

CLINICAL TRIAL SYNOPSIS

Study Title	A Phase 1, Multi-Center, Open-Label, Dose-Escalation, Safety, Pharmacokinetic, and Pharmacodynamic Study of CX-4945 Administered Orally to Patients with Advanced Solid Tumors, Castleman's Disease or Multiple Myeloma
Sponsor	Cylene Pharmaceuticals, Inc. 5820 Nancy Ridge Drive, Suite 200 San Diego, CA 92121 Telephone: (858) 875-5100 Fax: (858) 875-5101
Study Rationale	CK2 is a serine/threonine protein kinase distributed in the cytoplasmic and nuclear compartments of multiple cell types. Elevated CK2 activity has been associated with malignant transformation and aggressive tumor growth and overexpression of CK2 has been documented in multiple types of cancer. CK2 has emerged as a potential anticancer target and inhibition of CK2 represents a potential therapeutic strategy to target a specific molecular defect perpetuating many cancers. CX-4945 has demonstrated potent inhibition of CK2 enzymatic activity. Molecular mechanism of action studies suggest the antitumor activity of CX-4945 is attributed to disruption of cell cycle control, induction of apoptosis and anti-angiogenesis activity.
Study Objectives	<p>Primary Objective</p> <ul style="list-style-type: none"> • To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of CX-4945 when administered orally twice daily for 3 consecutive weeks in 4 week (28 day) cycles over a range of doses. <p>Secondary Objectives</p> <ul style="list-style-type: none"> • To establish the pharmacokinetics (PK) of CX-4945 when administered orally. • To observe patients for evidence of CX-4945 antitumor activity using pharmacodynamic (PD) assessments. • To establish the dose recommended for future Phase 2 trials with CX-4945. • To observe patients for evidence of CX-4945 antitumor activity by objective radiographic assessment.
Study Design	Open label, multicenter, dose-escalation, safety, pharmacokinetics, and pharmacodynamics study.
Duration	Treatment repeats every 4 weeks (28 days) in the absence of disease progression or unacceptable toxicity.
Planned Total Sample Size	Approximately 40 patients will be enrolled sequentially into dosing cohorts. Approximately 30 patients may participate in

	<p>the dose escalation phase. Once the MTD has been established, up to 10 additional patients may be enrolled at the recommended Phase 2 dose level to confirm safety, pharmacokinetic and pharmacodynamic parameters.</p>
<p>Test Article, Administration and Dose-Escalation Scheme</p>	<p>During the treatment phase of the study, CX-4945 will be administered in 4-week cycles consisting of twice daily dosing for 21 days followed by a 7 day rest period. The proposed daily dosing regimen will be based on the available data from</p> <p>The starting dose will be 90 mg administered orally twice daily (180 mg total daily dose). This starting dose is based on the non-clinical toxicology and TK studies conducted using similar dosing schedules in rats and dogs.</p> <p>Study drug will be prescribed as a fixed dose within each cohort, and will not be adjusted to individual body surface area.</p> <p>All enrolled patients will receive their initial dose of CX-4945 in the clinic according to their assigned cohort (Cycle 1, Day 1-treatment period). The first dose of study drug will be taken in the morning in a fed state (2 hours after a light breakfast), and the second dose will be taken 12 hours later, about two hours after the evening meal during the 21 day dosing period. After CX-4945 administration, patients will be NPO (except water) for 2 hours, after which, the patient may eat.</p> <p>The study drug will be taken with 6 ounces of water. As medically advisable, concomitant medications may be taken one hour before, or two hours following the study drug. Patients will continue to self-administer the study drug twice daily approximately 12 hours apart, two hours after their morning and evening meals.</p> <p>Dose increments in the first three cohorts will initially be increased by doubling the dose until the first Grade 2 toxicity is observed. All subsequent dose escalations will then be in 50% increments.</p>

	<p>Dose escalation will proceed according to the predetermined scheme until the stopping dose (dose \geq MTD) is reached due to dose limiting toxicity (DLT) occurring during the first cycle of treatment.</p> <p>The dose will be increased sequentially in cohorts of 3-6 evaluable patients according to the dose escalation scheme below until the stopping dose level has been identified. The decision to dose escalate will be based on the toxicity observations during the first cycle of treatment only. A minimum of 3 patients will be treated at each dose level.</p>
<p>Inclusion Criteria:</p>	<p>Patients meeting all of the following criteria will be considered for admission to the study:</p> <ol style="list-style-type: none"> 1. Signed, written IRB-approved informed consent 2. Histologically or cytologically confirmed malignancy or lymphoproliferative disorder known to over express CK2 which has failed standard therapies (surgery, radiotherapy, endocrine therapy, chemotherapy) or for which effective therapy is not available, including the following types: <ul style="list-style-type: none"> • Solid tumors <ul style="list-style-type: none"> • Lung cancer • Renal cell cancer • Breast cancer, including inflammatory breast cancer • Head and neck cancer – squamous cell • Prostate cancer • Castleman’s disease (multi-centric disease) • Hematological malignancy <ul style="list-style-type: none"> • Multiple myeloma Eligible patients must have quantifiable M-protein levels present in serum and/or urine 3. At least 18 years of age. 4. One or more tumors measurable on radiograph or CT scan, or evaluable disease defined as non-measurable lesions per RECIST (e.g., malignant ascites), or detection of protein M in serum and/or urine of patients with Multiple Myeloma (serum \geq 10 gm/L and urine \geq 200 mg/24 hr [must be 24 hour urine]). 5. Laboratory data as specified below: <ul style="list-style-type: none"> • Hematology: ANC $>$1500 cells/mm³, platelet count $>$100,000 cells/mm³ and Hemoglobin $>$ 9 gm/L

	<ul style="list-style-type: none"> • Hepatic: bilirubin <1.5 X ULN; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 2.5 X ULN. Patients with known liver metastases or liver neoplasms: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 5.0 X ULN • Renal: serum creatinine within normal limits (WNL), defined as $\pm 10\%$ of the institution's stated reference range, or a calculated creatinine clearance $> 60 \text{ mL/min/1.73 m}^2$ for patients with abnormal, increased, creatinine levels. Patients with Multiple Myeloma (only): serum creatinine ≤ 2.5 the institutional upper limit of the normal range and a calculated creatinine clearance $> 40 \text{ mL/min/1.73 m}^2$. • Coagulation: INR < 1.5 times normal, aPTT < 1.5 times normal. Patients receiving therapeutic doses of anticoagulant therapy may be considered eligible for the trial if INR and aPTT are within the acceptable therapeutic limits for the institution. <ol style="list-style-type: none"> 6. A negative pregnancy test (if female of childbearing potential). 7. Estimated life expectancy of at least 3 months 8. Karnofsky Performance Status $\geq 70\%$ 9. For men and women of child-producing potential, use of effective contraceptive methods during the study 10. Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agreement to abide by the study restrictions and to return to the clinic for the required assessments. Patients will be required to maintain a dosing record form throughout the trial.
<p>Exclusion Criteria:</p>	<ol style="list-style-type: none"> 1. Pregnant or nursing women. NOTE: Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; or abstinence) prior to study entry and for the duration of study participation. Should a man father a child, or a woman become pregnant or suspect she is pregnant while participating in this study, he or she should inform the treating physician immediately. 2. Seizure disorders requiring anticonvulsant therapy. 3. Known brain metastases (unless previously treated and well controlled for a period of ≥ 3 months). 4. Major surgery, other than diagnostic surgery, within 4 weeks prior to the first dose of test drug, minor surgery

	<p>including diagnostic surgery within 2 weeks (14 days) excluding central IV port placements and needle aspirate/core biopsies.</p> <ol style="list-style-type: none"> 5. Treatment with radiation therapy or surgery within one month prior to study entry. 6. Treatment with chemotherapy or investigational drugs within 21 days prior to the screening visit. Acute toxicities from prior therapy must have resolved to Grade ≤ 1 above baseline. 7. Patients with a history of a second malignancy within 3 years of the baseline visit excluding cutaneous carcinomas and in-situ carcinoma. 8. Concurrent severe or uncontrolled medical disease (i.e., systemic infection, diabetes, hypertension, coronary artery disease, congestive heart failure). 9. Active symptomatic fungal, bacterial and/or viral infection including active HIV or viral (A, B or C) hepatitis. 10. Difficulty with swallowing or an active malabsorption syndrome. 11. Chronic diarrhea (excess of 2-3 stools/day above normal frequency). 12. Gastrointestinal diseases including gastritis, ulcerative colitis, Crohn's disease, or hemorrhagic coloproctitis. 13. History of gastric or small bowel surgery involving any extent of gastric or small bowel resection. 14. Clinically significant bleeding event within the last 3 months, unrelated to trauma, or underlying condition that would be expected to result in a bleeding diathesis. 15. Patients who have exhibited allergic reactions to a similar structural compound or to a formulation component.
<p>Pharmacokinetic Assessments</p>	<p>The pharmacokinetic profile of CX-4945 will be determined in all patients. Serial heparinized blood samples will be collected after the administration of the first dose of study drug (Cycle 1). Trough levels will be collected prior to dose administration during Cycle 1, on Study Days 2, 8 and 15. In addition, serial heparinized blood samples will be collected after the administration of the study drug during Cycle 1 Day 21 and additional off-treatment blood samples will be collected during Cycle 1 Days 22 and 23.</p>

Pharmacodynamic Assessments	<p>Blood samples will be collected from all patients for pharmacodynamic assessments. These specimens will be collected on Cycle 1 Day 1 prior to the first dose, and again 4 and 8 hours after the first dose and on Cycle 1 Day 21 prior to the first dose of that day and again 4 and 8 hours after dosing.</p> <p>Patients may volunteer to participate in a fine needle aspirate/biopsy of an accessible lesion at baseline, and again within 24 hours of the last dose of study drug (Day 22) for assessment of pharmacodynamic assessments.</p>
Assessment of Response	<p>Response will be assessed according to the RECIST criteria for patients with measurable and non-measurable lesions per RECIST Reassessment of tumor will be done by the same methods used to establish baseline tumor measurements. All responding patients (CR and PR) must have their response confirmed 4 weeks after the first documentation of response. Patients with Multiple Myeloma will be assessed according to the International Myeloma Working Group uniform response criteria (CR, PR and PD) for M-protein. This response will be measured after each cycle of treatment.</p>