

Findings from the Phase I Clinical Trials of CX-4945, an Orally Available Inhibitor of CK2

Robert F. Marschke, Mitesh J. Borad, Ross W. McFarland, Ricardo H. Alvarez, John K.C. Lim, Claire S. Padgett, Daniel D. Von Hoff, Sean E. O'Brien, and Donald W. Northfelt
Front Range Cancer Specialists, Fort Collins, CO; Mayo Clinic Scottsdale, Scottsdale, AZ; M.D. Anderson Cancer Center, Houston, TX; and Cylene Pharmaceuticals, Inc., San Diego, CA

Abstract

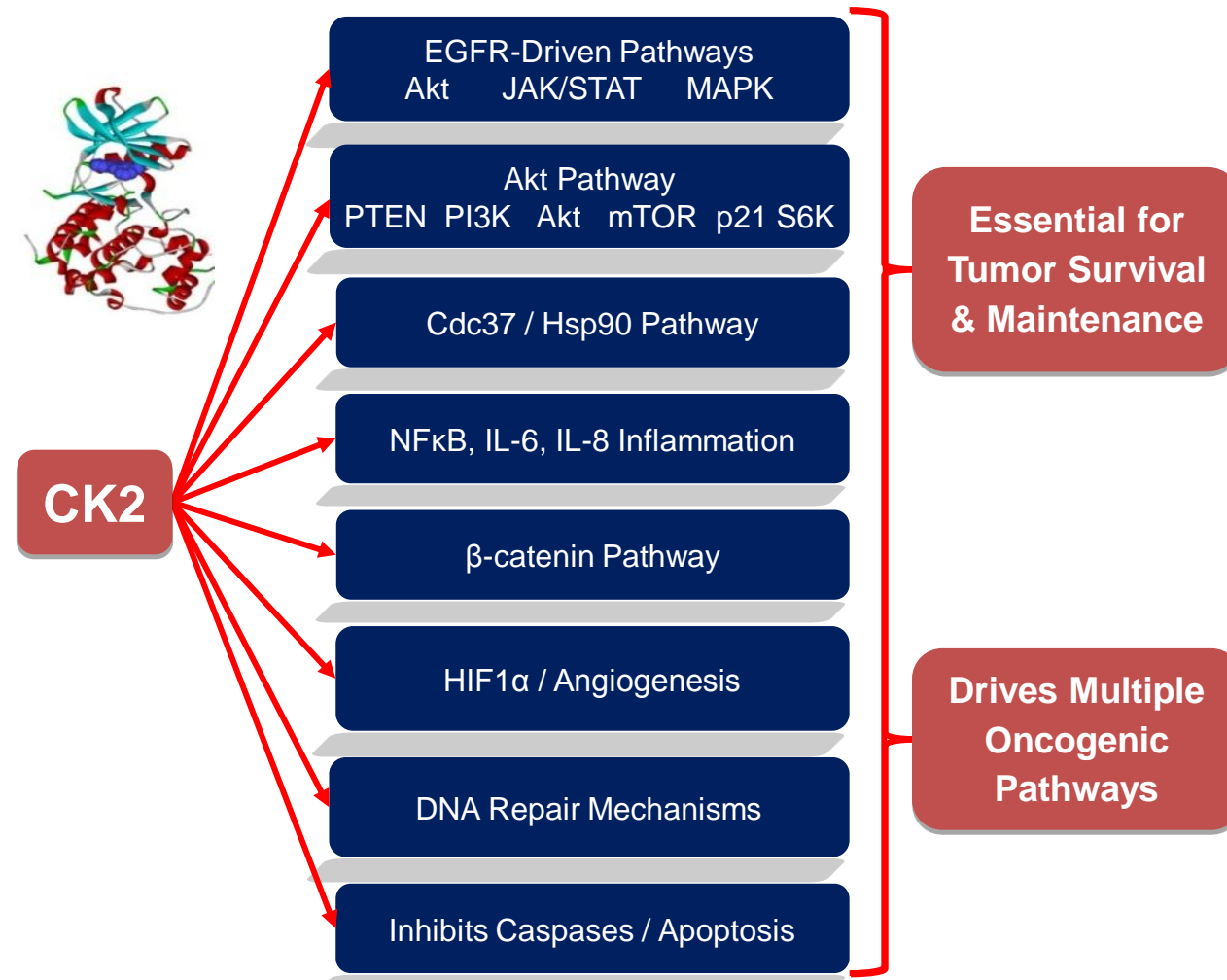
Background: CX-4945 is a first-in-class, orally available, small molecule that is an ATP competitive and highly selective inhibitor of CK2 protein kinase. CK2 is an attractive target for anticancer therapy because it is overexpressed and essential to the survival and maintenance of the cancer phenotype, it supports multiple oncogenic and cytokine signaling pathways, and it is an ideal target for mechanistically driven drug combination therapy.

Methods: Two phase I clinical studies with CX-4945 were conducted in patients with advanced solid tumors in escalating dose cohorts. CX-4945 was administered orally on two different dosing schedules; twice daily or four times daily, for the first 3 consecutive weeks of a 4 week cycle. All patients were evaluated for safety, pharmacokinetic and pharmacodynamic analyses, including biomarker measurements in peripheral blood mononuclear cells for phospho-proteins to assess the inhibition of CK2 protein kinase (P-Akt-S129) and downstream inhibition of the Akt signaling pathway (P-Akt-S473 and P-p21-T145), and of circulating tumor cells (CTC) and IL-6 and IL-8 levels in peripheral blood.

Results: Forty-four patients received oral doses of CX-4945 in these phase I studies, and the drug was deemed generally safe and well tolerated. Two cases of diarrhea and one case of hypokalemia were considered as dose limiting toxicities (DLTs), and these events were reversible. The pharmacokinetics of CX-4945 were linear and dose dependent, drug exposure-related biomarker responses were observed for inhibition of CK2 and for modulation of downstream pathways (Akt and p21), and evaluable patients revealed a trend in reduced CTC. Stable disease for at least 16 weeks was evident in 20% of treated patients, and patients showing the highest percentage decrease in IL-6 and IL-8 levels generally had the most durable stabilization of disease.

Conclusions: CX-4945 can be orally administered safely on two different dosing schedules. CX-4945 demonstrated dose-dependent pharmacokinetics, strong PK-PD relationships in regard to inhibition of the CK2 target and downstream pathways and modulation of chemokines and cytokines. Anti-tumor activity as a single agent was characterized as disease stabilization, and 9 patients were on study 16 weeks or longer. CX-4945 is now positioned for phase II studies in rational drug combinations with EGFR antagonists, DNA damaging agents and other mechanistically-driven combinations.

Background



- CK2 is a newly validated cancer target.
- CK2 promotes multiple cancer pathways and processes, and is essential for survival and maintenance of the cancer phenotype.
- CK2 is an ideal target for drug combination therapy
 - Enables extensive combinability with multiple classes of anticancer drugs.
 - Strong mechanistic rationale for combination with other anticancer drugs.

Patient Demographics

Table 1. Patient Characteristics and Tumor Types

Baseline Characteristics	Dose Schedule	
	BID Dose Schedule Total (N=27)	QID Dose Schedule Total (N=17)
Gender Male/Female	16/11	7/10
Age (years) Median (range)	67 (42-83)	60 (30-80)
Karnofsky Performance Status (Median 90%)	N (%)	N (%)
100%	6 (22%)	4 (24%)
90%	9 (33%)	8 (47%)
80%	11 (41%)	5 (29%)
70%	1 (4%)	0
Number of prior chemotherapy regimens Median (range)	4 (1-9)	5 (2-13)

Tumor Types

Tumor Types	BID Dose Schedule (N=27)	QID Dose Schedule (N=17)
Prostate	6	1
Lung	4	2
Breast & Inflammatory Breast	2	3
Thyroid (Papillary)	2	-
Ovarian	2	-
Pancreatic	2	-
Colorectal	2	4
Cholangiocarcinoma	2	3
Neuroendocrine	-	2
Sarcoma	-	2
Endometrial	1	-
GIST	1	-
Leydig Cell	1	-
Melanoma	1	-
Renal Cell	1	-

- Forty-four patients have enrolled into the study; the patient characteristics, including tumor type, are presented in Table 1.
- Patients received treatment with oral CX-4945 capsules for a median duration of 2 cycles (range: 1 – 22). Three patients presently continue on-study: one patient with papillary thyroid cancer for over twenty-two months, one patient with neuroendocrine cancer for over ten months, and one patient with non-small cell lung cancer for over four months. The summary of duration of treatment for study patients is presented in Table 2.

Table 2. Duration of Treatment for Study Patients

CX-4945 Dose Level (mg)	Total number of Patients in Cohort	Total Number of Cycles in the Cohort	Range in Number of Cycles Administered	Number of Patients with DLT
BID Schedule				
90 mg	3	4	1-2	0
160 mg	3	7	1-4	0
300 mg	4	12	1-6	0
460 mg	6	40	1-22 ^a	0
700 mg	3	11	2-6	0
1000 mg	8	12	1-4 ^a	1
QID Schedule				
300 mg	3	11	1-8	0
500 mg	3	5	1-2	0
600 mg	6	15	1-10 ^a	0
800 mg	5	6	1-4	2

^a Includes patients who are currently active.

Safety-Related Findings

BID Schedule

- Six patients have been treated successfully at the highest studied dose level of 1,000 mg on the BID schedule, with only one reported DLT (Grade 4 hypokalemia that was reversible with potassium supplementation).

QID Schedule

- The stopping dose has been identified as 800 mg, with two patients reporting Grade 3 diarrhea as dose limiting toxicities (DLTs).
- The maximum tolerated dose (MTD) on the QID schedule was identified as 600 mg, and six patients have been successfully dosed with no DLTs.
- Adverse Events**
 - Dose limiting adverse events have been responsive to treatment with anti-diarrheal agents, potassium supplementation and/or interruption or discontinuation of CX-4945 doses.
 - One drug related serious adverse event (SAE) was reported (hospitalization for treatment of Grade 4 hypokalemia).
 - Other reported adverse events have generally been of mild or moderate intensity.
 - A listing of all adverse events observed in ≥10% of patients, and deemed at least possibly related to CX-4945, is presented in Table 3.

Table 3. Incidence Table of Adverse Events Deemed at Least Possibly Related to CX-4945

Dose (mg) and schedule	90 BID	160 BID	300 BID	460 BID	700 BID	1000 BID	300 QID	500 QID	600 QID	800 QID	Overall
Gastro-intestinal disorders	1	1	4	4	2	4	3	0	5	2	26
Diarrhea	(33.3%)	(33.3%)	(100%)	(66.7%)	(66.7%)	(57.1%)	(100%)	(83.3%)	(100%)	(100%)	(65.0%)
Nausea	0	1	2	4	1	4	3	0	5	2	22
	(33.3%)	(50.0%)	(66.7%)	(66.7%)	(33.3%)	(57.1%)	(100%)	(83.3%)	(100%)	(100%)	(55.0%)
Vomiting	0	0	1	1	0	1	2	0	1	1	7
	(33.3%)	(50.0%)	(16.7%)	(16.7%)	(0)	(14.3%)	(66.7%)	(0)	(16.7%)	(50.0%)	(17.5%)
General disorders	1	2	1	1	1	0	2	0	1	1	9
Fatigue	(33.3%)	(33.3%)	(50.0%)	(16.7%)	(33.3%)	(0)	(66.7%)	(0)	(16.7%)	(50.0%)	(22.5%)
Nervous system disorders	1	1	0	0	0	1	0	0	0	0	4
Headache	(33.3%)	(33.3%)	(25.0%)	(0)	(0)	(33.3%)	(0)	(0)	(0)	(0)	(10.0%)
Metabolism & nutrition disorders	1	0	1	2	0	2	1	0	0	1	8
Anorexia	(33.3%)	(0)	(25.0%)	(33.3%)	(0)	(28.6%)	(33.3%)	(0)	(0)	(50.0%)	(20.0%)

Pharmacokinetics & Pharmacodynamics

Linear Pharmacokinetics (Figure 1)

- Pharmacokinetic parameters (C_{max} and AUC_{0-4hr}) of CX-4945 oral capsules at steady state were linear with dose level.
- The linearity of pharmacokinetic parameters at steady state was independent of the schedule of dose administration (BID or QID).

PK-PD Responses (Figure 2)

- Pharmacodynamic biomarkers in the patients' peripheral blood mononuclear cells (PBMCs) were modulated downward in a drug exposure-related manner.
- Strong biomarker responses were consistently observed when drug exposure levels reached an AUC_{0-4hr} of 4,000 ng.hr/ml on either the BID or QID schedules.
- Inhibition of the CK2 target (Figure 2)**
 - The degree of inhibition of P-Akt-S129 (specific marker for CK2) in PBMCs was related to drug exposure as measured by AUC.

Inhibition of downstream pathways (Figure 2)

- The degree of inhibition of these key phospho-proteins in PBMCs when compared with pre-treatment levels (P-Akt-S473 and P-p21-T145) was related to drug exposure as measured by AUC.
- Inhibition of IL-6 and IL-8 (Figure 3)**
 - Decrease from baseline in these chemokine/cytokine levels following the first cycle of treatment with CX-4945 was associated with the duration of disease stabilization.
 - Specifically, patients showing the highest percentage decrease in these levels generally had the most durable stabilization of disease.

Trend for Reduction in Circulating Tumor Cells (CTCs) (Figure 4)

- Patients were assessed for CTCs using a specially enhanced enumeration method, and those with evaluable numbers of CTCs at baseline were followed serially.
- These patients showed a trend for decreased CTCs over time.

Figures

Figure 1. Linear Pharmacokinetics. Pharmacokinetic parameters (C_{max} and AUC_{0-4hr}) are linear with dose level at steady state.

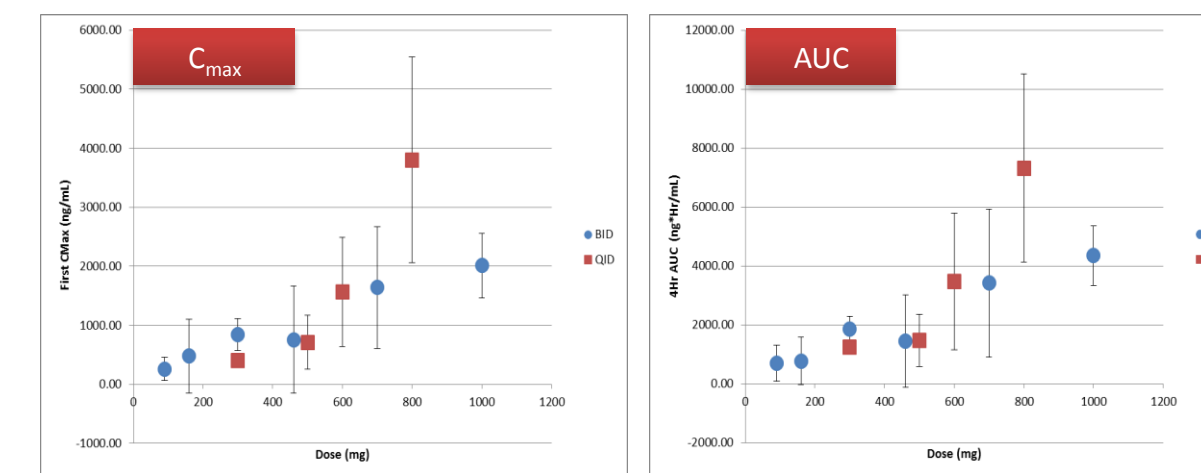


Figure 2. Pharmacokinetic-Pharmacodynamic Responses in PBMC. Biomarker reductions in PBMC indicate robust inhibition of CK2 and downstream pathways (Akt, p21) in a drug exposure (AUC) related manner.

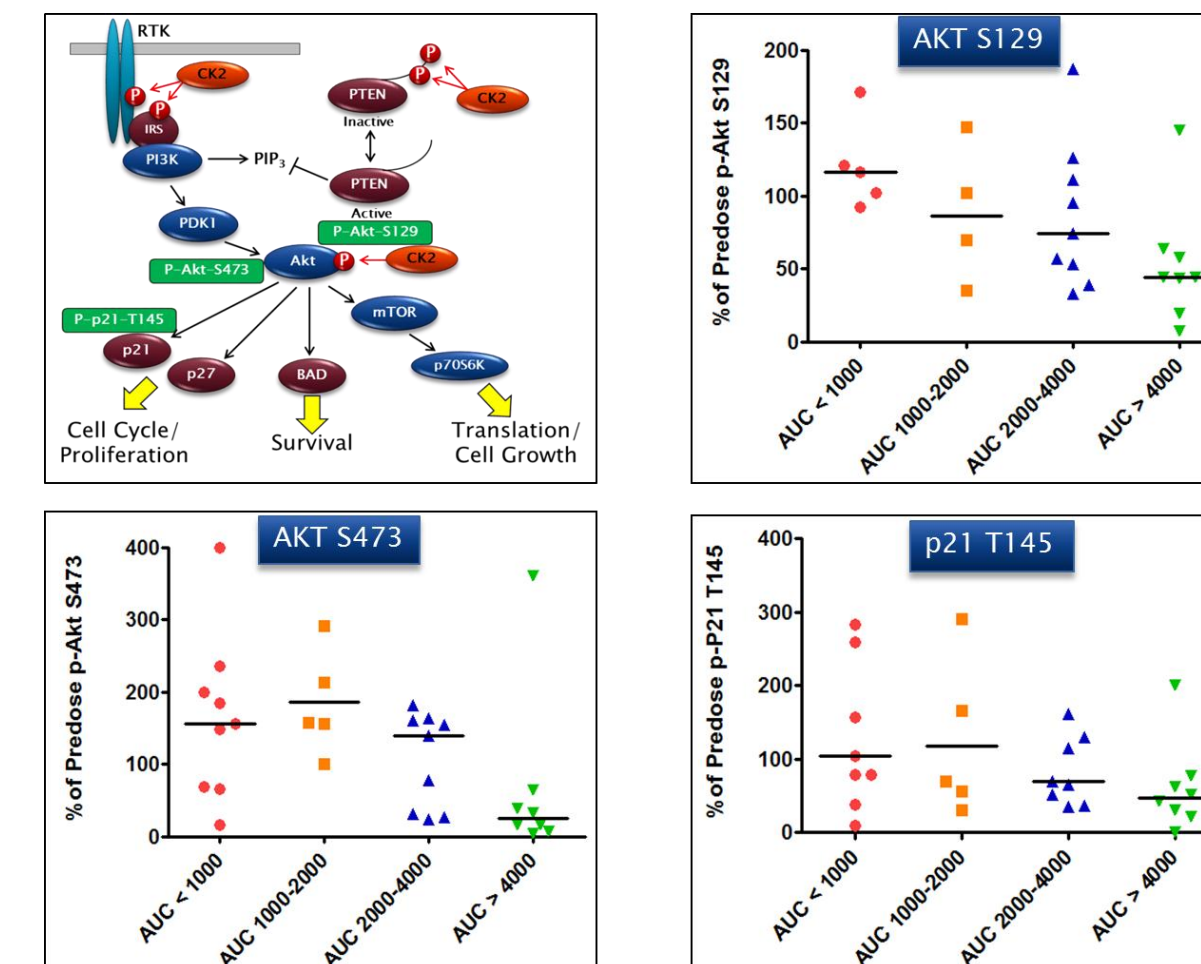
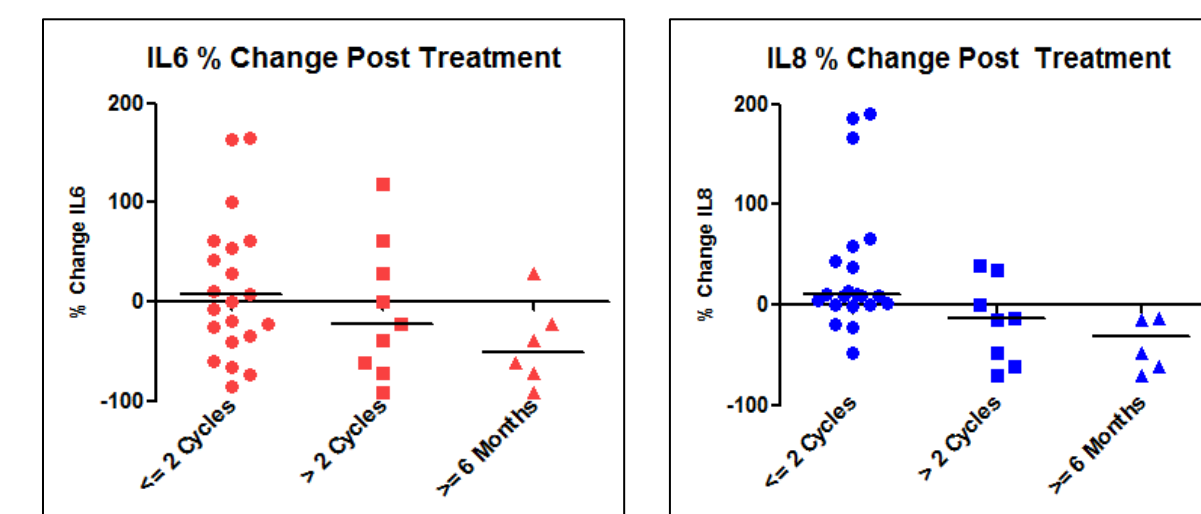
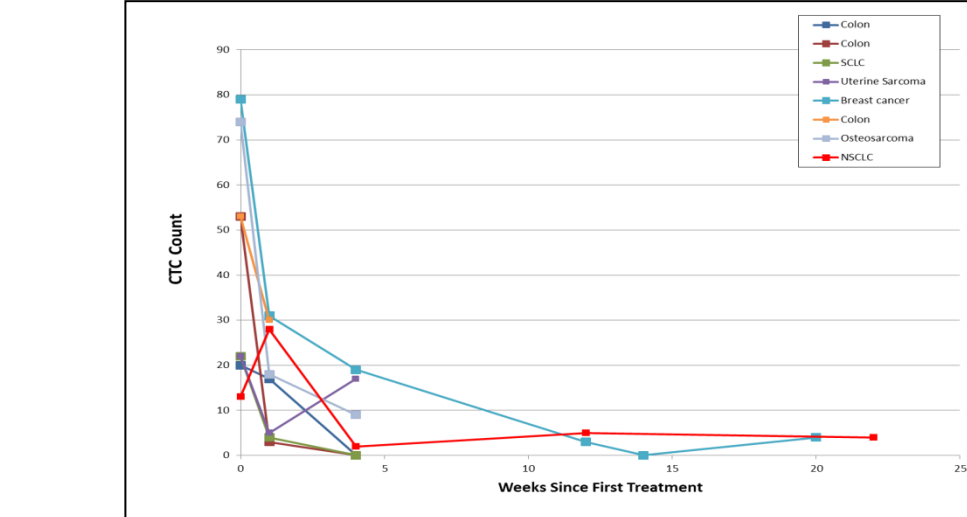


Figure 3. Inhibition of IL-6 and IL-8. Percentage decrease in IL-6 and IL-8 levels from baseline, when measured after the first cycle of treatment, was associated with duration of disease stabilization.



Figures

Figure 4. Trend for Reductions in CTC. Patients who had evaluable circulating Tumor Cell (CTC) counts were followed serially using a specially enhanced CTC enumeration method by Apocell (Houston, Texas). These patients showed a trend for decreased CTC count over time.



Clinical Activity

- Nine Patients Demonstrated Disease Stabilization for 16 Weeks or Longer (Table 4)

Table 4. Patients with Disease Stabilization of 16 Weeks or Longer.

Tumor Type	Dose/Schedule	Best Response	Time on Study (Weeks)	Most Recent Treatment	
				Agent	Weeks
NSCLC	160mg BID	SD	16	Investigational	4
Prostate	300mg BID	SD	24	Docetaxel/Bevacizumab	12
Thyroid	460mg BID	SD	88*	Investigational	36
Leydig	460mg BID	SD	48	Investigational	21
Thyroid	700mg BID	SD	24	Investigational	14
NSCLC	1000mg BID	SD	18*	Paclitaxel/Carboplatin/Bevacizumab	16
Cholangiocarcinoma	300mg QID	SD	32	Gemcitabine	18
NET	500mg QID	SD	44*	Gemcitabine + Investigational	12
Breast	800mg QID	SD	16	Paclitaxel	36

*Currently on Study

CX-4945 Phase I: Conclusions

- CX-4945 is the first small molecule CK2 inhibitor in clinical trials, and provides the first evidence that CK2 may be inhibited safely in humans.**
- Pharmacokinetics are linear on BID and QID schedules.
- BID schedule highest tolerated dose studied was 1,000 mg BID.
- QID schedule stopping dose was 800 mg, and the MTD was 600 mg.
- AEs were generally of mild to moderate intensities.
 - DLTs were experienced by two patients with diarrhea and one patient with hypokalemia. These events were reversible with treatment.
- Best single agent anti-tumor activity observed was stable disease**
 - Nine patients had durable disease stabilization of 16 weeks or longer.
- Robust PK-Drug Exposure Related PD Responses.**
 - Inhibition of CK2 was observed at tolerated doses.
 - Downstream pathway inhibition (Akt and p21) was observed at tolerated doses.
 - Reductions in IL-6 and IL-8 levels following the first cycle of treatment were associated with the duration of disease stabilization.
 - CTC counts trended downward in evaluable patients on study.
- Implications of Findings for Future Studies.**
 - These Phase I studies proved that CX-4945, an oral CK2 inhibitor, can be administered safely to humans, and exert a pharmacodynamic response.
 - A spray dried dispersion (SDD) formulation for oral administration is being studied in the clinic.
 - CK2 supports multiple oncogenic signaling pathways, and represents an ideal target for rational drug combination therapies in various cancers.
 - Phase II studies are planned for CX-4945 in rational combination with approved agents for a number of different cancer types.