# Preliminary phase 1 data of single agent RX-3117, an oral antimetabolite nucleoside

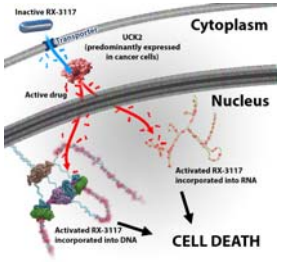
Drew Rasco[1], Christine Peterson[2], and Ely Benaim[2], [1]South Texas Accelerated Therapeutics, San Antonio, TX, [2]Rexahn Pharmaceuticals Inc., Rockville, MD

## Abstract # 345

Background: RX-3117 is an oral small-molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117's efficacy in xenograft models (Colo-205, H460, H69 and CaSki), which are moderately sensitive or resistant to gemcitabine, indicates that RX-3117 may have the potential to treat tumors that do not respond to gemcitabine or have become gemcitabine resistant. Emerging data from the second clinical study of RX-3117 as a single agent in pts with solid tumors is described below.
Methods: This is a Phase 1 study (NCT02030067) designed to evaluate safety, tolerability and PK following increasing doses of RX-3117. Primary objectives include safety/ tolerability and to determine the MTD and a recommended phase 2 dose/schedule (RP2D); secondary objectives were pharmacokinetics (PK) and antitumor activity (RECIST v1.1). Pts received RX-3117 3 times per week for 3 weeks followed by 1 week of rest. Plasma concentrations were measured using a validated LC-MS/MS assay, and noncompartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4.
Results: RX-3117 given orally as API in capsules was moderately rapidly absorbed without a marked lag time, and with median $T_{max}$ usually observed at 2 to 3 hr. After $T_{max}$, elimination was biphasic with about half of $AUC_{last}$ (0-48 hr) observed in the first 8 hr, and over 80% by 24 hr. Apparent terminal $T_{1/2}$ did not exhibit dose-dependent or time-dependent pharmacokinetics, with mean values over the dose range 60 to 1500 mg ranging from 11.6 to 16.2 hr after the 1st dose, and from 13.8 to 20.2 hr after the 7th dose (Day 15 of dosing). $C_{max}$ and $AUC_{last}$ increased fairly linearly with dose, but in a less than proportional manner, possibly reaching a plateau by the 1500 mg dose. Over the dose range of 30 to 1500 mg, mean $C_{max}$ ranged from 32 to 1635 ng/mL after the 1st dose, and from 99 to 1210 ng/mL after the 7th dose. Over the same dose range, mean $AUC_{last}$ ranged from 164 to 18,236 hr*ng/mL after the 1st dose, and from 702 to 11,950 hr*ng/mL after the 7th dose. Accumulation was generally minimal. The most frequent related adverse events noted to date were mild to moderate fatigue and nausea, mild diarrhea, mild vomiting, mild anorexia and moderate dehydration; no dose limiting toxicities have been reported.

Conclusions: At the doses tested, RX-3117 appears to be well tolerated..

## RX-3117 Proposed Mechanism




| | Gemcitabine | RX-3117 |
|---|---|---|
| Phosphorylation (activation) Enzyme | Deoxycytidine kinase (dCK) | Uridine-cytidine kinase 2 (UCK2) |
| Degradation by Cytidine Deaminase | Fast deamination | Slow deamination |
| DNA Methyl –transferase 1 Activity | Yes | Yes |
| Membrane Transport | hENT - dependent | hENT -dependent |
| Incorporation | DNA & RNA | DNA & RNA |
| Synthesis Inhibition | DNA & RNA | DNA & RNA |

## Study Design

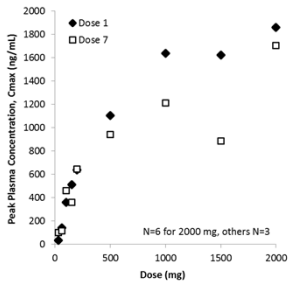
This is a Phase 1 multicenter, dose finding, open-label, single agent study of RX-3117 administered orally to subjects with advanced or metastatic solid tumors. One subject was treated per dose group until the appearance of a related grade 2 or greater adverse event, after which 3 subjects were treated using a modified Fibonacci schedule.

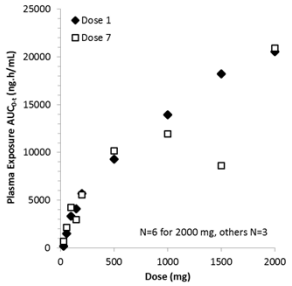
Males or females were treated 3 times a week for 3 weeks followed by 1 week off in each 28 day cycle.

Pharmacokinetic sampling was done at 0.5 hours ± 5 minutes, 1 hour ± 10 minutes, 2 hours ± 10 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes and 8 hours ± 10 minutes, 24 hours ± 10 minutes and 48 hours ± 10 minutes, after the oral administration of RX-3117 on Cycle 1 Day 1

## Preliminary Pharmacokinetic Results

### Dose-dependent Total Exposure

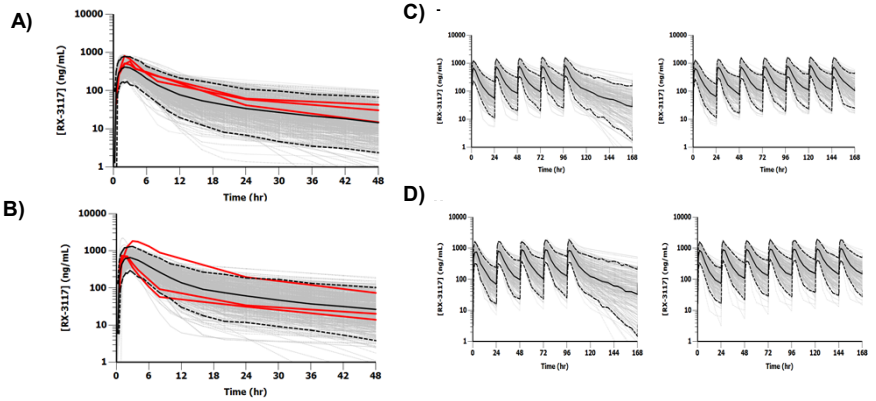



### Pharmacokinetic Summary

| Dose | Dose Day | Dose Number | Cmax (ng/mL) | Tmax (hr) | T1/2 (hr) | AUClast (hr*ng/mL) |
|---|---|---|---|---|---|---|
| 30 | 1 | 1 | 31.6 | 2 | 3.87 | 164 |
| 60 | 1 | 1 | 139 | 2 | 16.2 | 1481 |
| 100 | 1 | 1 | 357 | 2 | 15.4 | 3334 |
| 150 | 1 | 1 | 511 | 3 | 13.9 | 4116 |
| 200 | 1 | 1 | 637 | 2 | 13.3 | 5688 |
| 500 | 1 | 1 | 1104 | 2 | 16.7 | 9304 |
| 1000 | 1 | 1 | 1635 | 2 | 11.6 | 13927 |
| 1500 | 1 | 1 | 1622 | 3 | 11.8 | 18236 |
| 2000 | 1 | 1 | 1857 | 4 | 13.4 | 20837 |
| 30 | 15 | 7 | 98.9 | 2 | 8.23 | 702 |
| 60 | 15 | 7 | 113 | 4 | 15.7 | 2119 |
| 100 | 15 | 7 | 460 | 2 | 20.2 | 4257 |
| 150 | 15 | 7 | 360 | 3 | 15.1 | 2968 |
| 200 | 15 | 7 | 643 | 3 | 16.2 | 5536 |
| 500 | 15 | 7 | 941 | 3 | 15.3 | 10159 |
| 1000 | 15 | 7 | 1210 | 3 | 14.9 | 11950 |
| 1500 | 15 | 7 | 883 | 2 | 13.8 | 8600 |
| 2000 | 15 | 7 | 1474 | 2 | 13.8 | 14451 |

### Population PK Modeling

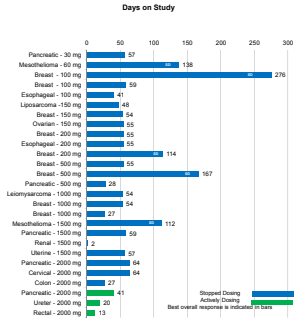



For the population PK compartmental modeling, the concentration data was analyzed using Phoenix NLME and WinNonlin. Plasma concentrations were modeled with a 3 compartment oral administration models (panels A and B). The actual pharmacokinetic data were initially used to validate the simulation model (panels A and B), and predict the more frequent dosing schedules in (panel C) 5/week and 7/week at 500 mg/day and (panel D) 5/week and 7/week at 700 mg/day.

## Predicted Plasma Exposures

| Dosing Schema | | Cmax (ng/mL) | AUC Day 1 (hr*ng/mL) | AUC Week 1 (hr*ng/mL) | AUC Week 3 (hr*ng/mL) |
|---|---|---|---|---|---|
| 500 QD X 5 | Mean (CV%) | 862 (30.6) | 6093 (31.2) | 42191 (43.3) | 44566 (47.4) |
| | 5th / 95th Percentile | 455 / 1341 | 3318 / 9911 | 19815 / 77741 | 20026 / 88987 |
| 700 QD X 5 | Mean (CV%) | 1024 (32.3) | 7507 (31.1) | 52429 (44.9) | 56491 (51.6) |
| | 5th / 95th Percentile | 571 / 1634 | 4062 / 11576 | 24500 / 98274 | 24312 / 113687 |
| 500 QD X 7 | Mean (CV%) | 868 (32.8) | 6143 (33.5) | 55618 (41.4) | 62095 (47.7) |
| | 5th / 95th Percentile | 453 / 1430 | 3014 / 9741 | 23297 / 102456 | 24053 / 122468 |
| 700 QD X 7 | Mean (CV%) | 1071 (29.0) | 7644 (31.0) | 69374 (38.2) | 77332 (43) |
| | 5th / 95th Percentile | 565 / 1617 | 4436 / 12042 | 34271 / 115663 | 34310 / 135740 |

## Treatment and Safety Profile




| Most Frequently Reported Adverse Events | N (%) |
|---|---|
| Fatigue | 13 (52.0) |
| Nausea | 6 (24.0) |
| Diarrhoea | 5 (20.0) |
| Anemia | 3 (12.0) |
| Pyrexia | 3 (12.0) |
| Decreased appetite | 3 (12.0) |
| Dehydration | 3 (12.0) |

## Conclusions

- Based upon the pharmacokinetic profile of 3 times per week dosing a more frequent (5 or 7 times per week) dosing scheduled is recommended.
- Preliminary pharmacokinetic data helped to validate the pharmacokinetic simulations to predict pharmacokinetic profiles at more frequent dosing.

## Investigator Disclosures

1. Christine Peterson, PhD – Rexahn Pharmaceuticals
2. Ely Benaim, MD – Rexahn Pharmaceuticals

For further information about RX-3117 and Rexahn Pharmaceuticals please contact Dr. Ely Benaim: benaime@rexahn.com, (240) 268-5300