In a phase I/II trial of bortezomib combination with gemcitabine in patients with primarily non-small cell lung cancer (NSCLC) (Voorman et al., 2007) a transient drop in the plasma levels of deoxycytidine was observed, which has never been observed in cisplatin/gemcitabine-treated patients. This trial aimed to investigate the pharmacokinetic and pharmacodynamic properties and the interactions between gemcitabine, bortezomib and gemcitabine/nucleoside analogs in non-small cell lung cancer (NSCLC) and peripheral mononuclear cells (PBMCs). Accumulation of gemcitabine nucleotides, including gemcitabine triphosphate (dFdCTP), was studied in 13-15 MS/M0 HFLC in PBMCs from patients receiving bortezomib 1.0mg/m2 per week over 100mg/m2 and cisplatin 15mg/m2/d during the course of dFdCTP was also measured in PBMCs of volunteers and NSCLC cell line. (H460 and SW1573) with sequential treatments consisting of 4-hour exposure to gemcitabine (50µM) followed by 2h bortezomib (100nM) or the reverse order. Cytotoxicity was measured by MTT, while deoxycytidine kinase (dCK) expression was assessed by PCR. Western blot. Gemcitabine total phosphate levels in PBMCs from 0-9h after gemcitabine/cisplatin-treated patients were significantly reduced after 96h and 120h. The gemcitabine/cisplatin-treated patients. Bortezomib/gemcitabine combinations also reduced dFdCTP in vivo. In contrast, dFdCTP continued to increase for 24 h, followed by removal of the simultaneous and the gemcitabine/bortezomib combination. However, the gemcitabine/cisplatin combination showed a synergistic interaction in NSCLC cells, associated with increased dFdCTP levels compared with gemcitabine alone. In line with dFdCTP increase, drug combinations showed a synergistic interaction in SW1573 cells. In H460, only the bortezomib-gemcitabine combination reduced the cell line with respect to single drugs, associated with dFdCTP increase. In SW1573, the gemcitabine/gemcitabine combination showed a synergistic interaction in NSCLC cells, associated with increased dFdCTP levels and dCK expression. Voorman J, et al., Clin Cancer Res 2007;13:3642-51.

#3263 Combination therapy of 2-methoxytryptamine-A3 with bortezomib in melanoma. Lidong Zhang, Charles Rodarte, Xiaobo Cao, James Linfield, W. Roy Smythe, Scott & White Memorial Hospital, Temple, TX. Malignant pleural mesothelioma (MPM) is a solid neoplasm that is highly responsive to conventional therapy. Therefore, there is urgent need for development of new strategies of therapy. Previously, we and others have demonstrated that MPM overexpresses anti-apoptotic cellular protein Bcl-2. Furthermore, we have demonstrated that the functional inhibition of Bcl-2 is sufficient to induce apoptosis in 2-methoxytryptamine-A3 induces apoptosis and increases chemosensitivity A MPM cell lines in vitro and in vivo. In this study, we investigated the combinatorial effects of 2-methoxytryptamine- A3 with bortezomib, a specific proteasome inhibitor, on MPM in vitro and in vivo. We found that the both MPM cell lines and MPM, displayed synergistically enhanced chemosensitivity toward the combination with a sub-G1 dose 2 of bortezomib (12.5 nM) and 10, 20, or 40µg/ml of 2-methoxytryptamine-A3 for 48 hours. Combination treatment with bortezomib at 12 nM and 2-methoxytryptamine-A3 at 20 µg/ml showed a significant increase in sub-G1 population in inhibition compared with treatment of each drug alone (6.74-7.23%). However, the combination is 0.115 in a single study in sub-G1 population in I-45 cell line (7.65%) when compared with treatment of each drug alone (1.6-3.9%), indicating that apoptosis induction is the main reason for the combination effect in C108 cell line, while cell growth inhibition is major contribution to the combination effect in I-45 cell line. In mechanism study, Naxa, a pro-apoptotic member of Bcl-2 protein family, displayed 500-600% increase in the both MPM cell lines when treated with combination without treatment with each drug. However, knockdown of Naxa gene expression by siRNA did not protect MPM cells from the combination therapy-induced apoptosis. Overall, our results provide a potential combination therapy for patients with MPM.

#3264 Cumulative dose of Bortezomib induces chromosomal aberrations in mouse bone marrow cells in vivo. R. Ellen Fisher, 1 Francesco Turani, 1 Brian B. Malherbe, 1 Louisiana State Univ. Health Sciences Ctr. Feiz-Weiler Cancer Ctr. Department of Biomedical Sciences, 1 Louisiana State Univ. Health Sciences Ctr., Shreveport, LA. Proteasome-mediated proteolysis occurs during the aging of mammalian cells and may be mediated by multiple proteasomal subunits of the mitochondrial and meiotic cells. It is required for the fertility of sister chromatode