PBMCs at an E:T of 10:1, followed by treatment with isotype control, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) for 4 or 72 hrs. **F)** Heat map of log-transformed AUC values of cytokines from the 71-plex MSD analysis of PBMCs alone, H1975 cells alone or H1975 + PBMCs (E:T of 10:1) treated with isotype control, amivantamab, cetuximab or EGFR/cMet-IgG2σ (IgG2σ) for 72 hours. **G)** Bar graphs representing the relative change (measured in panel F) over isotype control upon treatment with amivantamab, cetuximab and EGFR/cMet-IgG2σ (IgG2σ) antibodies for 72 hours. Graphs were limited to cytokines with greater than 1.5X increase for amivantamab treatment compared to isotype.

**Supplementary Figure S4. Amivantamab Fc interaction induces production of CC chemokines and EGFR/cMet downmodulation: A)** Heat map of log-transformed AUC values of cytokines from the 23-plex MSD analysis of immune cells alone, H1975 cells in the presence or absence of PBMCs (E:T=10:1) or each of the individual immune cells (E:T=5:1) namely NK cells, monocytes, M1 macrophages or M2c macrophages, followed by treatment with isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) for 4 hours. **B)** Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control actin) in H1975 samples treated for 48 hours with 10μg/ml of isotype control, amivantamab (Ami) or cetuximab in presence or absence of PBMCs from Donor#3. **C)** Percentage (%) change in inhibition of EGFR, pEGFR and cMet protein levels with 10μg/ml of amivantamab or cetuximab treatment in the presence of PBMCs compared to no PBMC.

**Supplementary Figure S5. The ability of amivantamab Fc interaction to enhance EGFR/cMet downmodulation varies among different PBMC donors: A)** Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control actin) in H1975 samples treated for 48 hours with 10μg/ml of isotype control or amivantamab in the presence or absence of PBMCs from seven different donors. **B)** Western blot (capillary electrophoresis using PeggySue)and **C)** densitometryof EGFR, pEGFR, cMet (normalized to loading control actin) performed following 48 hours treatment of H1975 cells with 10μg/ml of isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) in presence of PBMCs from seven additional donors.

**Supplementary Figure S6. Amivantamab Fc interaction potentiates downmodulation of EGFR and cMet in H1975 and SNU5 cells *in vitro*: A)** Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control actin) in H1975 samples treated for 48 ho urs with 10μg/ml of isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) in the presence or absence of PBMCs from Donor #6. **B)** Western blot (capillary electrophoresis using PeggySue)and densitometryof EGFR, pEGFR, cMet (normalized to loading control actin) performed following 48 hours treatment of H1975 cells with 10μg/ml of isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) in presence or absence of PBMCs from Donor#3. **C)** Densitometry of EGFR, pEGFR, cMet and pMet protein levels (normalized to loading control actin) in SNU5 samples treated for 48 hours with 10μg/ml of isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) in the presence or absence of PBMCs from Donor#3.

**Supplementary Figure S7. Amivantamab Fc interaction induced EGFR/cMet downmodulation correlates with monocyte composition: A)** Composition of NK cells (CD56+CD3-), Monocytes (CD14+), B cells (CD19+CD3-) and T cells (CD3+) within PBMCs from seven different donors. **B)** Correlation between the percentage (%) of NK cells, B cells and T cells in the PBMC sample of each donor and the percentage (%) change in EGFR inhibition with amivantamab treatment in the presence of PBMCs compared to no PBMC.

**Supplementary Figure S8. Monocytes are required for amivantamab Fc interaction induced EGFR/cMet downmodulation: A)** Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control Actin) performed following 48 hours treatment of H1975 cells with 10μg/ml of isotype control, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) in presence or absence of non-depleted PBMCs, NK cell depleted or monocyte (mono) depleted PBMCs from donor #3. **B)** Contour plots from multi-color flow cytometry showing the composition of the NK cells and Monocytes within PBMCs (from donor#6) after CD56 and CD14 positive selection respectively. **C)** Western Blot (capillary electrophoresis using PeggySue) and **D)** densitometry of EGFR, pEGFR, cMet (normalized to loading control actin) performed following 48 hours treatment of H1975 cells with 10μg/ml of isotype control or amivantamab (Ami) in presence or absence of non-depleted PBMCs, NK cell depleted or monocyte (mono) depleted PBMCs from donor #6.

**Supplementary Figure S9.** **Amivantamab Fc interaction with monocytes induces trogocytosis and EGFR/cMet downmodulation: A)** Contour plots from multi-color flow cytometry examining the composition of the NK cells (CD56+) and Monocytes (CD14+) within PBMCs after CD56 and CD14 negative selection respectively. **B)** Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control Actin) performed following 48 hours treatment of H1975 cells with 10μg/ml of isotype control, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) in presence or absence of intact PBMCs, isolated NK cells and isolated monocytes from donor #3. **C)** Representative images using confocal microscopy of monocytes labeled with AF488-CD11b, AF488-CD14 and Hoechst (nuclei) in co-culture with H1975 NucLight Red cells opsonized with AF647-labeled isotype control antibody at an E:T ratio of 5:1. Scale bar = 20µm.

**Supplementary Figure S10.** **Amivantamab Fc interaction with M1 and M2 macrophages induces trogocytosis:** Representative images using confocal microscopy of **A)** M1 or **B)** M2 macrophages labeled with AF488-CD11b, AF488-CD14 and Hoechst (nuclei) in co-culture with H1975 NucLight Red cells opsonized with AF647-labeled isotype control antibody at an E:T ratio of 5:1. **C)** Representative images taken at initial time point (t=0 min) after cold binding using confocal microscopy of co-culture of M1 or M2 Macrophages labeled with AF488-CD11b, AF488-CD14 and Hoechst (nuclei) with H1975 NucLight Red cells at an E:T ratio of 5:1 treated with AF647-labeled Isotype, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) antibodies. **D)** Representative images from confocal microscopy of co-culture of M1 or M2 Macrophages labeled with AF488-CD11b, AF488. -CD14 and Hoechst (nuclei) with H1975 NucLight Red cells at an E:T ratio of 5:1 treated with AF647-labeled Isotype, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) antibodies. White arrows point to trogocytosis events measured as transfer of AF647 labeled antibody from target cells into the M1 or M2 Macrophages. Scale bar = 20µm.

**Supplementary Figure S11.** **Macrophages are required for EGFR/Met downmodulation in vitro:** Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control Actin) performed following 48 hours treatment of H1975 cells with 10μg/ml of isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) in presence or absence of **A)** M1 macrophages (M1), **B)** M2a macrophages (M2a) or **C)** M2c macrophages (M2c)differentiated from monocytes isolated from donor #3.

**Supplementary Figure S12.** **Amivantamab Fc interaction is required for anti-tumor efficacy *in vivo* in H1975 and SNU5 xenografts:** **A)** Dosing schedule of subcutaneously injected H1975 cell line xenograft tumors. **B)** Graph showing change in mouse body weight over time and **C)** individual tumor volumes of subcutaneously injected H1975 xenograft tumors upon treatment with 10mg/kg isotype control, amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) (n=8 mice per treatment group) for 3 weeks BIW. **D)** Dosing schedule of subcutaneously injected SNU-5 cell line xenograft tumors. **E)** Graph showing change in mouse body weight over time and **F)** individual tumor volumes of subcutaneously injected SNU-5 xenograft tumors upon treatment with Vehicle (PBS), 5mg/kg amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) (n=8 mice per treatment group) for 3 weeks BIW.

**Supplementary Figure S13.** **Macrophages are required for amivantamab anti-tumor efficacy *in vivo*:** **A)** Densitometry of pEGFR and pMet protein (normalized to loading control GAPDH) in SNU5 tumor samples (n=8/group)treated with vehicle control or 5mg/kg of amivantamab (Ami) or EGFR/cMet-IgG2σ (IgG2σ) BIW for 1 week. p-values were calculated using One Way ANOVA; \* = p<0.05. **B)** Dosing schedule of subcutaneously injected H1975 cell line xenograft tumors treated with anti-CSF1R antibody to deplete macrophages followed by treatment with isotype, amivantamab or EGFR/cMet-IgG2σ (IgG2σ). **C)** Graph showing change in mouse body weight over time and **D)** individual Tumor volumes of subcutaneously injected H1975 xenograft tumors upon macrophage depletion using anti-CSF1R antibody followed by treatment with treatment with 10mg/kg isotype, amivantamab or EGFR/cMet-IgG2σ (IgG2σ) (n=8 mice per group) for 3 weeks BIW.

**SUPPLEMENTARY MOVIE LEGENDS**

**Supplementary Movie M1. Live cell imaging of monocyte mediated trogocytosis:** Movie made using confocal microscopy images taken every 11 minutes shows the transfer of AF647-labeled amivantamab from opsonized H1975 NucLight Red cells into monocytes labeled with Hoechst (nuclei).

**Supplementary Movie M2. Live cell imaging of M1 macrophage mediated trogocytosis:** Movie made using confocal microscopy images taken every 11 minutes shows the transfer of AF647-labeled amivantamab from opsonized H1975 NucLight Red cells into M1 labeled with AF488-CD11b/AF488-CD14 and Hoechst (nuclei).

**Supplementary Movie M3. Live cell imaging of M2 macrophage mediated trogocytosis:** Movie made using confocal microscopy images taken every 11 minutes shows the transfer of AF647-labeled amivantamab from opsonized H1975 NucLight Red cells into M2 labeled with AF488-CD11b/AF488-CD14 and Hoechst (nuclei).

**Supplementary Movie M4. Live cell imaging of M1 macrophage mediated trogocytosis in adherent co-culture:** Movie made using confocal microscopy images taken every 11 minutes shows the transfer of AF647-labeled amivantamab from adherent H1975 NucLight Red cells into M1 labeled with AF488-CD11b/AF488-CD14 and Hoechst (nuclei).

**Supplementary Movie M5. Live cell imaging of M2 macrophage mediated trogocytosis in adherent co-culture:** Movie made using confocal microscopy images taken every 11 minutes shows the transfer of AF647-labeled amivantamab from adherent H1975 NucLight Red cells into M2 labeled with AF488-CD11b/AF488-CD14 and Hoechst (nuclei).