ID: 00944
Type: Poster
Topic: Tumor treatment

THE MULTI-KINASE INHIBITOR EC-70124 SYNERGISTICALLY INCREASED THE ANTI-TUMOR ACTIVITY OF DOXORUBICIN IN SARCOMAS

Rene Rodriguez[1] , Oscar Estupiñan[1] , Laura Santos[1] , Aida Rodriguez[1] , Paula Costales[2] , Maria Ana Hermosilla[2] , Patricia Oro[2] , Veronica Rey[1] , Sofía T Menendez[1] , Francisco Moris[2]

1) Hospital Universitario Central de Asturias - Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain & Instituto Universitario de Oncología del Principado de Asturias, Oviedo, Spain & CIBER en oncología (CIBERONC), Madrid, Spain 2) EntreChem SL, Oviedo, Spain

Introduction: Cytotoxic drugs like doxorubicin remain as the most utilized agents in sarcoma treatment. However, advanced sarcomas are often resistant, thus stressing the need for new therapies aimed to overcome this resistance. Multi-kinase inhibitors provide an efficient way to target several pro-tumorigenic pathways using a single agent and may constitute a valuable strategy in the treatment of sarcomas, which frequently show an aberrant activation of pro-tumoral kinases.

Objectives: In this work we aimed to study the antitumor activity of EC-70124, an indolocarbazole analog that have demonstrated a robust ability to inhibit a wide range of pro-survival kinases. In addition, we analyzed the ability of EC-70124 to prevent drug resistance and synergize with doxorubicin.

Methodology: We used both cell-of-origin models of sarcoma and sarcoma patient-derived primary cell lines. Cell survival, apoptotic induction, cell cycle progression, DNA damage and the existence of a synergistic interaction were analyzed after drug treatments. Drug effect on signalling proteins was studied using phospho-antibody arrays and Western-blotting analysis. Interaction between drugs and ABC transporters were characterized using substrate and inhibition assays. Finally, *in vivo* tumor growth and pharmacodynamic response after drug treatments were evaluated in xenografts models.

Results: Evaluation of the phospho-kinase profile in cell-of-origin sarcoma models and/or sarcoma primary cell lines evidenced that PI3K/AKT/mTOR, JAK/STAT or SRC were among the most highly activated pathways. In striking contrast with the structurally related drug midostaurin, EC-70124 efficiently prevented the phosphorylation of these targets and robustly inhibited proliferation through a mechanism associated to the induction of DNA damage, cell cycle arrest and apoptosis. In addition, EC-70124 was able to partially reduce tumor growth *in vivo*. Importantly, this compound inhibited the expression and activity of ABC efflux pumps involved in drug resistance. In line with this ability, we found that the combined treatment of EC-70124 with doxorubicin resulted in a synergistic cytotoxic effect *in vitro* and increased anti-tumor activity of doxorubicin *in vivo*.

Conclusions: Altogether, these results uncover the capability of the novel multikinase inhibitor EC-70124 to counteract drug resistance in sarcoma and highlight its therapeutic potential when combined with current treatments.

[files191=2;500;500][fileShow][/files]