

# Phase I Clinical Trial of CX-3543, a Pro-Apoptotic Antitumor Agent

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## Abstract

**Background:** CX-3543 is a novel small molecule designed to target a protein-rDNA interaction that is critical to cancer cells and thus induces apoptosis. Preclinically, CX-3543 demonstrated potency in suppressing xenograft tumor growth with a broad therapeutic window, and no drug resistance has been observed *in vitro* to date. The objectives of this phase I study are: to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs), to establish the pharmacokinetics (PKs), and to determine the recommended dose for further clinical development of CX-3543.

**Methods:** Eligible patients with advanced solid tumors or lymphomas whose tumors had progressed on, or for whom there are no standard therapies, receive CX-3543 in successive dose cohorts at: 10, 20, 40, 80 and 160 mg/m<sup>2</sup>. Dosing is by one or two hour intravenous infusion daily for five consecutive days repeated on a three week cycle. Therapy is continued until the patient shows signs of intolerance to CX-3543, or evidence of advancing disease. Response by RECIST is determined after every 2 cycles.

**Results:** Twenty-one patients with solid tumors (3-8 patients per cohort) have received intravenous CX-3543, and doses have been well tolerated; nine grade 3 adverse events have been reported during the study, but none of these are deemed related to CX-3543. To date no objective tumor responses have been observed, but three patients have had disease stabilization durations of longer than four months. CX-3543 has demonstrated good linearity in PK parameters between the dose cohorts, with a terminal half life of approximately 10 hours following the first dose.

**Conclusions:** To date, CX-3543 has shown no drug related toxicity and has predictable PKs. No DLTs have yet been observed at the highest protocol dose level, and the MTD remains to be defined in this phase I study. Further patient enrollment with an expanded dose escalation is ongoing.

## Background

- The rate of ribosomal RNA (rRNA) biosynthesis defines the proliferative state of cells, and this process is highly deregulated and increased in cancer cells. Indirect inhibition of rRNA biosynthesis through the targeting of upstream kinase pathways has been well demonstrated with drugs like bevacizumab, trastuzumab, imatinib and sunitinib.
- In contrast, CX-3543 directly inhibits aberrant rRNA biosynthesis in cancer cells by disrupting an essential protein-rDNA quadruplex interaction over-expressed in cancer cells.
- Derived from the structural template of the highly successful fluoroquinolone class of drugs, CX-3543 rapidly induces selective apoptosis in malignant cells *in vitro* and tumor growth inhibition in *in vivo* xenograft models.
- This is the first phase I clinical trial with an agent having this novel mechanism of action.

## Patients

- 21 patients enrolled in the study to date. (Table 1)
- 11 solid tumor types represented. (Table 2)

Table 1.

| Patient Characteristics |                       |
|-------------------------|-----------------------|
| Gender                  | <b>N (%)</b>          |
| Male                    | 13 (62)               |
| Female                  | 8 (38)                |
|                         | <b>Median (Range)</b> |
| Age (yrs)               | 68 (44-84)            |
|                         | <b>N (%)</b>          |
| Karnofsky PS            | 100 3 (14.3)          |
|                         | 90 9 (42.8)           |
|                         | 80 8 (38.1)           |
|                         | 70 1 (4.8)            |
|                         | <b>Median (Range)</b> |
| Prior Therapies         | 4 (1-7)               |

Table 2.

| Tumor Types      |  | N |
|------------------|--|---|
| Blampullary      |  | 1 |
| Bladder, Urinary |  | 1 |
| Gastric          |  | 1 |
| Liposarcoma      |  | 1 |
| Ovarian          |  | 1 |
| Renal Cell       |  | 1 |
| Head & Neck      |  | 2 |
| Lung             |  | 2 |
| Neuroendocrine   |  | 2 |
| Skin             |  | 4 |
| Colon & Rectum   |  | 5 |

## Safety

- No drug-related serious adverse events to date.
- Adverse events (AEs) deemed at least possibly related to drug have been reported at all studied dose levels, but all have been grade 1 or 2 in severity. (Table 3)
- Some patients experienced a transient grade 1 cough with a one-hour infusion at the highest dose level (160 mg/m<sup>2</sup>) that resolved spontaneously upon completion of the infusion.
- When the protocol was amended to extend the infusion duration to two hours, the cough resolved.
- Generally CX-3543 has been very well tolerated, with no observations to date of dose limiting toxicities. Since the maximum tolerated dose (MTD) has not yet been defined with this highest dose, the protocol has been amended to allow for further dose escalations to levels above 160 mg/m<sup>2</sup>.

Table 3.

| Numbers of Patients with AEs Deemed Possibly Related to Drug |           |    |    |    |     |
|--|-----------|----|----|----|-----|
| Dose Level (mg/m <sup>2</sup> )                              | 10        | 20 | 40 | 80 | 160 |
| <b>General</b>   |           |    |    |    |     |
| Port Redness   | Grade 1-2 | 1  |    |    |     |
| Fatigue  | Grade 1-2 | 2  |    |    | 1   |
| Chills   | Grade 1-2 | 1  |    |    |     |
| Chest Tightness  | Grade 1-2 |    |    |    | 2   |
| Fever  | Grade 1-2 |    | 1  |    |     |
| <b>Nutrition</b>   |           |    |    |    |     |
| Anorexia   | Grade 1-2 | 1  | 2  | 1  | 1   |
| <b>Central Nervous System</b>                                |           |    |    |    |     |
| Involuntary Movement   | Grade 1-2 |    | 1  |    |     |
| Dysgeusia  | Grade 1-2 |    |    | 1  |     |
| Headache   | Grade 1-2 |    |    | 1  |     |
| Sensory Neuropathy   | Grade 1-2 |    | 1  |    |     |
| <b>Laboratory</b>  |           |    |    |    |     |
| Elevated AST   | Grade 1-2 |    | 1  |    |     |
| Proteinuria  | Grade 1-2 |    |    |    | 1   |
| <b>Cardiac</b>   |           |    |    |    |     |
| Hypertension   | Grade 1-2 |    |    |    | 1   |
| <b>Respiratory</b>   |           |    |    |    |     |
| Cough  | Grade 1-2 |    |    |    | 2   |
| Throat Tickle  | Grade 1-2 |    |    |    | 1   |
| <b>Skin</b>  |           |    |    |    |     |
| Alopecia   | Grade 1-2 |    | 1  |    |     |
| <b>Blood &amp; Lymph</b>                                     |           |    |    |    |     |
| Thrombocytopenia   | Grade 1-2 |    | 1  |    |     |
| Anemia   | Grade 1-2 |    |    |    | 1   |
| Leucopenia   | Grade 1-2 |    |    |    | 2   |
| <b>Gastrointestinal</b>                                      |           |    |    |    |     |
| Diarrhea   | Grade 1-2 |    |    | 1  |     |
| Nausea   | Grade 1-2 |    | 1  | 1  |     |
| Vomiting   | Grade 1-2 |    |    |    | 1   |
| Stomatitis   | Grade 1-2 |    |    | 1  | 1   |

## Pharmacokinetics

- CX-3543 exhibits linear pharmacokinetic behavior on Day 1 of dosing, with proportional increases in AUC with dose level. (Figure 1)
- Plasma half life remained consistent at approximately 10 hours on Day 1 across all the dose levels. (Table 4)
- Extending the infusion duration to 2 hours at the 160 mg/m<sup>2</sup> dose level decreased the maximum plasma concentration (C<sub>max</sub>) as expected, but AUC remained linear, increasing in proportion with the dose level.

Figure 1

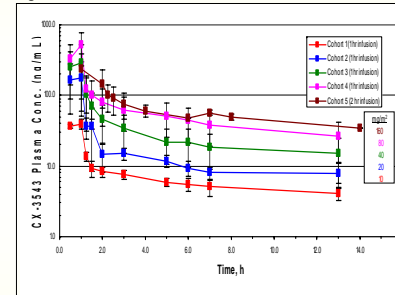


Table 4.

| Day 1 Average Pharmacokinetic Parameters |                          |                                 |                       |                           |                       |
|--|--------------------------|---------------------------------|-----------------------|---------------------------|-----------------------|
| Dose Level (mg/m <sup>2</sup> )          | C <sub>max</sub> (ng/mL) | AUC <sub>(0-∞)</sub> (ng.hr/mL) | T <sub>1/2</sub> (hr) | Cl <sub>s</sub> (L/hr/kg) | V <sub>d</sub> (L/kg) |
| 10 <sup>a</sup>                          | 41.1                     | 164.5                           | 9.9                   | 1.3                       | 18.5                  |
| 20 <sup>a</sup>                          | 173.7                    | 413.8                           | 11.7                  | 1.2                       | 20.8                  |
| 40 <sup>a</sup>                          | 346.1                    | 734.9                           | 10.0                  | 1.3                       | 19.9                  |
| 80 <sup>a</sup>                          | 564.2                    | 1142.8                          | 7.0                   | 1.5                       | 16.3                  |
| 160 <sup>b</sup>                         | 238.7                    | 1597.7                          | 12.0                  | 2.3                       | 44.1                  |
| Median                                   | -                        | -                               | 10.0                  | 1.3                       | 19.9                  |
| Range                                    | -                        | -                               | 7.0 - 12.0            | 1.2 - 2.3                 | 16.3 - 44.1           |

<sup>a</sup>One hour infusion

<sup>b</sup>Two hour infusion

## Evidence of Activity

- Six patients presented stable disease at the disease evaluation following two cycles of treatment, and three of these had disease stabilization for at least 4 months.
- Median duration of disease stabilization for these patients is 14 weeks. (range 9 – 24 weeks) (Table 5)
- Two patients with the longest duration of disease stabilization (16 and 24 weeks, respectively) are continuing on study at present.

Table 5.

| Evidence of Biological Activity (SD or Better During Assessment After 2 Cycles) |                |               |               |                  |
|---|----------------|---------------|---------------|------------------|
| Patient #   | Tumor Type     | Best Response | No. of Cycles | Duration (Weeks) |
| 2   | Colon & Rectum | SD            | 3             | 9                |
| 3   | Prostate       | SD            | 6             | 17               |
| 5   | Head & Neck    | SD            | 4             | 10               |
| 9*  | Neuroendocrine | SD            | 9*            | 24*              |
| 11  | Prostate       | SD            | 4             | 12               |
| 12*   | Colon & Rectum | SD            | 6*            | 16*              |

\* These patients presently still on study

## Conclusions

- CX-3543 is the first clinical compound with the novel mechanism of action of directly inhibiting the rRNA biosynthesis apparatus to induce apoptosis in cancer cells.
- CX-3543 is well tolerated, with no reports of serious adverse events deemed related to drug. Reported adverse experiences to date have been graded mild to moderate (i.e., Grade-1-2) in severity.
- A transient grade 1 cough was noted with the one hour infusion at the highest dose level of 160 mg/m<sup>2</sup>. This cough resolves spontaneously upon the completion of infusion, and has not limited dose administration when the infusion duration is extended to 2 hours.
- The maximum tolerated dose (MTD) has not yet been defined, and the protocol has been amended to allow continued dose escalations to levels above 160 mg/m<sup>2</sup>.
- Stable Disease (SD) has been observed in six patients when assessed after 2 cycles, with the longest period of stable disease to date of 24 weeks.
- Day 1 pharmacokinetic parameters are linear and predictable at all dose levels studied to date.
- Additional patients will continue to be enrolled at escalating dose levels until the MTD is defined. Fourteen additional patients will then be enrolled at the MTD to expand the patient safety and pharmacokinetic database.