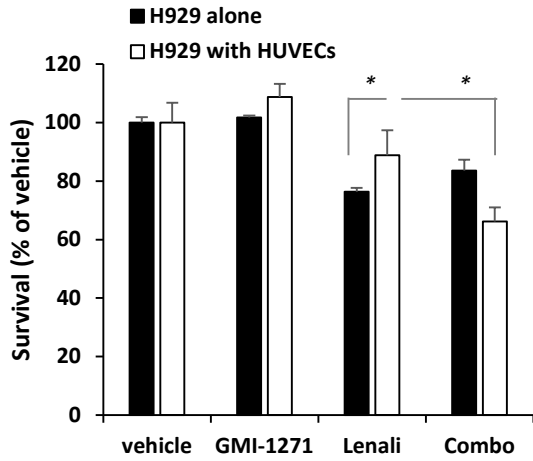
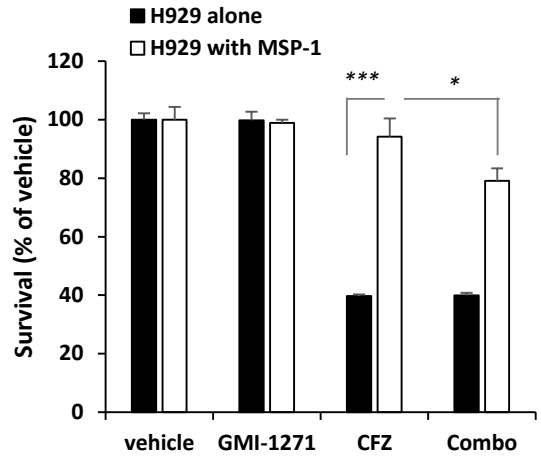


Supplementary Figure 1

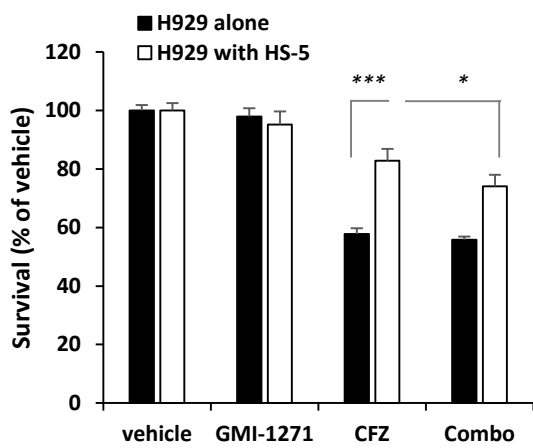
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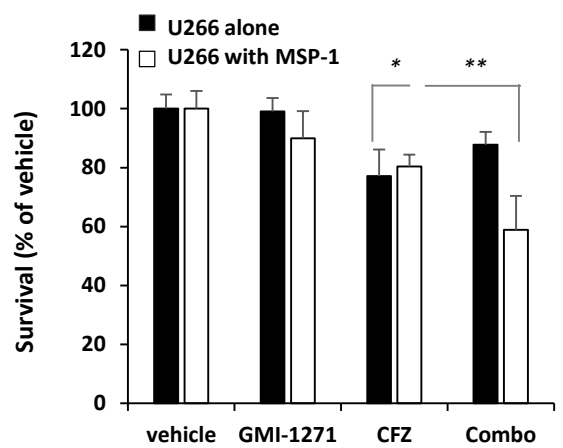
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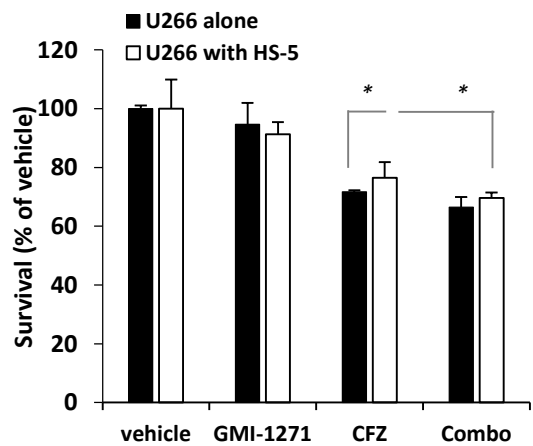
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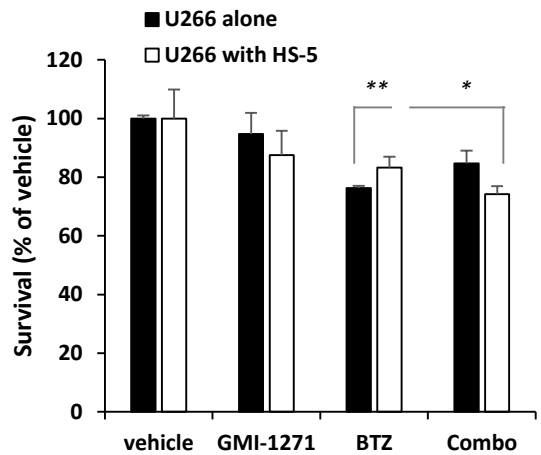
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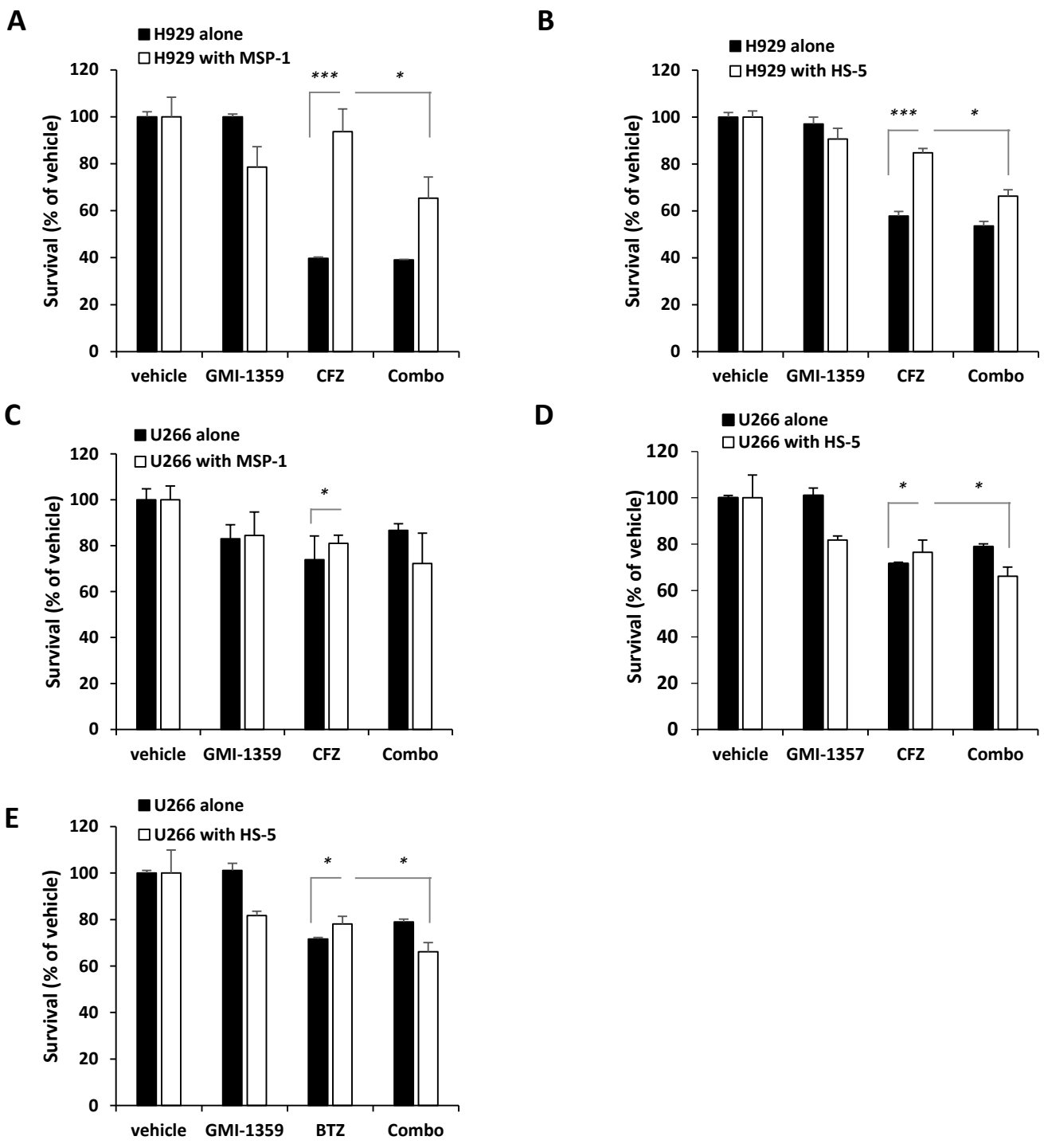


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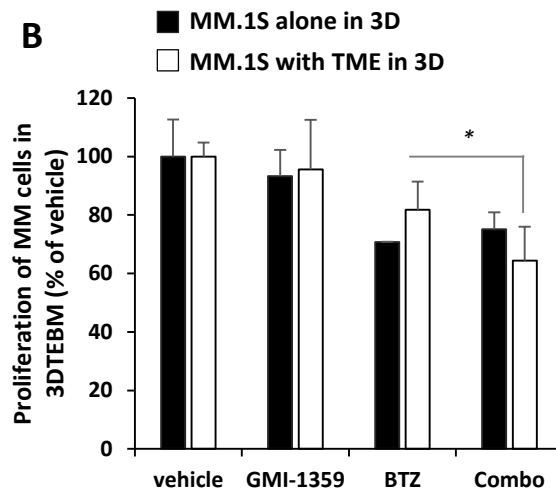
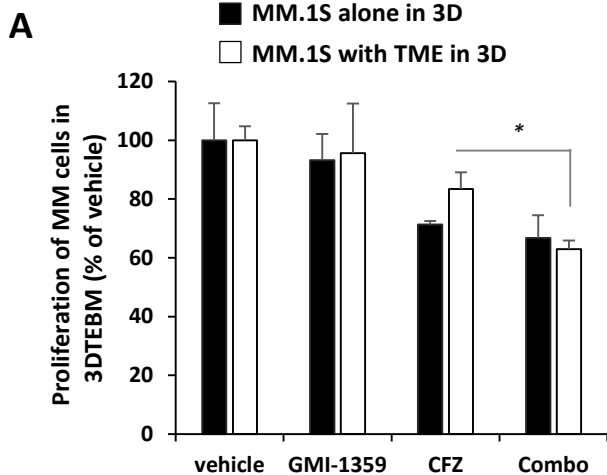
Supplementary Figure 1 Combination of GMI-1271 with lenalidomide, carfilzomib or bortezomib overcomes stroma-induced drug resistance in vitro. Survival of H929 cells treated with GMI-1271 (20 μ M) and cultured with or without HUVECs +/- lenalidomide (Lenali, 1 μ M) (A), with or without MSP-1 +/- carfilzomib (CFZ, 5nM) (B), and with or without HS-5 +/- CFZ (C). Survival of U266 cells treated with GMI-1271 (20 μ M) and cultured with or without MSP-1 +/- CFZ (5 nM) (D), with or without HS-5 +/- CFZ (E), and with or without HS-5 +/- BTZ (5 nM) (F). Survival of MM cells was tested at 24 hours using MTT assay. Results are representative of at least three independent experiments and demonstrated as mean \pm s.e.m. with statistical significance for p values less than 0.05 calculated using unpaired Student's t-test (* p <0.05; ** p <0.01; *** p <0.001).

Supplementary Figure 2



Supplementary Figure 2 Combination of GMI-1359 with carfilzomib or bortezomib overcomes stroma-induced drug resistance in vitro. Survival of H929 cells treated with GMI-1359 (20 μ M) and cultured with or without MSP-1 +/- carfilzomib (CFZ, 5nM) **(A)**, and with or without HS-5 +/- CFZ **(B)**. Survival of U266 cells treated with GMI-1359 (20 μ M) and cultured with or without MSP-1 +/- CFZ (5 nM) **(C)**, with or without HS-5 +/- CFZ **(D)**, and with or without HS-5 +/- BTZ (5 nM) **(E)**. Survival of MM cells was tested at 24 hours using MTT assay. Results are representative of at least three independent experiments and demonstrated as mean \pm s.e.m. with statistical significance for p values less than 0.05 calculated using unpaired Student's t -test (* p <0.05; *** p <0.001).

Supplementary Figure 3



Supplementary Figure 3 Combination of GMI-1359 with carfilzomib or bortezomib overcomes stroma-induced drug resistance in vitro in the 3D tissue culture model. MM.1S-GFP cells were cultured with and without accessory cells (recapitulating tumor microenvironment, TME) and treated with or without GMI-1359 (25 μ M), alone or in combination with carfilzomib (CFZ; 10 nM) (**A**) or bortezomib (BTZ; 10 nM) (**B**) in 3DTEBM for 48 hours. Scaffolds were then digested with collagenase and the number of surviving MM.1S-GFP+ cells was analyzed by flow cytometry. Results are representative of at least three independent experiments and demonstrated as mean \pm s.e.m. with statistical significance for p values less than 0.05 calculated using unpaired Student's t -test (* p <0.05).