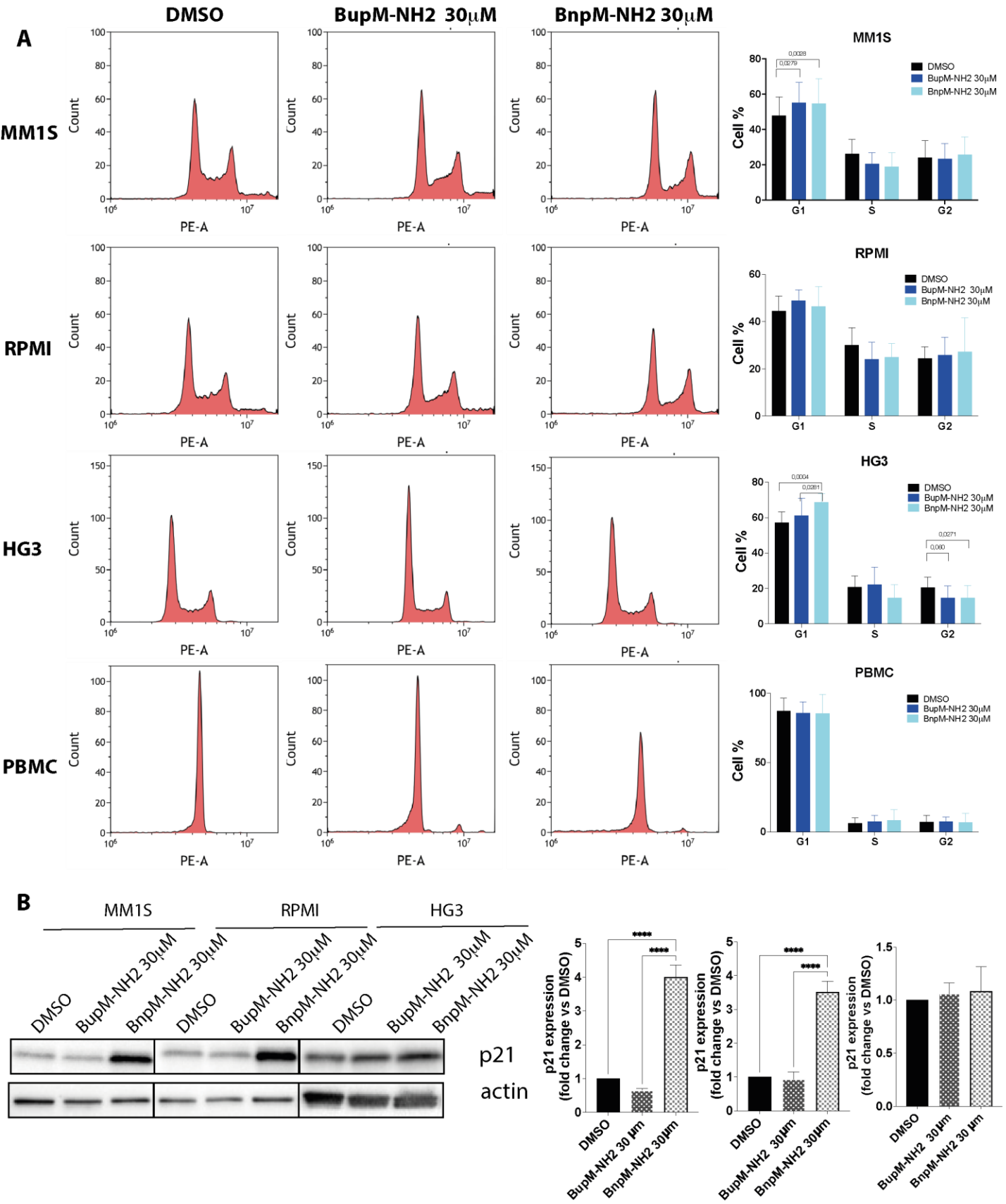
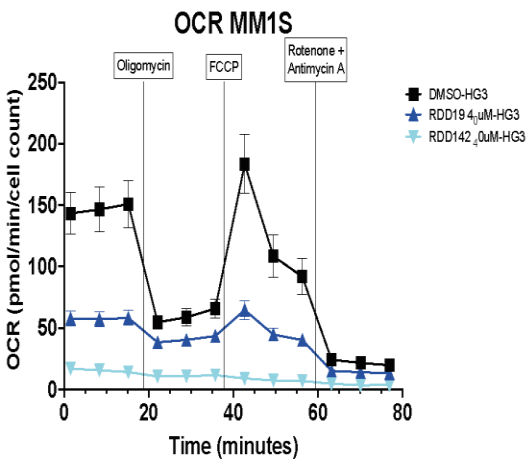
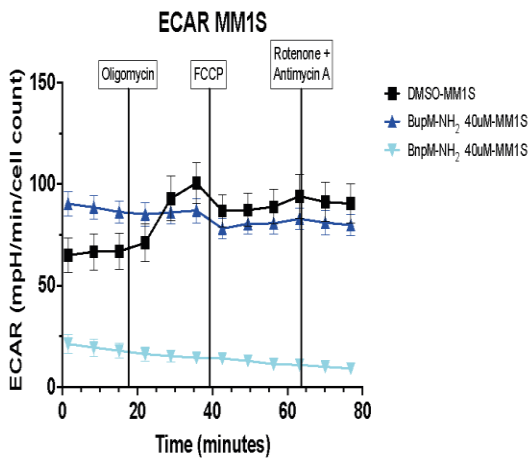
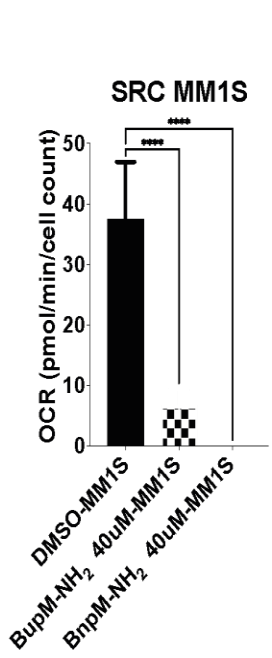
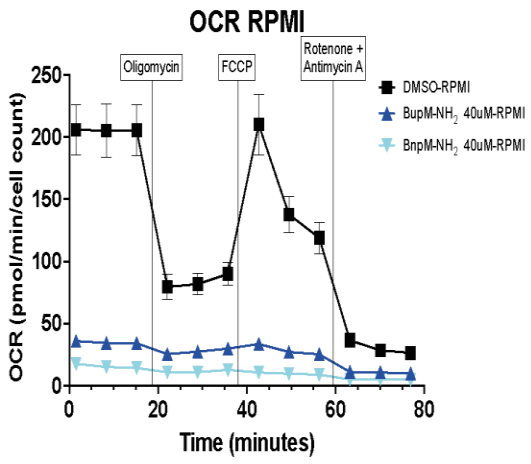


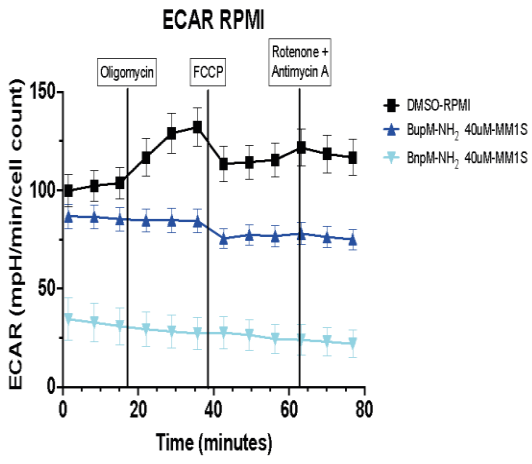
Supplementary Figure 1. Precursors of Darunavir analogues, BupM-NH2 and BnpM-NH2 halt the cell cycle of MM and CLL cells in the G1 phase. A) The cell cycle of MM1S, RPMI-8226, and HG3 treated with BupM-NH2 and BnpM-NH2 (30 μM) for 48h was assessed via FACS after PI staining. The cycle phases (G1, S, G2) were quantified by Kaluza and displayed in a bar graph. Data, shown as mean ± SD, were derived from at least three independent experiments. Significant differences ($P \leq 0.05$) were identified using one-way ANOVA with Tukey's post-hoc analysis. B) Expression levels of p21 in MM1S, RPMI-8226, and HG3 cells after BupM-NH2 and BnpM-NH2 (30 μM) treatment for 48 h were assessed via WB. The intensity of the p21 bands, normalized against actin, is depicted in a bar graph. Data, presented as mean ± SD, were obtained from at least three independent experiments. Significant differences ($P \leq 0.05$) were determined by one-way ANOVA with Tukey's post analysis.

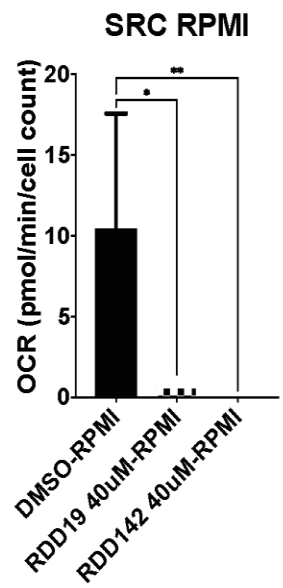


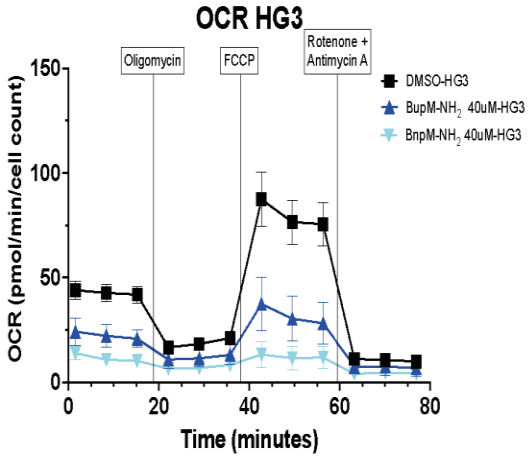


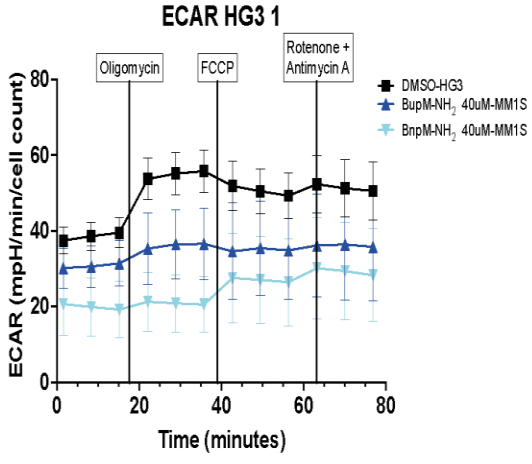


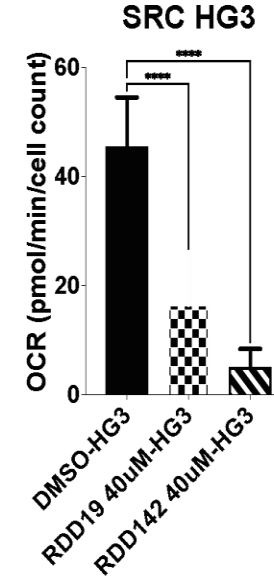










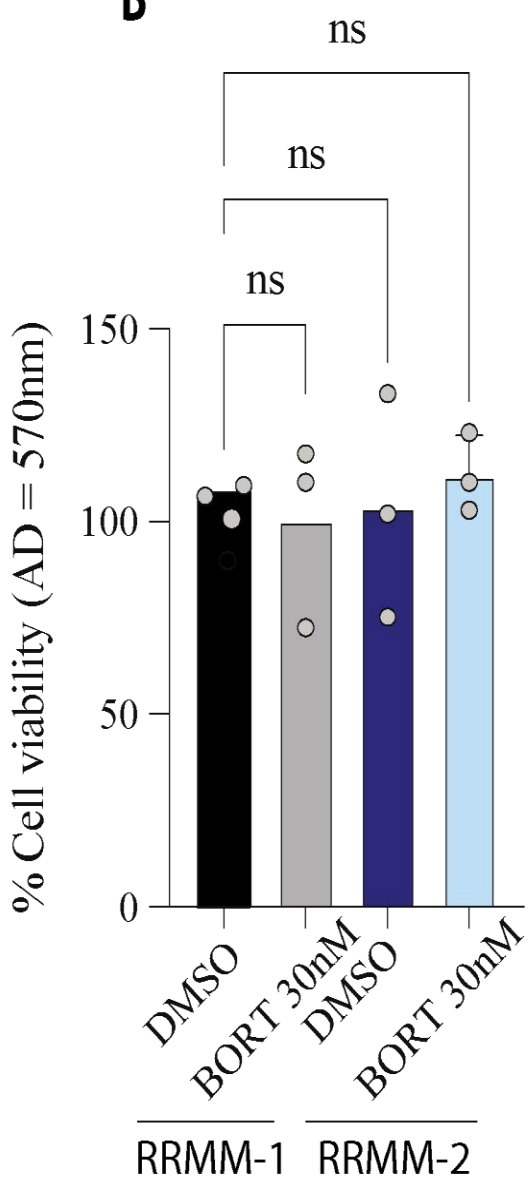


Supplementary Figure 2. BupM-NH2 and BnpM-NH2 drastically reduce SRC in MM and CCL. Mito Stress test, performed on Seahorse XFe96, measured the SRC in MM1S, RPMI-8226, and HG3 cells treated with BupM-NH2 or BnpM-NH2 (30 μM) for 24 h. The graph shows the basal respiration/acidification points and changes after the addition of oligomycin, FCCP, and antimycin A/rotenone. SRC represents the mitochondrial reserve for cells to produce ATP in response to stress-induced metabolic demand, calculated as maximal respiration minus routine respiration, using OCR and ECAR. Bar graphs show SRC of MM1S, RPMI, and HG3 cells upon treatment with BupM-NH2 and BnpM-NH2. P-values were determined using one-way ANOVA with Tukey's post hoc analysis. Differences were considered significant at $P \leq 0.05$.

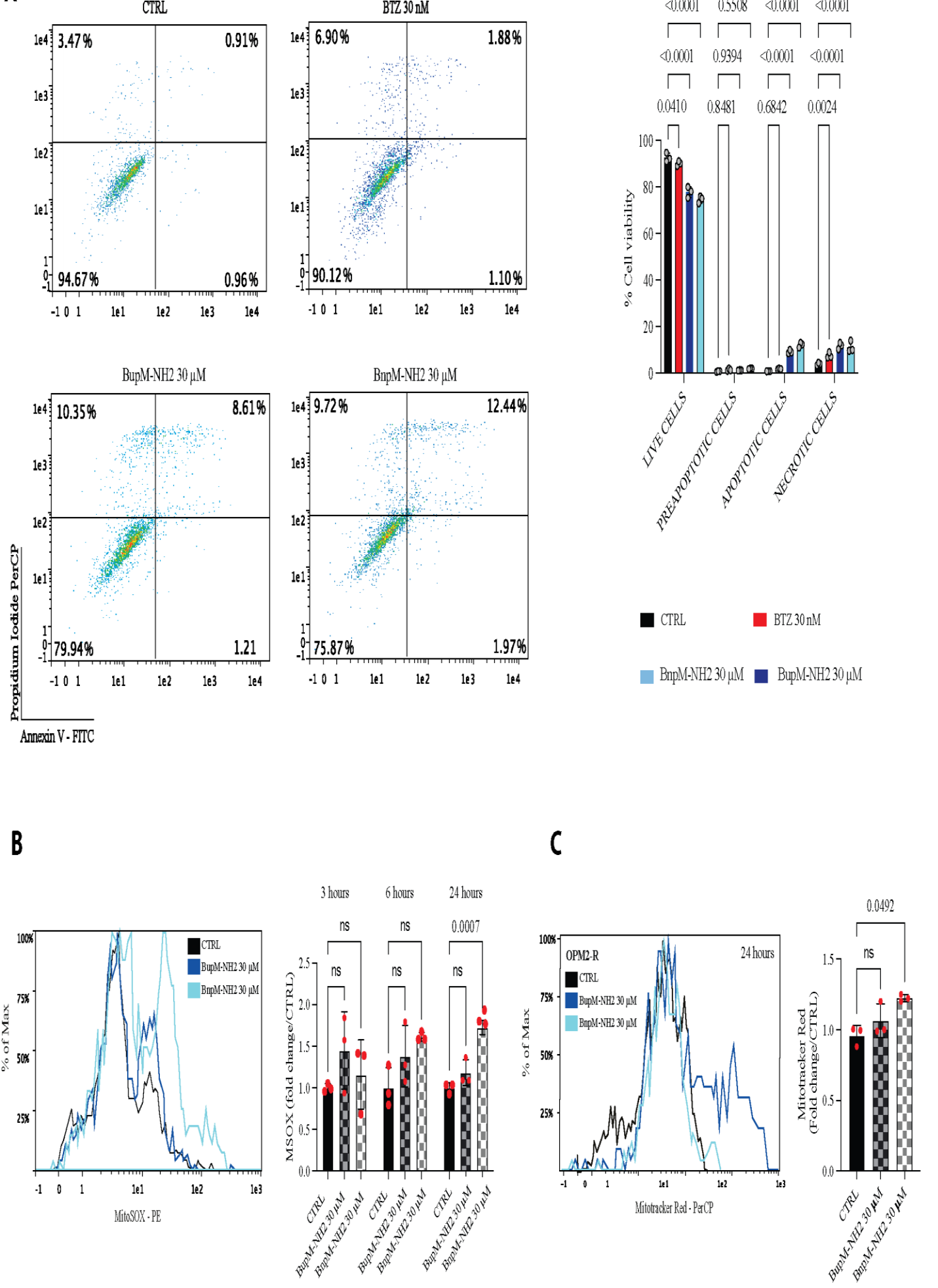
A

Patients	FASE	Age	Gender	Hb (g/dL)	eGFR	R-ISS stage	FISH	Cytogenetic Risk	LDH (UI/L)
R68/24	NDMM	72	Male	13,1	58	2	No alterations	Standard	160
R69/24	NDMM	54	Female	7,6	45	3	del17p	High	260
R163/24	NDMM	76	Female	7,4	60	2	amp1q	High	190
R57/24	RRMM	56	Female	7,1	72	3	del17p, t 4,14	High	450
R45/23	RRMM	63	Male	10,6	80	1	No alterations	Standard	132
R67/22	RRMM	56	Male	9,6	40	3	del17p	High	352
R04/22	RRMM	62	Male	9,2	60	1	No alterations	Standard	190
R281/24	RRMM	55	Male	11,5	66	2	t 11,14	Standard	290

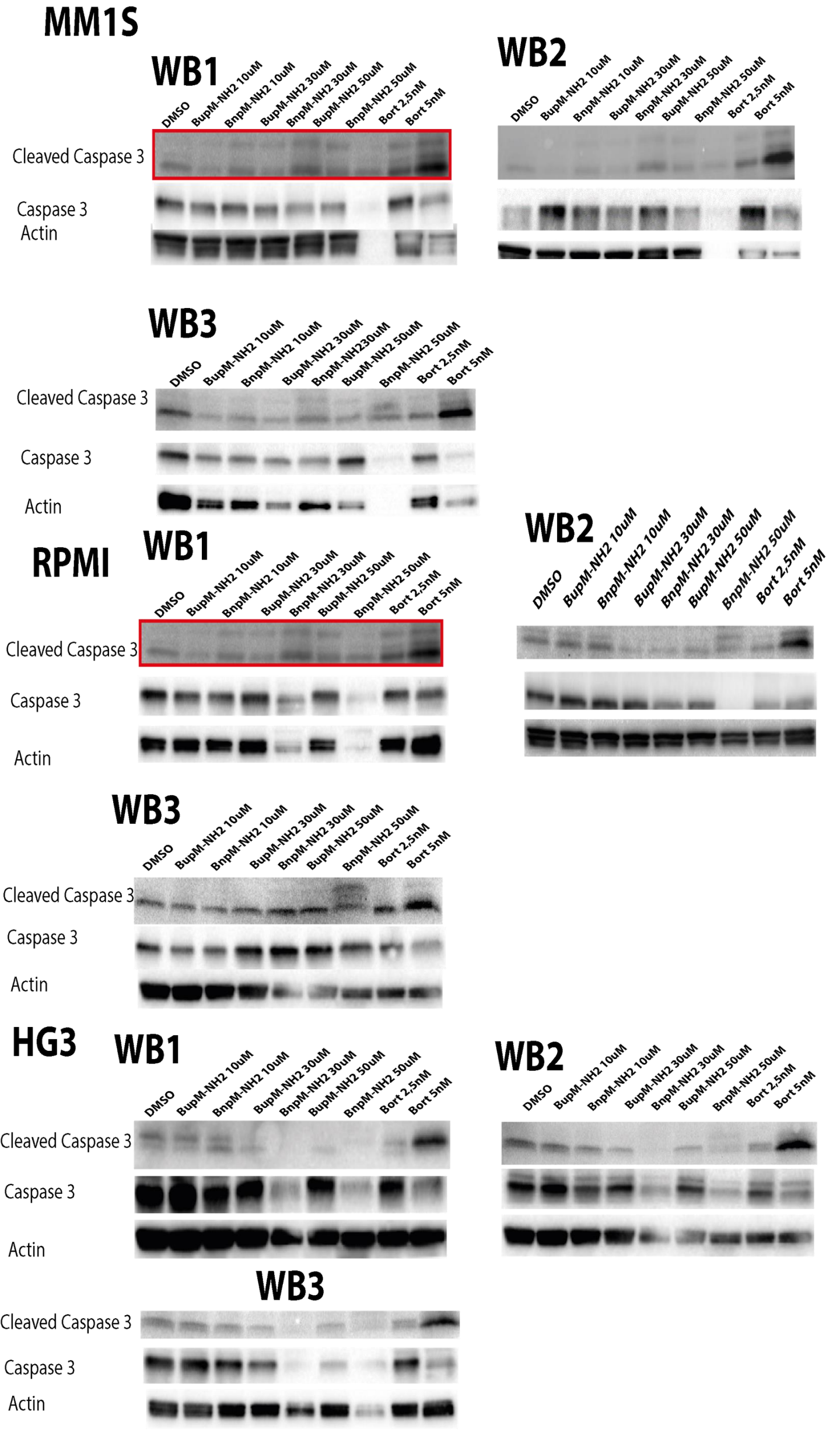
B



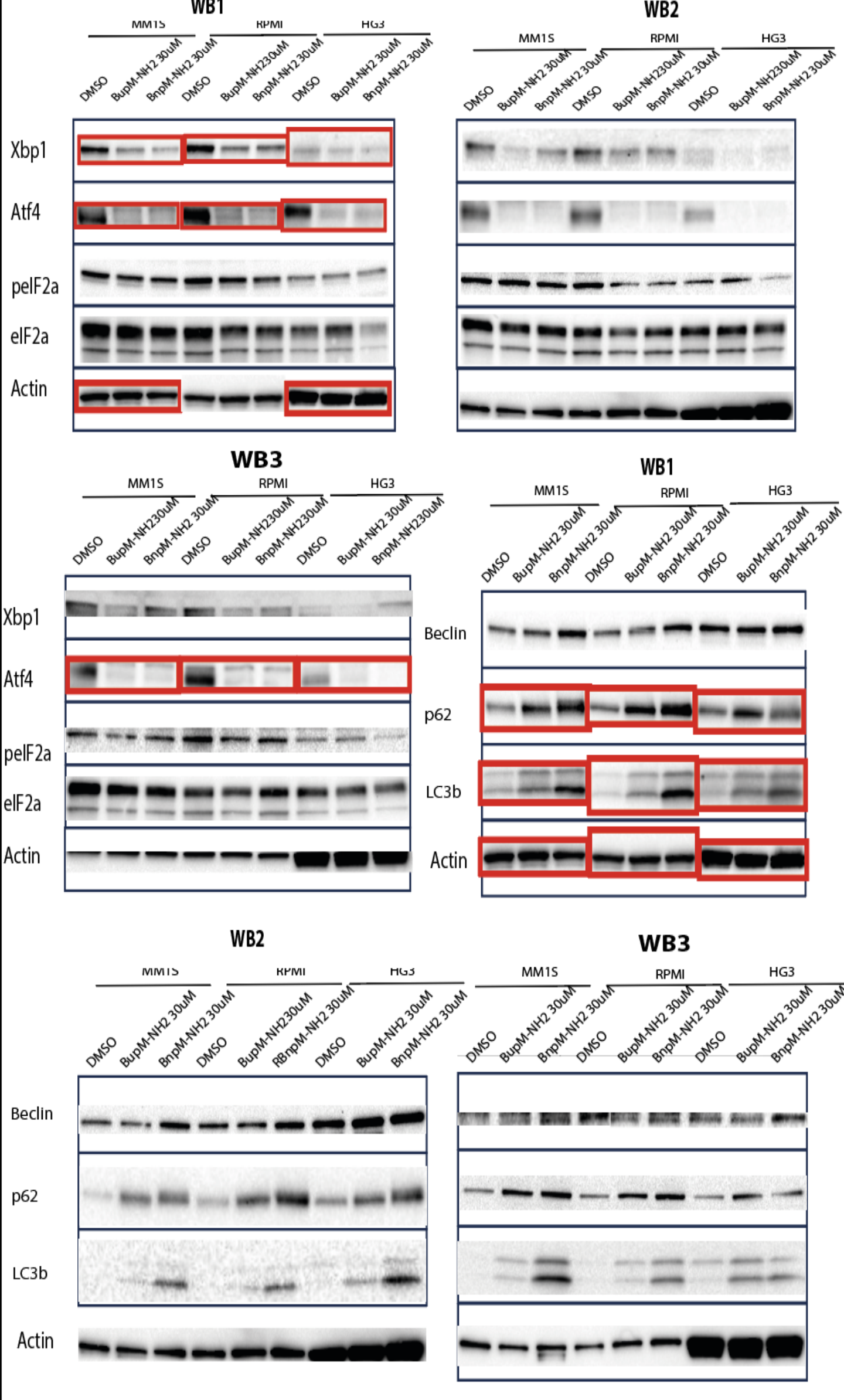
Supplementary Figure 3. "Patient-derived MM cells were resistant to bortezomib. A) Table showing patient characteristics: patient demographics, cancer mutations and histopathological grades; B) MM isolated from patients resistant to bortezomib-lenalidomide-dexamethasone (RRMM1 and 2) were tested in vitro with bortezomib 30nM for 48h. Cell viability was assessed using the MTS assay. For statistical analysis, Student's t-test was used for comparison between groups." Differences were considered significant when $P \leq 0.05$. All data are represented as mean ± SEM.



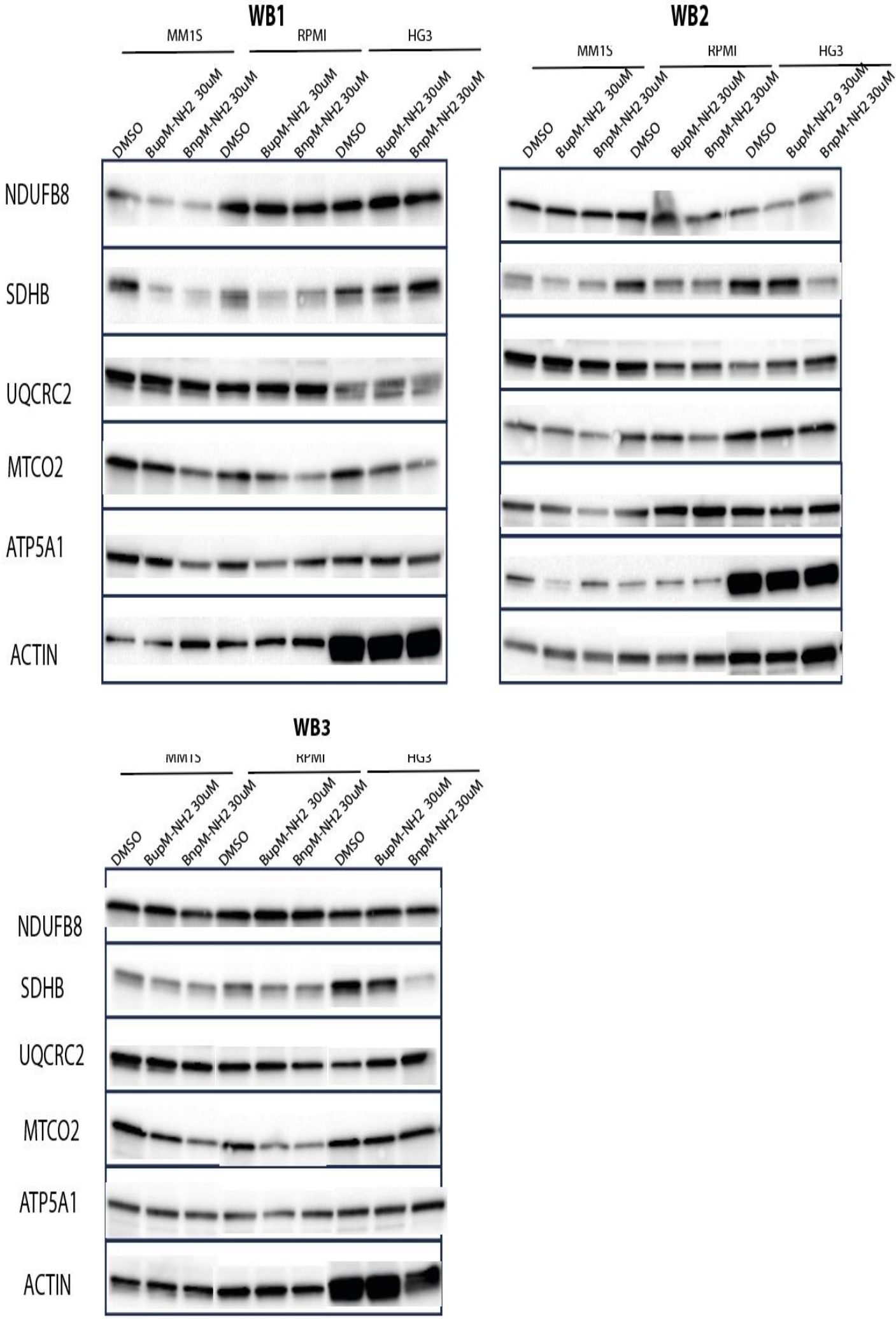
Supplementary Figure 4. BupM-NH2 and BnpM-NH2 exhibit cytotoxicity against bortezomib-resistant MM cells (OPM2-R). A) OPM2-R cells were treated with 30 nM bortezomib, 30 mM BupM-NH2, or BnpM-NH2 for 48 h. Cytotoxic effects were evaluated using fluorescence-activated cell sorting (FACS) to quantify the proportions of viable, apoptotic, and necrotic cells. The results, representing the percentage of viable cells from three experiments, are illustrated in the bar graph. B) The impact of BupM-NH2 and BnpM-NH2 on ROS production and mitochondrial mass in OPM2-R cells was assessed after 24-hour treatment by FACS, using MitoSOx and MitoTracker staining. . P-values were determined using one-way ANOVA with Tukey's post hoc analysis. Differences were considered significant at $P \leq 0.05$..



Suppl. Figure 5. Raw Western Blot included in Figure 2



Suppl. Figure 6. Raw data for Western Blots included in figure 3.



Suppl. Figure 7. Raw data for Western Blots included in figure 5.