



STUDY PROTOCOL

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

DRAFT 4

Protocol Number: C4-08-001

Cylene Pharmaceuticals, Inc.
5820 Nancy Ridge Drive, Suite 200
San Diego, CA 92121
Telephone: (858) 875-5100
Fax: (858) 875-5101

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2. 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 found 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	To determine the safety and tolerance of CX-4945 when administered orally twice daily for 3 consecutive weeks in 4 week (28 day) cycles over a range of doses: Primary Objective <ul style="list-style-type: none"> To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of CX-4945 Secondary Objectives <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.

Comment [A1]: Update per IND and AKT information.

Planned Total Sample Size	Approximately 40 patients will be enrolled sequentially into dosing cohorts. Approximately 30 patients may participate in 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.
Test Article, Administration and Dose-Escalation Scheme	<p>CX-4945 will be supplied as oral capsules in 30 mg strength.</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 non-clinical toxicology and PK studies conducted using similar dosing schedules.</p> <p>The starting dose 90 mg administered orally twice daily has been determined and is based on the pre-clinical toxicology findings and calculated as one-tenth of the estimated severely toxic dose (STD₁₀) in the rat.</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. 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>Toxicity is defined as an adverse event that has an attribution of possibly or probably related to the investigational 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>CX-4945 dose cohorts: Level 1: 90 mg/dose BID (total daily dose 180 mg) Level 2: 180 mg/dose BID (total daily dose 360 mg) Level 3: 360 mg/dose BID (total daily dose 720 mg) Level 4: 540 mg/dose BID (total daily dose 1080 mg) Level 5: 810 mg/dose BID (total daily dose 1620 mg) Level 6: 1200 mg/dose BID (total daily dose 2400 mg)</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 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 <p>which has failed standard therapies (surgery, radiotherapy, endocrine therapy, chemotherapy) or for which effective therapy is not available.</p> 3. At least 18 years of age. 4. One or more tumors measurable on radiograph or CT

	<p>scan, or evaluable disease defined as non-measurable lesions per RECIST, elevated tumor markers (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]).</p> <p>5. Laboratory data as specified below:</p> <ul style="list-style-type: none"> • Hematology: ANC >1500 cells/mm³, platelet count $>100,000$ cells/mm³ and Hemoglobin > 9 gm/L • 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 mL/min/1.73 m² 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 mL/min/1.73 m². • Coagulation: INR < 1.5 times normal, aPTT < 1.5 times normal. <p>6. A negative pregnancy test (if female of childbearing potential).</p> <p>7. Estimated life expectancy of at least 3 months</p> <p>8. Karnofsky Performance Status $\geq 70\%$</p> <p>9. For men and women of child-producing potential, use of effective contraceptive methods during the study</p> <p>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>
<p>Exclusion Criteria:</p>	<p>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.</p>

	<ol style="list-style-type: none"> 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 including diagnostic surgery within 2 weeks (14 days) excluding central IV port placements and needle aspirate/core biopsies. 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.
Pharmacokinetic Assessments	<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. Patient samples will be</p>

	<p>evaluated for p21-T145 phosphorylation and inhibition of AKT signaling pathways (PBMCs), reduction of IL-6 and IL-8 (serum). 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 Cycle 1 Day 21 prior to the first dose of that day and again 4 and 8 hours after dosing (Collection of PBMC's only at the Day 21 time points of 4 and 8 hours).</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 p21-T145 phosphorylation and Ki67 in tumor cells.</p> <p>When a consistent reduction in one or more of these pharmacodynamic markers is detected (i.e., observed over two dose cohorts), two additional pharmacodynamic measures will be initiated through an amendment to the protocol.</p> <p>These pharmacodynamic assessments would possibly include the assessment of circulating tumor cells in all study patients and FDG-PET scans taken at baseline and after 21 days of treatment in selected patients who volunteer to participate in this separate study. A separate informed consent form will be administered to these patient volunteers who will participate in the FDG-PET scan.</p>
<p>Study Assessments:</p>	<p>Screening Period (Day -14 to -1)</p> <ul style="list-style-type: none"> • Informed Consent • Complete medical and surgical history • Physical examination, weight and vital signs • Karnofsky Performance Status • 12-lead electrocardiogram • Concomitant medications • Tumor measurements, Imaging CT or MRI scan (not necessary if one has been conducted within the previous 28 days) <p>Laboratory assessments:</p> <ul style="list-style-type: none"> • Clinical chemistries [glucose, sodium, potassium, chloride, CO₂, calcium, phosphorus, BUN, creatinine, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT, (LDH will also be collected for patients with Multiple Myeloma)] • C-Reactive Protein – patients with Multiple Myeloma or Castleman's Disease – only • M-protein – patients with Multiple Myeloma only • CBC with differential and platelet count • Coagulation parameters: [PT/INR, aPTT] • Pregnancy test (for nonsterile women of childbearing potential) • Urinalysis [specific gravity, pH, dipstick for glucose, protein, ketones with microscopic if any values are

	<p>abnormal]</p> <p>During the first four cycles of treatment the patient will visit the clinic weekly for drug administration and assessments.</p> <p>Cycle 1 Day 1 Treatment Period assessments and initial in-clinic dose administration:</p> <ul style="list-style-type: none"> • Baseline signs and symptoms • Physical examination* • Weight, vital signs • Karnofsky performance status* • CBC and platelet count* • Clinical chemistries* • C-Reactive Protein* – patients with Multiple Myeloma and Castleman’s Disease only • M-protein – patients with Multiple Myeloma only • Pharmacokinetic sample collections (serial collection through the post-dose hour 8 time point) [NOTE: During Cycle 1, patients will need to return to the clinic on the morning of Day 2 for trough level sample collection prior to the administration of the Day 2 morning dose.] • Pharmacodynamic sample collection.(Samples will be collected pre-dose and 4 and 8 hours post-dose) • ECG – Prior to the first dose on Day 1, and again 1, 2 and 4 hours after the administration of the study drug. • FNA(optional) – Samples will be collected prior to the administration of the first dose of study drug and again on Study Day 22 during the first Cycle of treatment. • Concomitant medications • Evaluation of adverse events <p>*These procedures do not need to be repeated at this visit if the Screening visit occurred ≤4 days prior, the parameters were found to be WNL and the patient has had no intercurrent events</p> <p>Cycle 1 Day 21 assessments:</p> <ul style="list-style-type: none"> • Weight, vital signs • CBC and platelet count • Clinical chemistries • Pharmacokinetic sample collections [NOTE: During Cycle 1, patients will receive only the morning dose of study drug. PK blood sample collection will occur prior to this dose, serially through post-dose hour 12 and 24, 36 and 48 hours after the dose (Days 22 and 23).] • Pharmacodynamic sample collection (Pre-dose, 4 and 8 hours post-dose.) • ECG – prior to dose administration
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	<ul style="list-style-type: none"> • Concomitant medications • Evaluation of adverse events <p>Subsequent Cycles: Day 1 assessments: Prior to administration of the study drug:</p> <ul style="list-style-type: none"> • Physical exam* • Weight, vital signs • Karnofsky performance status* • CBC and platelet count, clinical chemistries* • C-Reactive Protein – patients with Multiple Myeloma and Castleman’s Disease only* • M-protein – patients with Multiple Myeloma only* • Coagulation parameters* • Urinalysis* • Pregnancy test (women of childbearing potential)* • Concomitant medications • Evaluation of adverse events <p>*May be performed within 72 hours of the treatment visit.</p> <p>Day 8 and Day 15 visit assessments (All Cycles):</p> <ul style="list-style-type: none"> • Weight, vital signs • CBC and platelet count • Clinical chemistries • Trough CX-4945 blood levels (during Cycle 1 only) • Concomitant medications • Evaluation of adverse events <ul style="list-style-type: none"> • Beginning with Cycle 4, patients will visit the clinic every other week (Day 1 and Day 15) for study assessments during the 4 week cycle. • At time of patient discontinuation, Day 1 assessments (except for serial PK blood sample collection) will be repeated. <p>Tumor response assessment will be performed after every other cycle (2 cycles).</p>
<p>DLT definition</p>	<p>A DLT is considered when a patient has:</p> <ul style="list-style-type: none"> • Grade 3 or 4 non-hematologic toxicity (excluding nausea, vomiting or fever that is managed by maximum antipyretic treatment, fatigue that is concomitantly managed and excluding alopecia). • Grade 4 neutropenia (i.e., ANC < 500/mm³) lasting ≥ 5 days. • Grade 4 thrombocytopenia or platelet count < 25,000/mm³ of any duration.

	<ul style="list-style-type: none"> • Febrile neutropenia defined as a Grade 3 or Grade 4 neutropenia with fever $\geq 38.5^{\circ}\text{C}$ and/or infection requiring antibiotic or antifungal treatment. • Failure of the patient's peripheral blood counts to recover to an ANC $\geq 1,500/\text{mm}^3$ and to a platelet count of $\geq 100,000/\text{mm}^3$ within 14 days of the delivery of treatment with CX-4945. <p>For the purpose of assessment of DLT, the following guidelines will be used explicitly in adjunction to above criteria.</p> <ol style="list-style-type: none"> 1. Time of occurrence. Any \geq Grade 3 toxicity occurring within the first Treatment Cycle of the patient, in which the relationship to CX-4945 cannot be ruled out. 2. Duration of laboratory toxicity. Any Grade 3 toxicity for > 7 days and that requires treatment for correction (i.e., exclude those for < 7 days and/or do not require corrective treatment.) 3. Treatment delays and dose modification <ol style="list-style-type: none"> a. Treatment delays > 7 days due to toxicity. b. Dose modifications are required due to toxicity. 4. Toxicities that will not be determined as DLT. <ol style="list-style-type: none"> a. Grade 3 nausea, vomiting and fever that respond to therapy. b. Grade 3 nausea, vomiting and fever < 24 hours without any treatment c. Grade 3 fatigue that is managed to maintain basic activities. d. Any Grade 3 nonhematologic laboratory abnormalities with a baseline assessment of grade 1 or 2 (e.g., LFTs.) <p>CTCAE version 3 will be used to grade adverse events and toxicities.</p>
<p>Assessment of Response</p>	<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 4-6 weeks after the first documentation of response.</p> <p>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>