# 3rd TRANSAutophagy CA15138 Annual Meeting 2019

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## POSTER

## ABSTRACT BOOK

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# Annual Meeting 2019

## Abstract N°21

# Vistusertib (AZD2014), a dual mTOR kinase inhibitor, overcomes paclitaxel resistance in anaplastic thyroid carcinoma

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Resistance to chemotherapeutic agents represents a major issue in anticancer therapy. Anaplastic thyroid carcinoma (ATC) has a poor prognosis due to its aggressive behavior and resistance to treatment. Alterations in the PI3K/AKT/mTOR pathway and/or high expression of ATP binding cassette transporters, such as P-glycoprotein and breast cancer resistance protein (BCRP), are frequently linked to chemo-resistance. Autophagy is a key player in the metabolic and therapeutic stress response and represents a potential target for anticancer therapy. Autophagy induction in response to chemotherapeutics may contribute to both drug efficacy as well as drug resistance. We assessed the therapeutic efficacy of dual mTOR kinase inhibitor vistusertib (AZD2014) and paclitaxel (PTX) in combination in ATC cells. Rho- cell line was generated from parental human thyroid carcinoma 8505C via the selection of cells with a low accumulation of rhodamine 123 (P-glycoprotein and BCRP substrate). Rho- cells were 10-fold more resistant to PTX compared to 8505C cells and more tumorigenic. Both vistusertib and PTX induced autophagosome formation in the investigated cell lines. In combination, vistusertib sensitized Rho- cells to PTX via autophagy induction and proliferation inhibition, indicating a synergistic effect between the two compounds. Additionally, vistusertib and PTX combination in Rho- and 8505C cells inhibited cell migration and invasion *in vitro*. Furthermore, vistusertib and PTX combination effectively suppressed tumor growth of ATC xenografts in immunodeficient NSG mice *in vivo*. Considering chemo-resistance and high invasive properties of ATC, described combined approach could be useful for the design of novel targeted treatment strategies in this malignancy.