A Novel Small Molecule Nucleoside Analog, RX-3117, Shows Potent Therapeutic Activity in Combination with Nab-paclitaxel and Checkpoint Inhibitors in Xenograft Models

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ABSTRACT # 413P

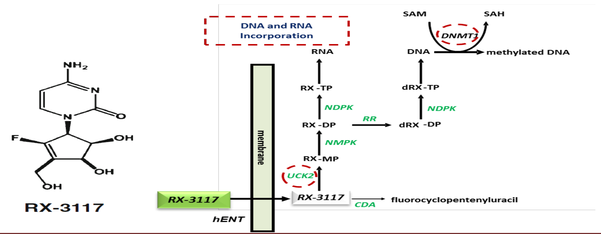
A novel nucleoside analogue, RX-3117, is being evaluated in a Phase IIa study in patients with advanced pancreatic and bladder cancer. RX-3117 shows promising antitumor activity in xenografts including patient-derived xenografts resistant to gemcitabine. Here we demonstrate the preclinical effects of combination therapy with RX-3117 + Abraxane or anti-PD1 immunotherapy. Methods: One colorectal (MC38), pancreatic (Pan02) syngeneic xenograft and patient-derived pancreatic (CTG-0723) xenograft model were exposed to 60 mg/kg RX-3117 po, 5 days on, 2 days off for three weeks. Pan02 and MC38 received RX-3117 alone or in combination with 100µg anti-PD1, ip. PDx CTG-0723 received one cycle of RX-3117, followed by a second cycle of RX-3117 + 10 mg/kg Abraxane, iv. MC38 tumor-infiltrating lymphocytes were measured at days 5 and 12 with RX-3117. Results: In MC38 at day 28, RX-3117 or anti-PD1 showed TGIs of 90% and 93%, whereas the combination showed 99% TGI. Differences were also observed in TILs. Relative to vehicle (CD4+:10.6+/-1.6, CD8+: 8.6+/-1.1), %CD4+ (17.4+/-1.4) and CD8+ cells (12.3+/-1) increased. %MDSCs decreased on Day 5 in blood (42+/-7.7 vs 29+/-6). %CD8+ increased (9.6+/-3.3 vs 12.3+/-3.2) and %MDSC decreased (15.4 +/- 3.7 vs 10.6 +/- 3.3) in tumor on Day 12. In Pan02, RX-3117 + anti-PD1 resulted in a day 32 TGI of 60%. Anti-PD1 had a day 32 28% TGI. In CTG-0723, the first cycle of RX-3117 at 10, 30 and 60 mg/kg produced TGIs of 33%, 46% and 77%. The second cycle, RX-3117 + Abraxane, day 46 TV showed TGIs of 55%, 58% and 83%.
Conclusions: We demonstrate the antitumor effect of RX-3117 as a single agent and in combination with Abraxane or anti-PD-1. The combination of RX-3117/anti-PD1 in MC38 produced 7 survivors compared to 2 of 10 by anti-PD1 alone, indicating RX-3117 may mobilize the right population of lymphocytes to enable anti-PD-1 to work. In Pan02, RX-3117 exhibited better TGI than anti-PD-1. In CTG-0723, the combination of RX-3117 and Abraxane showed additive TGI. These studies demonstrate the therapeutic potential of RX-3117 in multiple cancers and validate the combination of RX-3117 with anti-PD1 in several cancer types.

INTRODUCTION

The antimetabolite RX-3117 (fluorocyclopentenylcytosine), is an orally available small molecule cytidine analog. This class of molecules has been widely used for the treatment of various types of cancers and works by mimicking physiological nucleosides in regard to uptake and metabolism. These molecules, which includes gemcitabine and capecitabine, are incorporated into newly-synthesized RNA and DNA and result in synthesis inhibition and chain termination. Similar to other anti-metabolites, RX-3117 interferes with cell division and nucleic acid synthesis, causes cellular arrest in the G1 phase and induces apoptosis. RX-3117 requires activation by uridine-cytidine kinase 2 (UCK2) to its active phosphates, and enzyme predominantly found in cancer tissue. In previous studies we have shown RX-3117 to be efficacious in various xenograft models, including several gemcitabine-resistant xenografts. In this study, we demonstrate the anti-cancer activity of RX-3117 in additional models and show the synergistic and/or additive effects when RX-3117 is combined with immuno-oncology agents in these models.

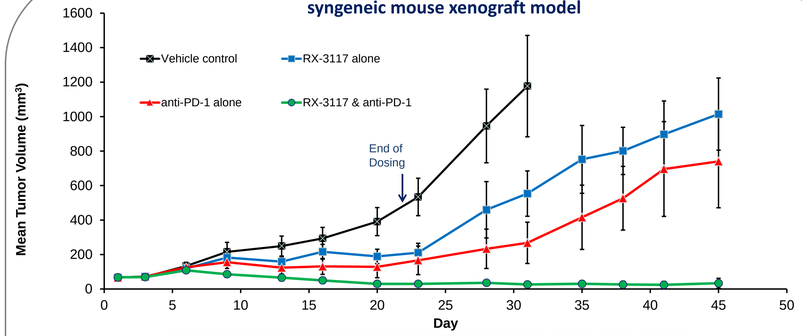
MATERIALS & METHODS

In Vivo Tumor Studies: One colorectal (MC38; Charles River Laboratories) and one pancreatic (Pan02; Crown Bio) syngeneic xenograft were exposed to 60 mg/kg RX-3117 po, 5 days on, 2 days off for three weeks. A patient-derived pancreatic xenograft (CTG-0723; Champions Oncology) was exposed to 10, 30 or 60 mg/kg RX-3117 for 1 cycle (3 weeks, 5 days on, 2 days off), and then received 10, 30 or 60 mg/kg RX-3117 + 10 mg/kg Abraxane iv, for the second cycle, starting on day 29. Pan02 and MC38 received RX-3117 alone or in combination with 100 ug anti-PD1, ip. In addition, MC38 tumor-infiltrating lymphocytes, CD4+, CD8+ and MDSCs, were measured at days 5 and 12 following exposure with RX-3117.



RESULTS

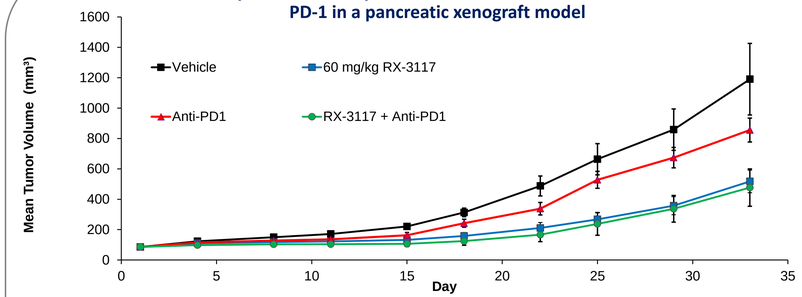
Synergistic effects of RX-3117 ± anti-PD-1 in the colorectal cancer MC38 syngeneic mouse xenograft model



Treatment Group	TGI Day 28	PR	CR	TFS
Vehicle	-	2	0	0
RX-3117 (60 mg/kg)	80%	0	0	0
anti-PD-1 RMP1-14 (100 µg)	93%	1	3	2
RX-3117 + anti-PD-1	99%	2	7	7

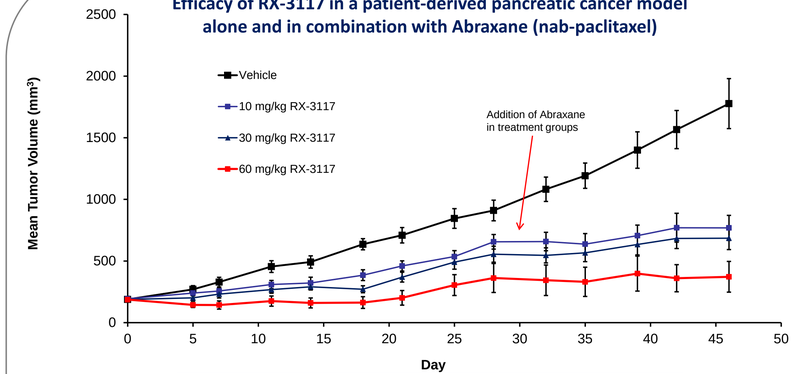
	Day 5 Blood		Day 12 Tumor	
	Vehicle	RX-3117	Vehicle	RX-3117
CD4+	10.6 ± 1.6	17.38 ± 1.35	1.96 ± 0.31	1.89 ± 0.24
CD8+	8.6 ± 1.1	12.27 ± 0.92	9.57 ± 3.28	12.25 ± 3.16
MDSC	42.4 ± 7.7	29.02 ± 6.16	15.36 ± 3.7	10.57 ± 3.26

Antitumor activity and tolerability of RX-3117 alone and in combination with anti-PD-1 in a pancreatic xenograft model



Treatment Group	TGI Day 22	TGI Day 32
Vehicle	-	-
RX-3117 (60 mg/kg)	69%	57%
anti-PD-1 RMP1-14 (100 µg)	37%	29%
RX-3117 + anti-PD-1	80%	61%

Efficacy of RX-3117 in a patient-derived pancreatic cancer model alone and in combination with Abraxane (nab-paclitaxel)



Treatment Group	TGI	
	Day 21	Day 46
Vehicle	-	-
10 mg/kg RX-3117	49%	64%
30 mg/kg RX-3117	65%	68%
60 mg/kg RX-3117	97%	88%

CONCLUSION/DISCUSSION

In this series of studies, we demonstrate the additive and sometimes synergistic antitumor effects of RX-3117 as a single agent and in combination with Abraxane or immuno-oncology agents in several distinct xenograft models.

- RX-3117/anti-PD1 in MC38 proved highly synergistic, producing 7 out of 10 surviving mice compared to 2 of 10 by anti-PD1 alone, indicating RX-3117 may mobilize the right population of lymphocytes to enhance the activity of anti-PD-1
- In the highly treatment-resistant pancreatic Pan02 model, RX-3117 exhibited better TGI than anti-PD-1 alone
- In the patient derived model CTG-0723, the combination of RX-3117 and Abraxane showed additive TGI
- In the CTG-0723 model, the addition of Abraxane proved highly additive when combined with RX-3117, whereas the patient from whom the tumor sample was taken showed clinical resistance to Abraxane alone, indicating that the combination of RX-3117 and Abraxane is effective in tumors that are unresponsive to single-agent Abraxane

These studies demonstrate the therapeutic potential of RX-3117 in multiple cancers and validate the combination of RX-3117 with standards of care and anti-PD1 in several cancer types.

REFERENCES

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Investigator Disclosures

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