SHP2 inhibitors show anti-myeloma activity and synergize with bortezomib in the treatment of multiple myeloma.

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**Supplementary Table 1. Concentration-dependent combined effects of SHP099 and BTZ in RPMI-8226 and NCI-H929 cell lines.** Fa, fraction affected; CI, combination index. CI of < 1 represents synergism, CI of 1 or close to 1 represents additive effects, and CI of > 1 represents antagonism.

| Dose SHP099 (µM) | Dose BTZ (nM) | RPMI-8226 | Fa     | CI    | Dose SHP099 (µM) | Dose BTZ (nM) | NCI-H929 | Fa     | CI    |
|------------------|--------------|-----------|--------|-------|------------------|--------------|----------|--------|-------|
| 10               | 1.5          | 0.41243   | 0.77605|       | 10               | 1            | 0.26620  | 1.33957|       |
| 10               | 3.0          | 0.49798   | 0.99333|       | 10               | 2            | 0.59157  | 1.09967|       |
| 10               | 4.5          | 0.66667   | 0.86517|       | 10               | 3            | 0.89352  | 0.9696 |       |
| 20               | 1.5          | 0.42615   | 1.01876|       | 20               | 1            | 0.41731  | 1.25532|       |
| 20               | 3.0          | 0.61009   | 0.86352|       | 20               | 2            | 0.79685  | 0.86943|       |
| 20               | 4.5          | 0.74288   | 0.75553|       | 20               | 3            | 0.88657  | 1.01853|       |
| 30               | 1.5          | 0.47054   | 1.11706|       | 30               | 1            | 0.56713  | 1.05478|       |
| 30               | 3.0          | 0.65066   | 0.87882|       | 30               | 2            | 0.85648  | 0.80125|       |
| 30               | 4.5          | 0.79177   | 0.68602|       | 30               | 3            | 0.90509  | 0.95184|       |
Supplementary Table 2. Concentration-dependent combined effects of RMC-4550 and BTZ in RPMI-8226 and NCI-H929 cell lines. Fa, fraction affected; CI, combination index. CI of < 1 represents synergism, CI of 1 or close to 1 represents additive effects, and CI of > 1 represents antagonism.

| Dose RMC-4550 (μM) | Dose BTZ (nM) | RPMI-8226 | Dose RMC-4550 (μM) | Dose BTZ (nM) | NCI-H929 |
|---------------------|---------------|-----------|---------------------|---------------|-----------|
| 5                   | 1.5           | 0.22357   | 1.25193             | 5             | 1         |
| 5                   | 3.0           | 0.51009   | 0.86895             | 5             | 2         |
| 5                   | 4.5           | 0.68765   | 0.79127             | 5             | 3         |
| 10                  | 1.5           | 0.33656   | 1.0939              | 10            | 1         |
| 10                  | 3.0           | 0.56765   | 0.84983             | 10            | 2         |
| 10                  | 4.5           | 0.76998   | 0.66291             | 10            | 3         |
| 20                  | 1.5           | 0.3753    | 1.78113             | 20            | 1         |
| 20                  | 3.0           | 0.71421   | 0.75869             | 20            | 2         |
| 20                  | 4.5           | 0.9088    | 0.40428             | 20            | 3         |

Supplementary Figure 1. Decreased p-SHP2 and SHP2 expression in bortezomib resistant myeloma cell lines. (A) Images show the most representative blots of p-SHP2 and SHP2 in bortezomib-resistant RPMI-8226 and NCI-H929 cells (BTZR). Bortezomib naïve MM cells (WT) were used as controls and GAPDH was used as loading control. (B) The graph represents the relative quantification for indicated proteins expression as mean ± SD of three independent experiments. * p< 0.05 and ** p < 0.01.
Supplementary Table 3. Combination index of bortezomib combination treatment with SHP099 in bortezomib resistant cell lines (RPMI-8226 BTZR and NCI-H929 BTZR). Fa, fraction affected; CI, combination index. CI of < 1 represents synergism, CI of 1 or close to 1 represents additive effects, and CI of > 1 represents antagonism.

| Dose SHP099 (μM) | Dose BTZ (nM) | RPMI-8226 BTZR | Fa | CI | Dose SHP099 (μM) | Dose BTZ (nM) | NCI-H929 BTZR | Fa | CI |
|------------------|---------------|----------------|-----|----|------------------|---------------|---------------|-----|----|
| 10               | 40            | 0.37196        | 1.15501 | 10 | 40             | 0.40988        | 1.16467       |
| 10               | 45            | 0.58104        | 0.93948 | 10 | 45             | 0.46802        | 1.04129       |
| 10               | 50            | 0.63128        | 1.07786 | 10 | 50             | 0.47674        | 1.14822       |
| 20               | 40            | 0.43841        | 1.36703 | 20 | 40             | 0.45640        | 1.36182       |
| 20               | 45            | 0.60535        | 1.09011 | 20 | 45             | 0.56395        | 0.92289       |
| 20               | 50            | 0.70421        | 1.06299 | 20 | 50             | 0.63953        | 0.76677       |
| 30               | 40            | 0.52512        | 1.33988 | 30 | 40             | 0.53488        | 1.16716       |
| 30               | 45            | 0.65964        | 1.10873 | 30 | 45             | 0.64244        | 0.77337       |
| 30               | 50            | 0.73906        | 1.08169 | 30 | 50             | 0.72093        | 0.613660      |

Supplementary Table 4. Combination index of bortezomib combination treatment with RMC-4550 in bortezomib resistant cell lines (RPMI-8226 BTZR and NCI-H929 BTZR). Fa, fraction affected; CI, combination index. CI of < 1 represents synergism, CI of 1 or close to 1 represents additive effects, and CI of > 1 represents antagonism.

| Dose RMC-4550 (μM) | Dose BTZ (nM) | RPMI-8226 BTZR | Fa | CI | Dose RMC-4550 (μM) | Dose BTZ (nM) | NCI-H929 BTZR | Fa | CI |
|-------------------|---------------|----------------|-----|----|-------------------|---------------|---------------|-----|----|
| 5                 | 40            | 0.36277        | 1.18783 | 5  | 40             | 0.28218        | 1.43393       |
| 5                 | 45            | 0.43377        | 1.18505 | 5  | 45             | 0.52228        | 0.85041       |
| 5                 | 50            | 0.48918        | 1.29082 | 5  | 50             | 0.74752        | 0.60653       |
| 10                | 40            | 0.4658         | 0.96395 | 10 | 40             | 0.4901         | 0.95428       |
| 10                | 45            | 0.55325        | 0.96167 | 10 | 45             | 0.60396        | 0.81445       |
| 10                | 50            | 0.61268        | 1.07063 | 10 | 50             | 0.78465        | 0.58571       |
| 20                | 40            | 0.52294        | 1.06275 | 20 | 40             | 0.51733        | 1.22027       |
| 20                | 45            | 0.5645         | 1.13654 | 20 | 45             | 0.64851        | 0.89139       |
| 20                | 50            | 0.65385        | 1.09704 | 20 | 50             | 0.86881        | 0.47022       |