A novel nucleoside analog, RX-3117, is being evaluated in a Phase Ia 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-PD-1 (CTG-0723) xenograft model were exposed to 60 mg/kg RX-3117 per ip, 5 days on, 2 days off for three weeks. Pan02 and MC38 received RX-3117 alone or in combination with anti-PD-1 (100 µg) i.p. The first cycle of RX-3117 + 10 mg/kg Abraxane, to which tumor-infiltrating lymphocytes were measured at days 5 and 12. RX-3117, results in MC38 xenografts. In day 5 to 29. RX-3117 + anti-PD1 showed TGI of 90% and 65%, whereas the combination showed 99% TGI. Differences were also observed in TGI. Relative to vehicle (ODH 10.0 ± 3.1, ODH 8.5 ± 1.1, %CD4+ [17.4 ± 4.4] and CD8+ cells (12.3 ± 3.2) increased. VMDSCs decreased by Day 12 in tumor in Day 12 in Pan2. RX-3117 + anti-PD1 resulted in a day 32 TGI of 60%. Anti-PD1 had a day 32 28% TGI. CTG-0723, the first cycle of RX-3117 at 10, 30 and 60 mg/kg produced TGI of 33%, 46% and 77%. The second cycle, RX-3117 + Abraxane, day 46 TV showed TGI of 50%, 83% and 85%. Conclusions: We demonstrate the additive or synergistic effects of RX-3117 as a single agent and in combination with Abraxane or anti-PD-1. The combination of RX-3117 and Abraxane in CTG-0723 produced 7 survivors compared to 2 of 10 by anti-PD1 alone. RX-3117 may mobilize the right population of lymphocytes to enhance the activity of anti-PD-1. A novel small molecule nucleoside analog, RX-3117, shows potent therapeutic activity in combination with nab-paclitaxel and checkpoint inhibitors in xenograft models.

**INTRODUCTION**

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

**MATERIALS & METHODS**

In Vivo Tumor Studies: One colorectal (MC38), one pancreatic (Pan02) and two bladder (CTG-0723) xenograft models were exposed to 60 mg/kg RX-3117 per ip, 5 days on, 2 days off for three weeks. A patient-derived pancreatic xenograft (CTG-0723) was exposed to 10, 30 and 60 mg/kg RX-3117 per ip, 5 days on, 3 days off, and then received 30, 60 or 80 mg/kg RX-3117 + 10 mg/kg Abraxane for the second cycle, starting on day 29. Pan02 and MC38 received RX-3117 alone or in combination with 100 µg anti-PD1, i.p. In addition, MC38 tumor-infiltrating lymphocytes, CD4+ and CD8+ T cells 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 xenograft model

**CONCLUSION/DISCUSSION**

In this series of studies, we demonstrate the additive and synergistic antitumor effects of RX-3117 as a single agent and in combination with Abraxane or immunotherapy agents in several distinct xenograft models. RX-3117 and anti-PD-1 together showed lower TGI 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-PD1 alone. In the patient xenograft 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 addition of Abraxane in the patient xenograft model CTG-0723 in the patient xenograft model CTG-0723, the combination of RX-3117 and Abraxane showed additive TGI.

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**Investigator Disclosures**

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