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 dose-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-IgG2α (IgG2α) 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 10 g/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 10 g/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 10 g/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) densitometry of EGFR, pEGFR, cMet (normalized to loading control actin) performed following 48 hours treatment of H1975 cells with 10 g/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 urs with 10 g/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 densitometry of EGFR, pEGFR, cMet (normalized to loading control actin) performed following 48 hours treatment of H1975 cells with 10 g/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 10 g/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 8

A) Densitometry of EGFR, pEGFR and cMet protein levels (normalized to loading control Actin) performed following 48 hours treatment of H1975 cells with 10 μg/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 10 μg/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 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 10 μg/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 10 μg/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 9. 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 10 g/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
type 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 10 g/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 12**

### Table A

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<th>Group</th>
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<th>Dose (mg/kg)/Route</th>
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<td>Isotype CTRL</td>
<td>10mg/kg/IP</td>
<td>BIW</td>
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<td>Amivantamab</td>
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<tr>
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<td>IgG2α</td>
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</tbody>
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### Graph B

**Mean % Body Weight Change (±SEM)**

- Isotype Control
- Ami
- IgG2α

**Days post tumor implantation**

### Graph C

**Tumor Volume (mm³)**

- Isotype Control
- Ami
- IgG2α

**Days post implantation**

### Table D

<table>
<thead>
<tr>
<th>Group</th>
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<th>Actual Dosing Schedule/Days</th>
<th>Administration route</th>
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<td>0mg/kg</td>
<td>BIW x 3 weeks</td>
<td>i.p.</td>
</tr>
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<td>2</td>
<td>Amivantamab</td>
<td>5mg/kg</td>
<td>BIW x 3 weeks</td>
<td>i.p.</td>
</tr>
<tr>
<td>3</td>
<td>IgG2α</td>
<td>5mg/kg</td>
<td>BIW x 3 weeks</td>
<td>i.p.</td>
</tr>
</tbody>
</table>

### Graph E

**Body weight (g)**

- Vehicle PBS
- Ami
- IgG2α

**Days post tumor implantation**

### Graph F

**Tumor Volume (mm³)**

- Isotype Control
- Ami
- IgG2α

**Days post implantation**
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-IgG2α (IgG2α) (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-IgG2α (IgG2α) (n=8 mice per treatment group) for 3 weeks BIW.
Supplementary Figure 13. 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.