# Pamiparib as a non-P-glycoprotein substrate PARP inhibitor can overcome *ABCB1*-mediated multidrug resistance in Ovarian cancer cells

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## Abstract

Ovarian cancer is commonly treated with debulking surgery followed by platinum-taxane based chemotherapy and targeted therapy (PARP inhibitors). However, a key challenge facing these therapies is drug resistance caused by various mechanisms, one of which is the P-glycoprotein (P-gp, encoded by the ABCB1 gene) mediated multidrug resistance. Tumor cells with high P-gp protein expression extrude P-gp substrate drugs from intracellular space and reduce drug efficacy. Since Paclitaxel and some PARP inhibitors such as Olaparib are P-gp substrates, their clinical benefit may be compromised in primary or acquired P-gp positive patients. Pamiparib, on the other hand, is PARP inhibitor that is not P-gp substrate, therefore, it is reasonable to hypothesize that Pamiparib will have better efficacy in P-gp high Ovarian tumors.

To test this hypothesis, Paclitaxel or Olaparib acquired resistant cell lines were developed through prolonged *in vitro* culture of sensitive A2780 cells (P-gp negative) with stepwise increased concentrations of individual drug. Both Paclitaxel and Olaparib resistant cells (A2780pacR and A2780olaR, respectively) highly express P-gp protein and are cross-resistant to each other, indicating this acquired resistance is mediated by P-gp protein upregulation. Indeed, P-gp protein inhibitor Verapamil can largely restore sensitivity to Paclitaxel and Olaparib in A2780pacR and A2780olaR cells, while over-expression of P-gp protein into parental A2780 cell line recapitulated the resistant phenotype. In contrast to Paclitaxel and Olaparib, Pamiparib as non P-gp substrate, is equally sensitive to parental A2780, A2780pacR and A2780olaR cell lines and not affected by P-gp expression. Consistently, intracellular drug concentration of Pamiparib is equivalent in A2780 and A2780olaR cells, however, decreased cellular Olaparib was detected in resistant cell line. These findings have been further confirmed in Olaparib resistant CDX model, in which Pamiparib showed tumor growth inhibition while Olaparib did not. The results highly suggest that Pamiparib as a non-P-gp substrate PARP inhibitor can overcome *ABCB1*-mediated drug resistance in tumors and may provide additional clinical benefits to Ovarian cancer patients.