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Pre-clinical studies of EC2629, a highly potent FR targeted DNA crosslinking agent

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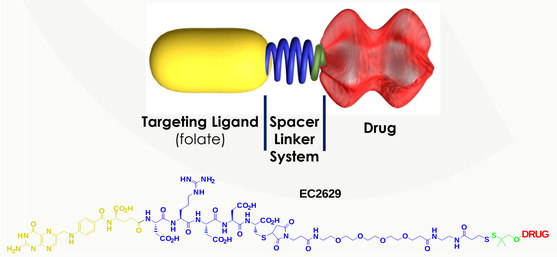
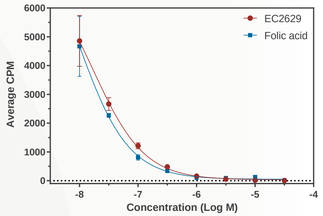
Introduction

Folate receptor (FR) targeted small molecule drug conjugates (SMDCs) have shown promising results in early stage clinical trials with vintafolide and EC1456. In our effort to develop FR targeted SMDCs with varying mechanisms of action, we have now built EC2629, a folate conjugate of a DNA crosslinking agent based on a novel DNA-alkylating moiety . This agent was found to be extremely potent with an *in vitro* IC50 ~ 100 x lower than any other folate SMDC we have created to date. Treatment of nude mice bearing FR positive human xenografts led to cures in 100% of the mice at very low doses (300 nmol/kg) using a convenient once a week schedule. The observed activity was not accompanied by any noticeable weight loss (up to 20 weeks post end of dosing) or major organ tissue degeneration. Complete responses were also observed in other FR-positive drug resistant (paclitaxel and cisplatin) models. When evaluated against FR-positive PDX models of ovarian, endometrial and triple negative breast (TNBC) cancers, EC2629 showed significantly greater anti-tumor activity than EC1456 or standard of care (SOC) treatments. Taken together, these studies demonstrated that EC2629 with a distinct DNA reacting mechanism has significant anti-tumor growth activity in numerous models, including those which were drug resistant, thus lending support to our planned clinical development of this novel FR-targeted agent.

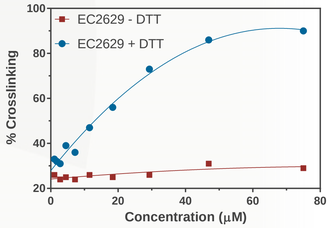
Modular design of Folate SMDC



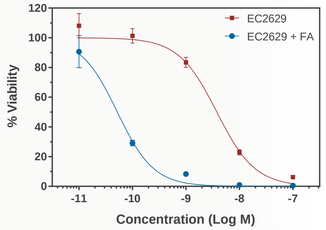
High affinity FR mediated binding



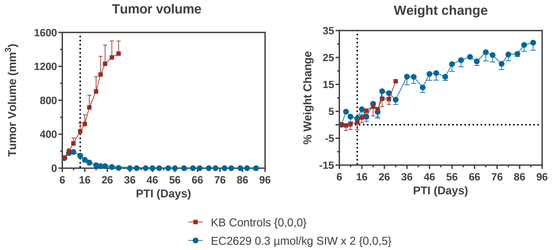
EC2629 crosslinks DNA only following release of free drug



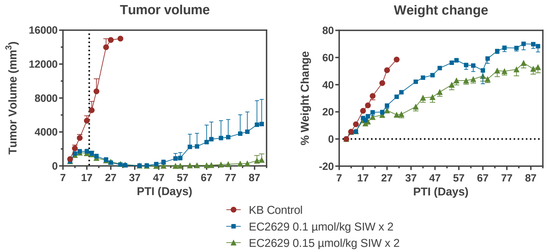
Picomolar potency against FR expressing cells *in vitro*



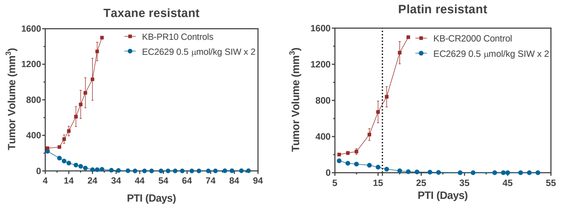
EC2629 has curative activity using a low dose, once a week dosing regimen



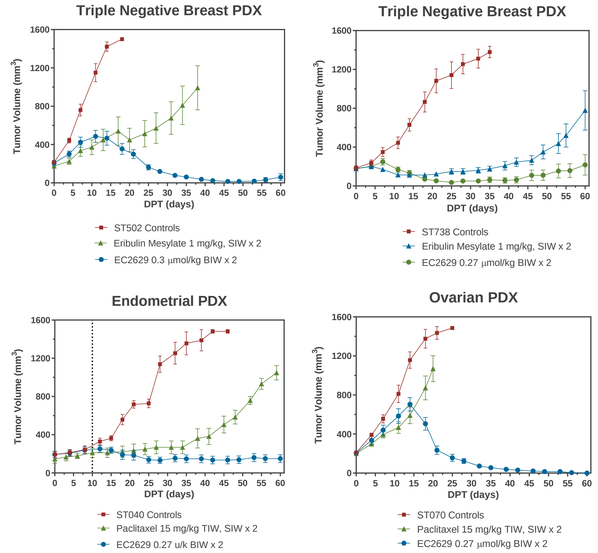
EC2629 is highly active against a rat tumor xenograft model



EC2629 is active against drug resistant tumor xenograft models



EC2629 is active against patient derived xenograft models



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