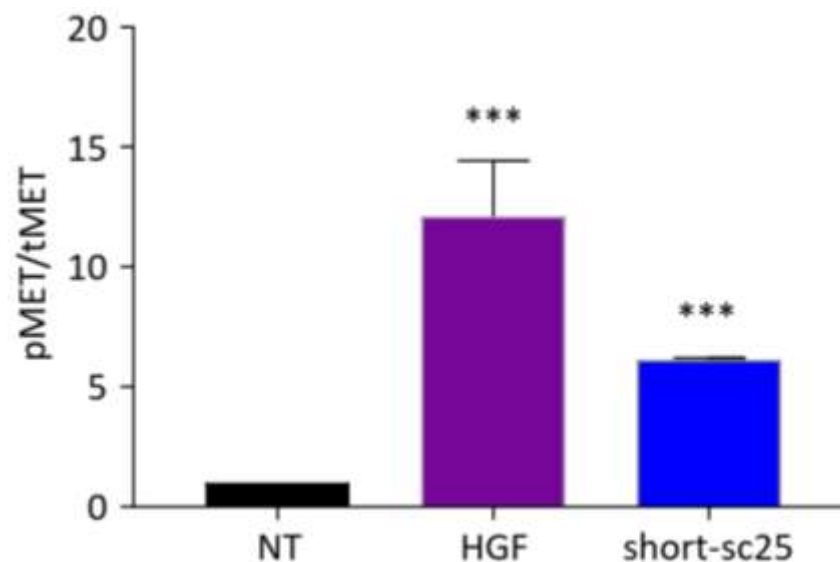
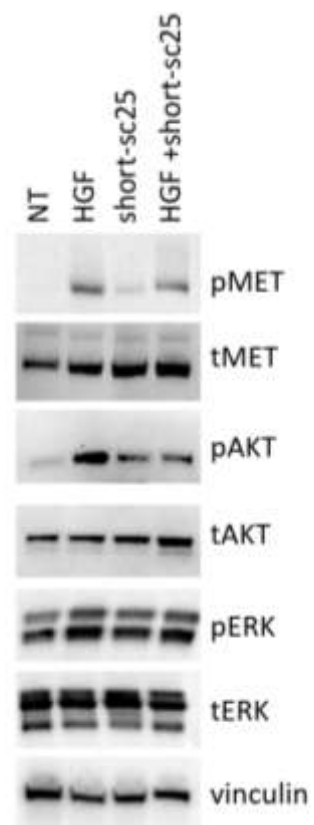


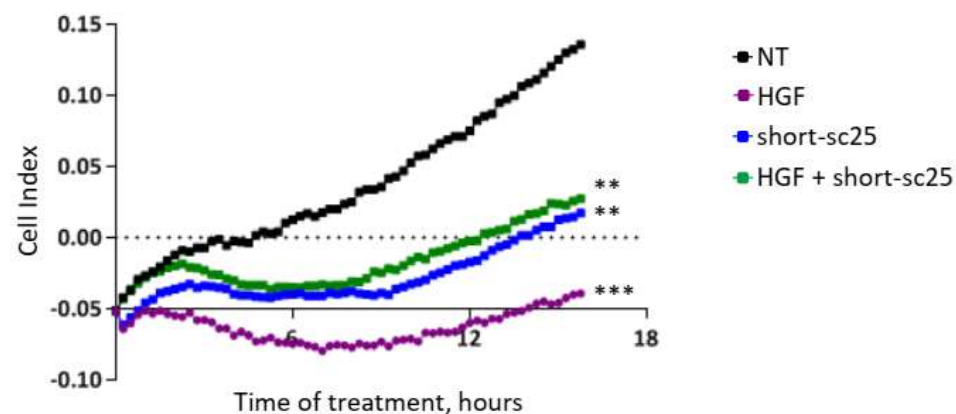
## Supplementary materials:



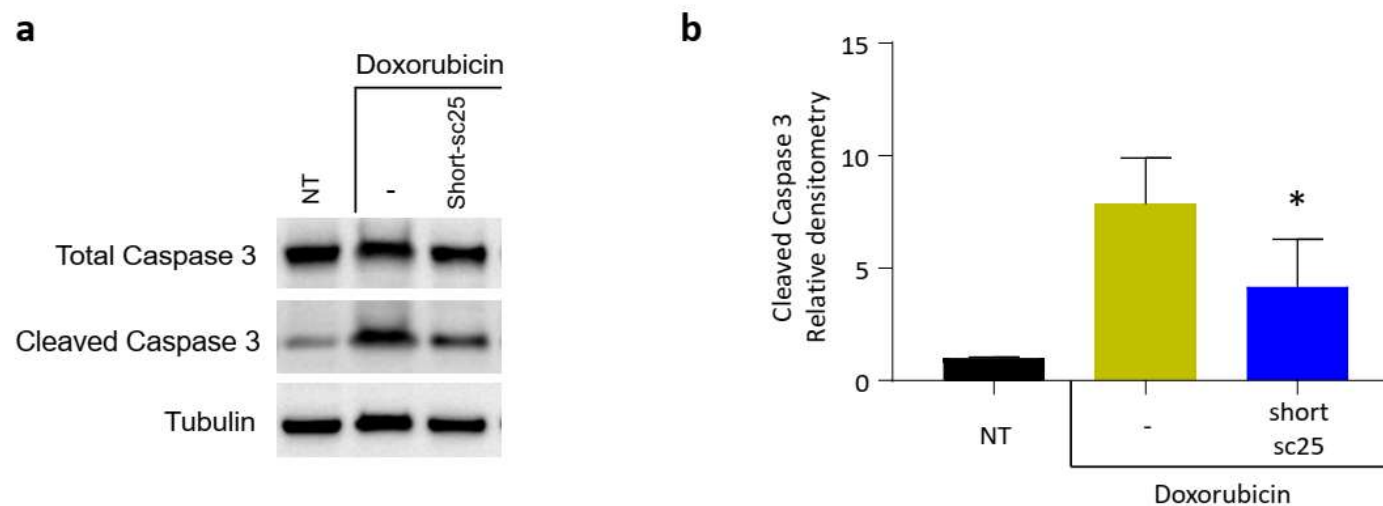
**Figure S1.** Short-sc25 induces MET activation. Sub-confluent A549 cells were serum-starved for 24 h and then stimulated for 15 min at 37 °C with HGF (100 ng/mL) or short-sc25 (0.5  $\mu$ M). Total cell lysates were resolved by electrophoresis and analyzed by Western blot with anti-MET phospho-Tyr1234/1235 or anti-MET antibodies. Graph represents phospho-MET versus total MET ratio; values were determined by densitometry analysis of immunoblot signals obtained from 3 independent experiments. \*\*\*  $p < 0.001$  T-test of Non-Treated (NT) cells versus HGF-treated or short-sc25 treated cells.



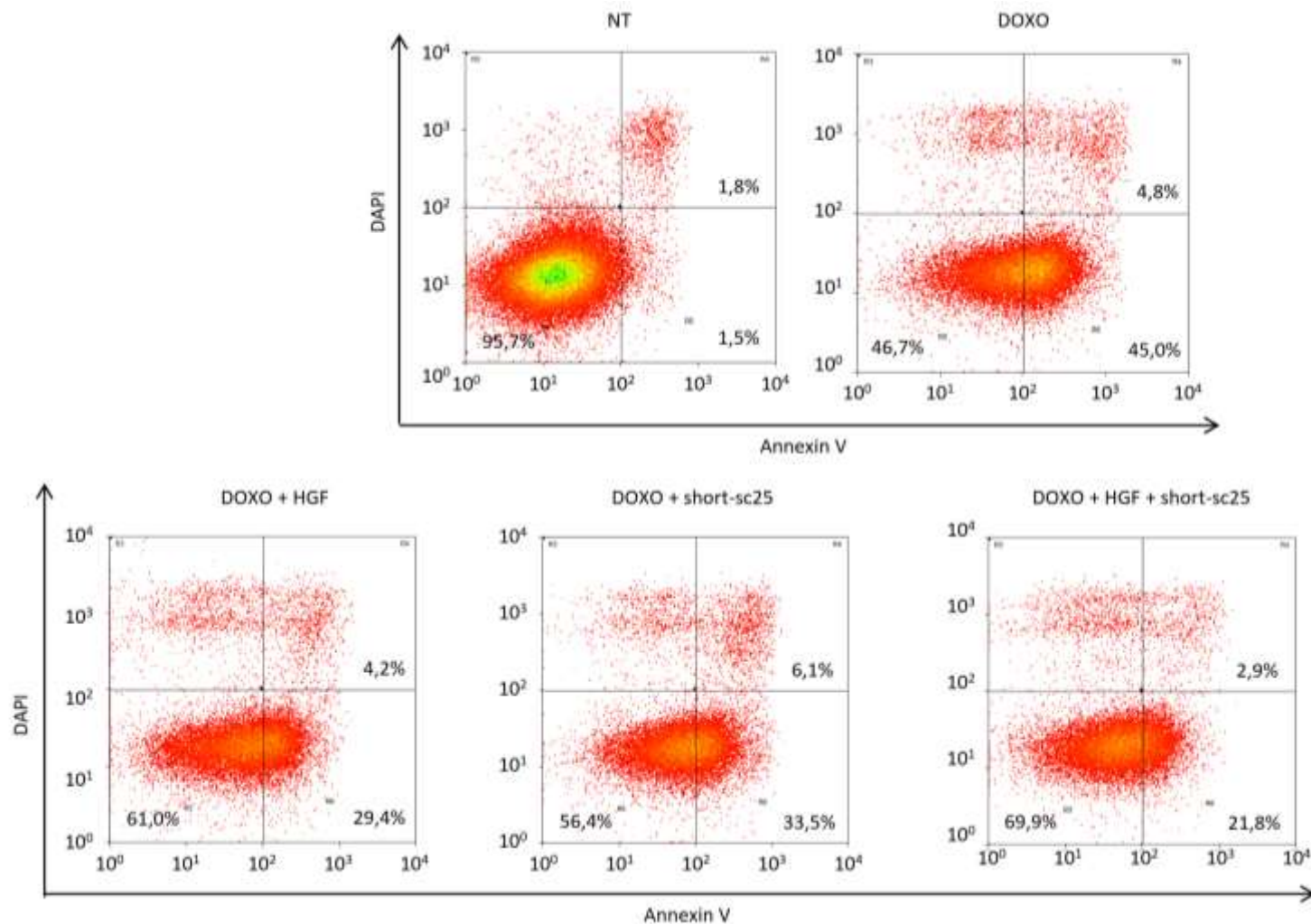
**Figure S2.** Activity of short-sc25 in combination with HGF. Serum-starved A549 cells were stimulated for 15 min with HGF (100 ng/mL), short-sc25 (0.5  $\mu$ M), or both molecules in combination. Total cell lysates were analyzed by immunoblotting. Vinculin was used as loading control. MET phosphorylation and total MET levels were measured using anti-MET antibodies recognizing the major phosphorylation site (Tyr1234/1235) or the C-terminal tail of the molecule, respectively. AKT phosphorylation was measured using anti-AKT antibodies recognizing the phosphorylated Ser473, and ERK phosphorylation was measured using anti-ERK antibodies recognizing the phosphorylated Thr202/Tyr204.



**Figure S3.** Short-sc25 induces scattering of A549 cells. A549 cells were seeded in E-plates (Roche Diagnostics, Mannheim, Germany, 8,000 cells/well) in complete culture medium, and treated with HGF (5 ng/mL), short-sc25 (100nM), or the combination of the two molecules. Electrical impedance was monitored continuously for 16 hrs using an X-Celligence RTCA device (Roche Diagnostic). The electronic readout of cell–sensor impedance is displayed in real-time as Cell Index, a value directly influenced by cell shape and spreading. Addition of HGF induces cell shrinkage and dissociation [1], that results in a decrease of cell index. NT: Non-Treated cells. Data reported in the plots are representative of at least three independent experiments. \*\*\*:  $p \leq 0.001$ ; \*\*:  $p \leq 0.01$  T- test of treated versus untreated cells at the end of the experiments..



**Figure S4.** Short-sc25 inhibits caspase-3 activation in H9C2 cells treated with doxorubicin. **(a)** Immunoblotting analysis of lysates from H9C2 cells treated with short-sc25 (100 nM) for 3 h and then exposed to doxorubicin (25  $\mu$ M) for 1hr. Tubulin (p55) was analyzed as loading control. **(b)** Graph representing cleaved versus total caspase-3 ratio, relative to Non-Treated (NT) cells. Values were determined by densitometry analysis of immunoblot signals obtained from 3 independent experiments. \*  $p < 0.05$  T-test of doxorubicin + short-sc25 treated cells versus doxorubicin alone.



**Figure S5.** Short-sc25 protects A549 cells from doxorubicin-induced apoptosis. A549 cells were seeded in 6-well plates (300,000 cells/well) in complete cell culture medium. The following day, cells were starved for 24 h and then treated with HGF (50 ng/mL), short-sc25 (0,5  $\mu$ M) or the combination of the two molecules for further 24 hrs. Cells were then exposed to doxorubicin (4  $\mu$ M) and after 24 h stained with Annexin V-APC and DAPI. Analysis was performed using a CyANADP apparatus (Dako, Santa Clara, CA), and data were elaborated with Summit 4.3 software (Dako).

## References

- 1 Buus, R.; Faronato, M.; Hammond, D.E.; Urbé, S. and Clague, M.J. Deubiquitinase activities required for hepatocyte growth factor-induced scattering of epithelial cells. *Curr. Biol.* **2009**, *19*, 1463–1466