**Supplementary Figure S1.**

Quantitative reverse transcription PCR analysis showing mRNA levels of 20S proteasome subunits in cisplatin-resistant variants from A549, H1299, H1975, SBC3, and SBC5 cells.

**Supplementary Figure S2.**

The effect of the immunoproteasome inhibitor PR957 on cisplatin-resistant (CR) variants derived from (**a**) A549, (**b**) H1299, (**c**) H1975, (**d**) SBC3, and (**e**) SBC5 lung cancer cell lines by MTT assay.

**Supplementary Figure S3.**

(**a**) Western blot analysis showing the accumulation of ubiquitinated proteins after carfilzomib (CFZ) treatment. (**b**) Quantification of western blot analysis shown in (**a**) and normalized to actin.

**Supplementary Figure S4.**

Simultaneous knockdown of PSMB5, PSMB8, and PSMB9 by small interfering RNA (siRNA) in the cisplatin-resistant variants of A549 and H1299. (**a**) Knockdown efficiency of PSMB5, PSMB8, and PSMB9 was confirmed by western blot analysis. Simultaneous knockdown of PSMB5, PSMB8, and PSMB9 suppressed 20S proteasome chymotrypsin-like activity (**b**) but did not impair cell viability (**c**). The effects of the triple knockdown on the sensitivity to cisplatin (**d**) and carfilzomib (CFZ) (**e**) were analyzed by MTT cell proliferation assay. NT, non-target. \*\**P*<0.01, Welch t test.

**Supplementary Figure S5.**

Combination of antioxidant agent and carfilzomib (CFZ) in the cisplatin-resistant (CR) variants of A549 and H1299. (**a**) 1000 mol/L of glutathione (GSH) or 100 mol/L of N-acetylcysteine (NAC) reduced intracellular reactive oxygen species levels. The effect of antioxidant agent on the sensitivity of CFZ was analyzed by MTT cell proliferation assay in the CR variants of A549 (**b**) and H1299 (**c**). \*\**P*<0.01, \*\*\**P*<0.001, Welch t test.

**Supplementary** **Figure S6.**

Western blot analysis showing the expression of proteins involved in controlling G2/M cell cycle progression in the indicated cells after carfilzomib (CFZ) treatment.

**Supplementary Figure S7.**

Western blot analysis showing the expression of proteins involved in endoplasmic reticulum stress in the indicated cells after carfilzomib (CFZ) treatment.