RX-3117 (fluorocyclopentenylcytidine) 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.