Pharmacokinetics of SPI-1620 in a Phase I, open label, ascending dose study of the safety, tolerability, pharmacokinetics and pharmacodynamics of the endothelin B receptor antagonist, SPI-1620, in recurrent or progressive carcinoma

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Objective: The primary objective of the Phase I study was to assess the safety and tolerability of SPI-1620 administered to patients with recurrent or progressive carcinoma who had failed all standard therapy. Secondary objectives were to assess PK and PD profiles of SPI-1620, and to identify the optimum dose of SPI-1620 to be used in future Phase II studies. The pharmacokinetic properties of SPI-1620 will be presented. Methods: Eligible patients received SPI-1620 by intravenous infusion over 1 min in an accelerated dose escalation scheme. SPI-1620 doses ranged from 0.5 μg/kg to 15.1 μg/kg. Serial blood samples were collected from each patient prior to infusion (0 min) and at pre-specified intervals from the start of the infusion. Human plasma samples were analyzed by a validated HPLC–MS/MS method. Descriptive PK parameters were determined by standard model independent methods based on the concentration–time data of each subject. Results & conclusion: The highest concentration of SPI-1620 was achieved by the end of infusion. SPI-1620 C max increased proportionally as a function of SPI-1620 dose while the AUC (0–T) increased in a more than dose proportional manner. The SPI-1620 T 1/2 was short and ranged from 4.38 min to 8.29 min. SPI-1620 had a low systemic clearance and small VD (approximately equal to the intravascular volume).


Endothelin-1-induced β-arrestin signalosome is linked to chemoresistance, EMT and stem-cell like properties in ovarian cancer cells

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The epithelial–mesenchymal transition (EMT) is known to play a crucial role in the aggressiveness of epithelial ovarian cancer (EOC), contributing to chemoresistance and cancer stem cell populations. In this tumor, the endothelin (ET)-1/endothelin A receptor (ETAR) axis, by regulating EMT and invasion, endows EOC cells with an increased chemoresistance. Here we examined whether β-arrestin-1 (β-ar1) can act as a nuclear hub orchestrating nuclear signaling in ETAR-driven EMT and chemoresistance. A significant higher expression of β-ar1 and ET-1/ETAR and the stronger presence of β-ar1 in the nuclear compartment upon ETAR activation are present in chemoresistant cells, compared to sensitive cells. In the nuclei, β-ar1 robustly interacts with β-catenin to form a nuclear complex localized on the ET-1 promoter region, leading to transcription of ET-1, demonstrating that β-ar1 drives the positive inter-regulation of ET-1 itself. This autocrine circuit is involved in β-ar1-driven appearance of EMT features and acquisition of stem-cell like properties. Moreover, at functional level, chemoresistant cells, with high nuclear β-ar1, display higher invasive potential and increased resistance to chemotherapeutic drugs. These effects were inhibited by ET-1 receptor blockade with macitentan, or by β-ar1 nuclear mutant.