**Supplemental Materials and Methods**

**Cell lines and drugs**. Mouse cell lines 595BzS, 595BzR, 589BzS and 589BzR were cultured as previously described (1). Briefly, cell were maintained in murine PC media containing RPMI 1640 (Lonza, Allendale, NJ), 15% fetal bovine serum (FBS) (Cellgro, Mediatech, Manassas, VA), 25 mmol/L HEPES (Lonza), 1mmol/L sodium pyruvate, 50 μmol/L beta-mercaptoethanol (Sigma-Aldrich, St. Louis, MO), 50 units/ml of penicillin and streptomycin (Thermo Fisher Scientific, Waltham, MA), 2 mmol/L $_{L}$-glutamine (Gibco Life Technologies, Grand Island, NY) and 0.5 ng/ml interleukin (IL)-6 (R&D Systems, Minneapolis, MN). Cells were split every 3 days and maintained at concentrations between 2-5x$10^6$ cells/mL.

Bortezomib (Bz) (Millennium Pharmaceuticals, Inc., Cambridge, MA) was dissolved in serum-free RPMI 1640.

**Fluorescence analysis and sorting.** To detect both intracellular and cell-surface CXCR4 expression, cells were first stained with anti-mouse CD184/CXCR4-PE (clone 2B11, eBioscience, San Diego, CA) antibody or Rat IgG2b kappa-PE isotype control (eBioscience) and then fixed using the Cytofix/Cytoperm Fixation/Permeabilization kit (BD Biosciences, San Jose, CA), blocked in buffer containing 30% FBS, 0.1% Saponin and 20 mM HEPES, and stained a second time with the same antibodies. Samples were analyzed using the FACSCalibur and FlowJo Software (Tree Star, Ashland, OR).

**Human gene expression profiling analysis.** Plasma cell purifications and gene expression profiling, using the Affymetrix U133Plus2.0 microarray (Affymetrix, Santa Clara, CA), were performed as previously described (2, 3). Gene expression profiles of $CD138^+$ bone marrow plasma cells from MM patients enrolled in the APEX (3) and MMTT3 (2) clinical trials were used in these studies. Signal intensities were pre-processed and normalized by GCOS1.1 software (Affymetrix). We performed permutation analyses to correlate *CXCR4* expression with patient survival in the APEX phase 3 trial (n=156) and total therapy 3 trial (TT3, n=214), respectively. The presented p value was based on the best cut-off (50% patients in high- or low-*CXCR4*

group) between these 2 parameters in each dataset. All statistical analyses were performed with the use of the statistical software R (Version 2.6.2) (http://www.r-project.org).

## References


1. Stessman HA, Baughn LB, Sarver A, Xia T, Deshpande R, Mansoor A*, et al.* Profiling bortezomib resistance identifies secondary therapies in a mouse myeloma model. *Mol Cancer Ther* 2013 Mar 27.

2. Shaughnessy JD, Jr., Qu P, Usmani S, Heuck CJ, Zhang Q, Zhou Y*, et al.* Pharmacogenomics of bortezomib test-dosing identifies hyperexpression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with total therapy 3. *Blood* 2011 May 31.

3. Mulligan G, Mitsiades C, Bryant B, Zhan F, Chng WJ, Roels S*, et al.* Gene expression profiling and correlation with outcome in clinical trials of the proteasome inhibitor bortezomib. *Blood* 2007 Apr 15; **109**(8)**:** 3177-3188.