

# A novel small molecule cytidine analog, RX-3117, shows potent efficacy in xenograft models, even in tumors that are resistant to treatment with gemcitabine

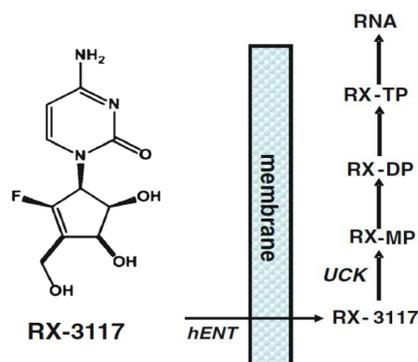
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## ABSTRACT # 819

RX-3117 (fluorocyclopentenylcytosine) is a novel small-molecule chemotherapeutic agent that belongs to the class of cytotoxic antimetabolite cytidine analogs. Cytidine analogs, including gemcitabine, have been widely used for the treatment of various types of cancer, both hematologic as well as solid. However, despite the success of gemcitabine, there is no oral formulation of gemcitabine and drug resistance is common. Thus, RX-3117 was synthesized as an oral formulation to overcome gemcitabine resistance with a better pharmacologic profile. In this study, the efficacy of RX-3117 was examined in 12 different human tumor (colon, non-small cell lung, small cell lung, pancreatic, renal, ovarian and cervical) xenograft models, grown subcutaneously in athymic nude mice. Not only has RX-3117 demonstrated potent efficacy in several cancer xenograft models but also oral treatment with RX-3117 results in dose-dependent tumor growth inhibition (TGI), even in tumors that are only moderately sensitive or resistant to gemcitabine. In the Colo-205, H460, H69 and CaSki models, gemcitabine treatment resulted in 28%, 14%, 25%, and 0% TGI, respectively, whereas oral treatment with RX-3117 induced 93%, 91%, 62%, and 66% TGI, respectively. This indicates that RX-3117 may have the potential to be used for the treatment of tumors that do not respond to gemcitabine. In order to extend the results established in cell line xenograft models, and to test efficacy in a potentially more clinically relevant system, RX-3117 was evaluated in a single primary low passage human pancreatic Tumorgraft™ CTG-0298, which is resistant to gemcitabine and has a favorable RX-3117 activating enzyme profile. Treatment with RX-3117 resulted in dose dependent TGI and was superior to the standard of care agent gemcitabine. This study successfully demonstrated preliminary efficacy and therapeutic potential of RX-3117.

## INTRODUCTION

RX-3117 is one of a class of cytidine analogs that are widely used for treatment of various types of cancer. For example, gemcitabine as a single agent is the standard care for pancreatic cancer and in combination with cisplatin it is widely used for the treatment of lung and bladder cancer [1-3]. Although gemcitabine has shown some efficacy, there are several limitations in its use. No oral formulation of gemcitabine is available and drug resistance is common, which may be due to loss of transporter, human Equilibrative nucleoside transporter 1 (hENT), and deoxycytidine-kinase (dCK) responsible for the first phosphorylation step. Similar to other antimetabolites, RX-3117 interferes with cell division and nucleic acid synthesis, arrests cells in G1 phase and induces apoptosis. RX-3117 shares some properties with other cytidine analogs, but its cytotoxicity profile, metabolism and mechanism of action make it distinct from these analogs [4]. First, RX-3117 shows cytotoxicity in several gemcitabine-resistant cell lines. Second, RX-3117 uptake is mediated by hENT. Third, RX-3117 needs to be activated by uridine-cytidine kinase (UCK) in order to be further phosphorylated to its active phosphates. Fourth, the active form of RX-3117 is incorporated into RNA and DNA, leading to inhibition of their synthesis. However, inhibition of DNA synthesis was more pronounced than that of RNA. Lastly, RX-3117 is synthesized as a oral formulation, enabling convenient administration. Oral bioavailability was characterized in mouse (74%) and dog (100%) in unpublished data. In this study, the efficacy of RX-3117 was successfully demonstrated not only in 12 different human tumor xenograft models but also in a single primary low passage human pancreatic Tumorgraft™ CTG-0298, which is resistant to gemcitabine.

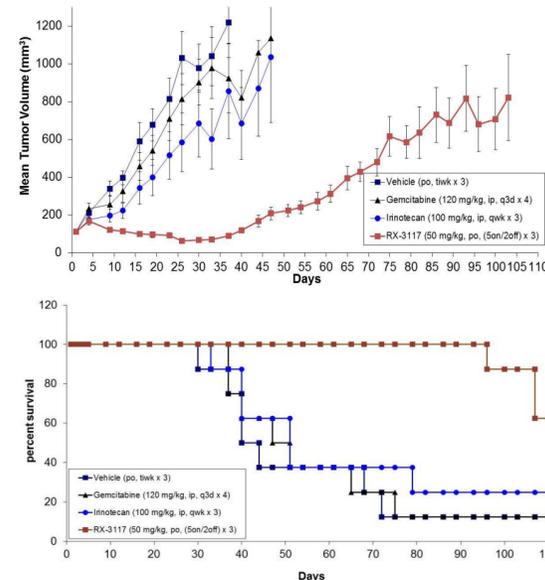


## MATERIALS & METHODS

**In Vivo Tumor Studies:** The efficacy of RX-3117 was examined in 12 different human tumor (HCT116, Colo205, HT29, A549, H460, MV522, H69, BxPC3, MiaPaca2, Caki-1, OVCAR3, CaSki) xenograft models, grown subcutaneously in athymic nude mice. RX-3117, gemcitabine or vehicle treatments were initiated when established tumors reached an average size of ~100 mm<sup>3</sup>. RX-3117 was evaluated in a single primary low passage human pancreatic Tumorgraft™ using CTG-0298. Tumor fragments from animals carrying the CTG-0298 model were implanted into nude mice and studies initiated at a mean tumor volume of ~164 mm<sup>3</sup>. The tumor volumes were measured twice weekly throughout the study duration, and efficacy was calculated based on the percentage inhibition of tumor volume (TGI, tumor growth inhibition).

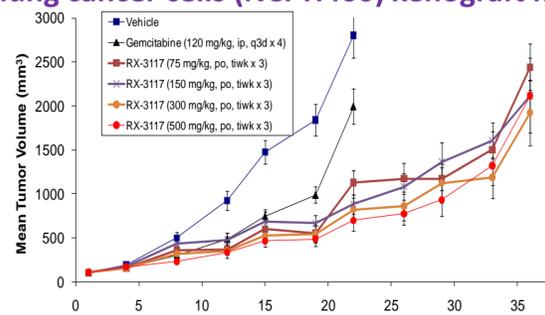
## RESULTS

### Effect of RX-3117 in Colo205 colorectal cancer nude mouse xenograft model



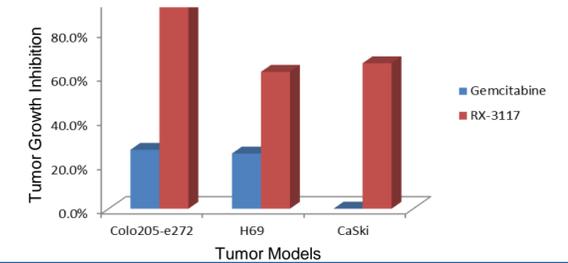
1. Orally administered RX-3117 showed favorable efficacy versus gemcitabine or irinotecan without significant changes in body weight (BW).
2. RX-3117 prolonged survival relative to treatment with other agents.

### Antitumor activity and tolerability of RX-3117 in human lung cancer cells (NCI-H460) xenograft model



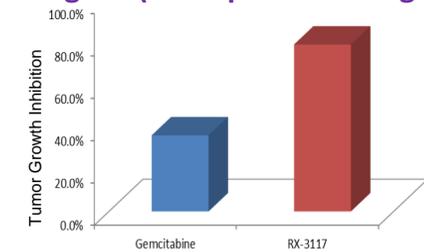
**RX-3117 inhibited tumor growth significantly with no BW changes even at high doses.**

### Efficacy of RX-3117 in gemcitabine-insensitive human tumor xenograft models (Colo205, H69 and CaSki)



**RX-3117 showed strong tumor growth inhibition in gemcitabine-insensitive models.**

### Efficacy of RX-3117 in primary human pancreatic cancer low-passage tumor graft (Champions Tumorgrafts™ CTG-0298)



**Treatment with RX-3117 resulted in greater tumor growth inhibition than gemcitabine**

## CONCLUSION/DISCUSSION

1. The efficacy of RX-3117 was examined in a variety of tumor types (Colon, Non-Small Cell Lung, Small Cell Lung, Pancreatic, Renal, Ovarian and Cervical) and RX-3117 has shown robust anti-tumor effects across a broad variety of types of tumors in animal models.
2. Orally administered RX-3117 showed significant tumor inhibition.
3. Treatment with RX-3117 resulted in strong tumor growth inhibition in gemcitabine-insensitive models, indicating that RX-3117 may have the potential to be used for the treatment of tumors that do not respond to gemcitabine.
4. This study clearly demonstrated preliminary efficacy and therapeutic potential of RX-3117.

## REFERENCES

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