

Phase I Clinical Trial of CX-3543, a Protein-rDNA Quadriplex Inhibitor

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Updated Abstract

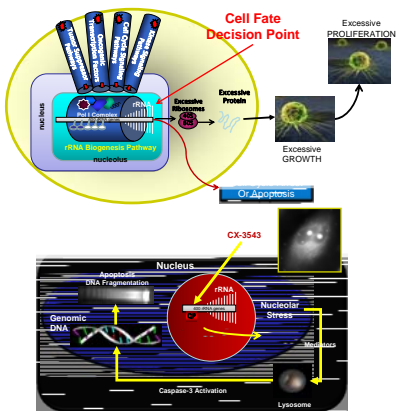
Background: CX-3543 is a targeted small molecule designed to inhibit over-expressed ribosomal RNA synthesis in cancer cells by disrupting an essential [protein-rDNA quadriplex] complex thereby inducing selective apoptosis. A Phase I clinical trial for CX-3543 was undertaken to identify the dose limiting toxicities (DLTs), maximum tolerated dose (MTD) and pharmacokinetics (PK) of this agent.

Methods: Eligible patients with advanced solid tumors received CX-3543 in successive dose cohorts at: 10, 20, 40, 80, 160, 240, 360 and 480 mg/m². Drug is administered by daily intravenous infusion on the first five consecutive days of a three week cycle and the infusion duration has varied from one hour to six hours. Response by RECIST is determined after every 2 cycles.

Results: Forty-two patients (M/F:25/17; median age 69, range 44-83) with colorectal cancer (9), prostate cancer (7), lung cancer (5), pancreatic cancer (5), head and neck cancer (3), renal cancer (2) and others (11) were treated with intravenous CX-3543 for a median of 2 cycles (range: 1-26). No drug-related serious adverse events (SAEs) have been encountered. DLTs of infusion-related cough, dyspnea without a decrease in O₂ saturation, muscle cramps and headache were identified at 480 mg/m². One patient receiving 360 mg/m² was discontinued due to transient, infusion-associated hypertension. These toxicities were fully reversible upon slowing or interruption of the infusion. MTD using the current dosing schedule was determined to be 360 mg/m². Other drug related adverse events were of mild to moderate intensity. Four patients demonstrated stable disease for longer than 4 months and one patient, who has experienced disease stabilization for longer than eighteen months, is currently continuing on study. CX-3543 demonstrated an increasing plasma terminal half life at the higher dose levels due to a "reservoir" effect, characterized by reversible binding and subsequent release of CX-3543 from blood cells.

Conclusions: CX-3543 administered as a 6 hour infusion for five consecutive days of a three week cycle is well tolerated and has shown disease stabilization in a number of patients enrolled in this Phase I study. The prolonged plasma terminal half life resulting from reversible blood cell binding supports less frequent dosing, and a phase I study using a weekly administration schedule is underway.

Background



Patients

42 patients have enrolled into the study, and the patient characteristics are presented in Table 1
 Patients were treated with intravenous CX-3543 for a median duration of 2 cycles (range: 1 – 26). One patient has remained on-study for over eighteen months, and presently continues on treatment. The duration of treatment for study patients is presented in Table 2.

Table 1. Patient Characteristics

Age - median (range)	69 (44-83)
Gender	
Male	25
Female	17
Karnofsky Performance Status	
100%	10
90%	19
80%	12
70%	1
Tumor Types	
Colorectal	9
Prostate	7
Lung	5
Pancreas	5
Head and Neck	3
Renal	2
Other	11
Prior therapies - median (range)	2 (1-7)

Table 2. Duration of Treatment for Study Patients

CX-3543 Dose Level (mg/m ²)	Total Number of Patients in Cohort	Total Number of Cycles in the Cohort	Range in Number of Cycles Administered	Number of Patients with DLT
10	3	11	2 - 6	0
20	4	8	1 - 3	0
40	3	22	2 - 26 ^a	0
80	3	15	1 - 12 ^b	0
160	8	16	1 - 6	0
240	3	6	2	0
360 ^c	14	27	1 - 2	1
480	4	6	1 - 2	2

^aIncluding one patient who was dose escalated to 240 mg/m². This patient remains on study at 240 mg/m².
^bIncluding one patient who was dose escalated to 160 mg/m².
^cThis dose level was defined as the MTD.

Safety

No drug related serious adverse events (SAEs) have been reported.
 The maximum tolerated dose has been defined at 360 mg/m², with reversible cough, dyspnea (without decrease in O₂ saturation), and headache identified as DLTs at the stopping dose of 480 mg/m².
 A listing of all adverse events observed in at least two patients, and that are deemed at least possibly related to quarfloxacin is presented in Table 3.

Table 3. Adverse Events Deemed at Least Possibly Related to CX-3543

Adverse Event ^a	10 - 80 mg/m ² N=13		160 mg/m ² N=8		240 mg/m ² N=3		360 mg/m ² N=14		480 mg/m ² N=4	
	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3	Grade 1/2	Grade 3
Anemia	2	-	1	1	-	2	-	1	-	1
Thrombocytopenia	1	-	-	-	-	1	-	1	-	1
Diarrhea	2	-	2	-	-	1	-	1	-	1
Nausea	2	-	2	-	1	-	5	-	-	-
Stomatitis	1	-	1	-	-	-	-	-	-	-
Vomiting	1	-	1	-	1	-	2	-	1	-
Chest discomfort	-	-	2	-	1	-	1	-	-	-
Chest pain	-	-	1	-	1	-	-	-	-	-
Chills	1	-	1	-	-	-	-	-	-	-
Fatigue	4	-	1	-	1	-	7	-	-	1
Fever	2	-	2	-	-	1	-	1	-	1
Increased creatinine	-	-	-	-	-	1	-	1	-	1
Anorexia	5	-	-	-	1	-	1	-	1	-
Muscle spasms	-	-	-	-	1	-	1 ^b	1	1	1
Extremity pain	-	-	-	-	-	2	1 ^b	-	-	-
Dysgeusia	1	-	-	-	1	-	-	-	-	-
Dyskinesia	1	-	1	-	-	-	-	-	-	-
Headache	1	-	1	-	-	5	1 ^b	1	1	1
Cough	1	-	5	-	3	-	9	-	2	1
Dyspnea	-	-	-	-	1	-	-	-	1	1
Throat irritation	-	-	2	-	-	-	-	-	-	-
Hypertension	-	-	1	-	1	-	3 ^b	-	1	-

^aNo grade 4 adverse events were reported.
^bListed adverse events have been reported in two or more patients taken across all dose levels.
^cAdverse events reported by one patient who was dose reduced from 480 mg/m².

Pharmacokinetics

The plasma terminal half life of CX-3543 was observed to increase with repeated dosing and with each dose level escalation, but without significant accumulation in CX-3543 plasma concentration.
 The pharmacokinetic sampling procedure was amended to collect whole blood and plasma specimens for analysis at each time point, and CX-3543 was observed to bind reversibly to blood cells.
 Analysis has determined that CX-3543 whole blood concentration is nearly ten times that of plasma concentration. (CX-3543 concentration versus time profile for whole blood and plasma is presented in Figure 1.)
 The reversible binding and subsequent slow release of CX-3543 from blood cells provides a "reservoir" effect to extend the CX-3543 plasma terminal half life.
 This pharmacokinetic property allows evaluation of a less frequent dosing schedule, and a phase I study of weekly intravenous CX-3543 administration is underway.

Evidence of Activity

Four patients demonstrated stable disease for 4 months or longer on CX-3543:
 1. At the 10 mg/m² dose level, one patient with prostate cancer had stable disease for six cycles.
 2. At the 160 mg/m² dose level, one patient with liposarcoma had stable disease for six cycles.
 3. At the 160 mg/m² dose level, one patient with anorectal cancer (intra-patient dose escalation from the 80 mg/m² dose level) had stable disease for twelve cycles.
 4. At the 240 mg/m² dose level, one patient with neuroendocrine islet cell cancer of the pancreas (intra-patient dose escalation from the 40 mg/m² dose level) remains on-study after completing 26 cycles of CX-3543.

Conclusions

The MTD for CX-3543 has been identified as 360 mg/m², with reversible DLTs of cough, dyspnea and headache experienced at the stopping dose of 480 mg/m².
 CX-3543 is well tolerated with no drug related SAEs, and other reported adverse events have been mild to moderate in intensity.
 Four patients have shown durable disease stabilization of 4 months or longer, and one of these patients continues on-study after more than eighteen months.

Pharmacokinetic analysis has shown CX-3543 to have an extended plasma terminal half life due to reversible blood cell binding. This allows evaluation of a less frequent dosing schedule, and a phase I study of weekly intravenous quarfloxacin administration is underway.

Figure 1. CX-3543 concentration versus time profile for whole blood and plasma (N=4).

