NMP inhibition and NAD metabolism

**Introduction**

MPC-9528 inhibited Nampt activity in vitro with an IC50 of 50 pM and suppressed NAD levels in tumor cells with a potency of 10 pM. It has a median tumor potency of 2.8 nM with a range of 10 pM to 60 nM in a screen of 100 cancer cell lines of diverse origin. NA reduced cell death induced by MPC-9528 in cell lines expressing Npnt, demonstrating mechanism-based activity. In contrast, NA did not prevent MPC-9528-induced cell death in 44 and 80% of 135 cancer cell lines screened, which correlated with low to undetectable Nampt expression. MPC-9528 showed synergistic tumor activity in vitro with chemotherapeutics that activate Npnt leading to NA death, such as the antalyloid agent temozolomide and the thymidylate synthetase inhibitor, 5-fluorouracil.

**Mechanism**

MPC-9528 induced regressions in xenograft models and NA administration blocked their activity. In contrast, NA did not prevent MPC-9528-induced lethality and weight loss.

**Toxicity of MPC-9528 and MPI-0487316**

In Naprt-deficient mice, NA prevented or reduced the severity of these adverse effects. In a 14-day toxicity study, body weight indicated in cohorts of ten for all dose groups. Plasma concentrations of NA prevented or reduced the severity of these adverse effects.

**Nicotinic acid prevents MPC-9528 toxicity in mice**

MPC-9528 toxicity in mice was reduced by coadministration of NA, which also blocked mortality in mice induced by high doses of MPC-9528. NA prevented or reduced the severity of these adverse effects.