STUDY PROTOCOL

Title: A Phase I, Multi-Center, Open-Label, Treatment Duration Increment, Expansion, Safety, and Pharmacodynamic Study of CX-4945 Administered Orally Twice Daily to Patients with Advanced Basal Cell Carcinoma

Protocol Number: CX-4945-07

Study Drug: CX-4945

IND: 102181

NCT: 03897036

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6.0	**Amendment 3.0**	**06 April 2022**

Supersedes:		
5.0	Amendment 2.0	25 September 2020
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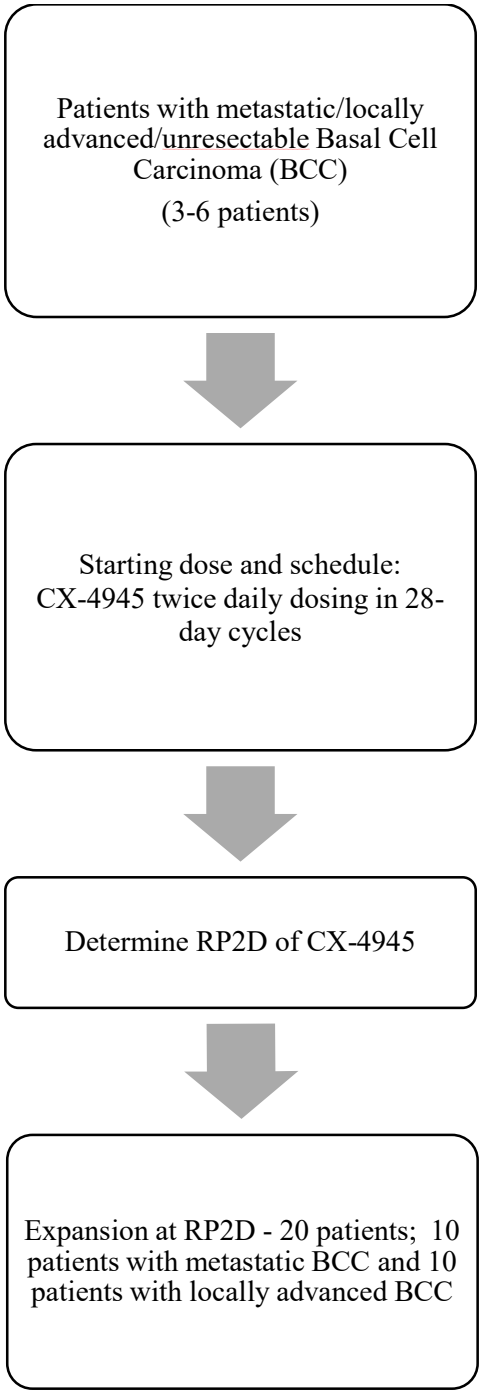
2. TREATMENT SCHEMA



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4. LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
API	Active pharmaceutical ingredient
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCC	Basal cell carcinoma
Bid	Twice daily (*bis in die*)
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CR	Complete Response
CRF	Case Report Form
CRO	Contract (Clinical) Research Organization
CT	Computerized (Axial) Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
HH	Hedgehog
HNSTD	Highest non-severely toxic dose
INR	International Normalized Ratio (for coagulation)
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
mBCC	Metastatic basal cell carcinoma
MRI	Magnetic resonance imaging
NPO	*nil per os* (nothing by mouth)
PD	Progressive Disease
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
Qid	Four times daily (*quarter in die*)
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SDV	Source Data Verification
SMO	Smoothened
SQ	Subcutaneous
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normality (For lab values)
WNL	Within normal limits

5. CLINICAL RESEARCH ETHICS

5.1. INSTITUTIONAL REVIEW BOARD (IRB)

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to Institutional Review Boards (IRBs).

5.2.ETHICAL CONDUCT OF STUDY

This study will be conducted in accordance with GCP of the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki.

5.3. PATIENT INFORMATION AND CONSENT

This study will be conducted in compliance with Title 21 Part 50 of the Code of Federal Regulations pertaining to patient informed consent. Prior to initiating any study-related tests or procedures, patients will be required to grant their written consent to participate in the study after being informed of the nature and purpose of the study, participation/termination conditions, and the potential risks and benefits.

6. SIGNATURE PAGE

Investigator Agreement: I confirm that I have read this Protocol and all applicable amendments included in the Protocol, and I agree to conduct the study as outlined herein.

Signature:_____Date:_____

Investigator Name (print): _____

7. INTRODUCTION

7.1. BACKGROUND

Advanced Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common cancer in the United States[1]. It is estimated that BCCs occur in 2 million Americans each year; this exceeds the incidence of all other cancers combined [2-4]. Almost all of these cases are small BCCs that can be effectively treated by dermatologists using several surgical modalities. However, locally advanced (unresectable) or metastatic BCC (mBCC) have a poor prognosis, with a mean survival ranging from 8 months to 3.6 years [5].

Basal cell carcinomas require the hedgehog (Hh) pathway for growth. The Hh ligand in the extracellular space binds to Patched (*PTCH1*), a 12-pass transmembrane receptor on the surface of cells. Hh binding relieves the inhibitory effect of *PTCH1* on Smoothened (SMO), a 7-pass transmembrane domain protein and a member of the G-protein coupled receptor superfamily. Signal transduction by SMO then leads to the activation and nuclear localization of *GLI1* transcription factors and induction of Hh target genes, many of which are involved in proliferation, survival, and angiogenesis. Hedgehog pathway inhibitors, such as vismodegib[6] and sonidegib phosphate, target the G-protein–coupled receptor Smoothened (SMO) and are recommended as first-line treatment for advanced BCC or mBCC by the National Comprehensive Cancer Network[7]. While initial response rates are about 50% in advanced and metastatic BCC, resistance to Hh inhibitor therapy generally develops within 6 to 8 months[8]. Better therapies are thus urgently required.

The mechanisms of both acquired and intrinsic resistance to Hedgehog inhibitors is largely due to reactivation of the Hedgehog pathway with mutations in pathway components, primarily in SMO[8].

CK2 is a highly conserved serine/threonine protein kinase ubiquitously distributed in the cytoplasmic and nuclear compartments of multiple cell types[9-11] .

CK2 affects the terminal-most Hh signaling components by promoting *Gli2* stability and *Gli2's* interaction with target genes *Gli1, Ccnd1, Ptch1*. Targeting CK2 circumvents challenges of emergence of resistance and a priori resistance seen with existing small molecule inhibitors targeting upstream at SMO[12]. Given the roles of CK2 on the terminal step of the hedgehog signaling pathway, CK2 inhibition is unlikely to be overcome by downstream mutations within this pathway[12]. These data thus suggest an immediately practical application of CX-4945 in Hh-driven tumors and possibly tumors resistant to SMO inhibitors.

7.2. BACKGROUND ON THE MOLECULE

[redacted]

[redacted]

[redacted]

[redacted]

7.3. RATIONALE FOR DOING THIS STUDY

[redacted]

7.4. DOSING REGIMEN AND STARTING DOSE

CX-4945 will be administered twice a day on a continuous basis. Each cycle will be 28 days (4 weeks) in duration and the first cycle will be used as the DLT observation period.

The starting dose will be 1000 mg BID (2000 mg total daily dose). This starting dose is based on three completed Phase I studies where patients were administered CX-4945 following a twice-daily (BID) or four-times-daily (QID) dosing regimen for 21 days followed by 7 days of rest. A total of 12 patients were treated at the 1000 mg bid dose level. Grade 3 or greater hypokalemia and hyponatremia associated to CX-4945 were reported but no drug-related severe diarrhea was noted. At the 1000 mg bid dose level, 1 out of 12 patients had DLT, grade 4 hypokalemia.

8. STUDY OBJECTIVES

Primary Objective

The primary objective of this study is to determine the recommended phase II dose (RP2D) and schedule of CX-4945 when administered orally twice daily for 28 consecutive days, in a 4-week (28 days) cycle, in patients with locally advanced or metastatic basal cell carcinoma (BCC).

Secondary Objectives

- To establish the safety and tolerability of CX-4945 in this patient population.
- To assess preliminary evidence of antitumor effects in this patient population by documentation of objective responses using standardized criteria.
- To evaluate the effect of CX-4945 treatment on the Hh signaling pathway using qRT-PCR in fresh-frozen tissue from patients with locally advanced BCC obtained at baseline and following CX-4945 treatment.

9. INVESTIGATIONAL PLAN

9.1. STUDY DESIGN AND PLAN

This is an open label, multicenter, treatment duration increment trial Phase I run-in study followed by two expansion cohorts to evaluate the safety, pharmacodynamic and preliminary antitumor activity of CX-4945 in patients with advanced basal cell carcinoma. All patients will receive CX-4945 until evidence of progression, intolerable toxicities most probably attributable to CX-4945, or withdrawal from the study. Day 1 of the study will be defined as the first day a patient receives CX-4945 (for the list of study assessments, please see the Study Flowchart in Appendix A).

This study population will consist of patients ≥ 18 years old with a histologically confirmed diagnosis of advanced BCC (metastatic BCC [mBCC] or locally advanced BCC as defined as follows) which has progressed on smoothened

inhibitor or that are intolerant to smoothened inhibitor (see Section 10.1.1, Inclusion Criteria).

Patients with mBCC are required to have histologic confirmation of a distant BCC metastasis (e.g., lung, liver, lymph nodes, or bone).

Patients with locally advanced BCC are required to have disease that is considered inoperable or to have a medical contraindication to surgery (see Section 10.1.1, Inclusion Criteria).

Patients with nevoid BCC syndrome (Gorlin syndrome) may enroll in this study but must meet the criteria for locally advanced or metastatic disease listed above.

In the phase I treatment duration increment part of the study, the 28-day continuous dosing of CX-4945 [1000 mg twice daily] will be explored. Dose cohort will initially include a minimum of 3 patients. A standard 3+3 design will be used. If no DLTs are seen in the 3 patients, the treatment duration increment part will be closed and the expansion cohorts will be opened.

If 1 patient out of 3 experiences a dose-limiting toxicity (DLT), up to 3 additional patients will be recruited (for a maximum of 6). If there are < 2/6 patients with DLT, this will be declared the dose for the Recommended Phase II Dose (RP2D), the Phase I will be closed and two expansion cohorts will be opened. If 2 out of 3, or 2 out of 6, patients experience DLT, the previous Phase I oral dosing regimen of 1000 mg BID (total daily dose 2000 mg) for 21 days followed by 7 days of rest will be selected for the expansion cohorts. The expansion cohorts will include 10 patients with locally advanced BCC and 10 patients with metastatic BCC.

During the treatment duration increment part, the first patient enrolled at the 28-day continuous dosing schedule must receive ≥ 75% planned doses with no observed DLTs before a second patient and a third patient are treated one week apart in that cohort. If no patient in the cohort experiences a Dose Limiting Toxicity (DLT) after the completion of Day 28 of the final patient in the cohort, then the Expansion Cohorts may proceed with the 28-day continuous dosing schedule.

Patients that have experienced a DLT may be offered the option to continue at the previous Phase I oral dosing regimen of 1000 mg bid (total daily dose of 2000 mg) for 21-day followed by 7 days of rest if this is considered safe by the Investigator and the Sponsor.

9.2. OUTCOME MEASURES

Primary Outcome Measure:
The primary endpoint for this study is the determination of RP2D.

Secondary Outcome Measures:
The secondary outcome measures are the following:

- The number and attribution of all adverse events (including vital signs, physical findings, and clinical laboratory results) in patients who received any amount of study drug.
- The objective response will be assessed separately for patients with mBCC and locally advanced BCC. For patients with mBCC, RECIST will be used (see Appendix B). For patients with locally advanced BCC, a composite response endpoint will be used that incorporates externally visible tumor dimension and tumor ulceration, as well as RECIST for lesions with a RECIST-measurable component (see Appendix C). In patients achieving a clinical response, tumor biopsies will be used in the final determination of complete versus partial response.
- Absence of residual BCC in patients with locally advanced BCC achieving a clinical response to CX-4945, as measured by pathological review.
- The changes in *GLI1* expression in fresh-frozen tissue as measured by qRT-PCR.

9.3. DEFINITION OF DLT

Dose limiting toxicity (DLT) will be defined as any of the following drug related adverse events occurring during Cycle 1:

- Grade 3 or 4 non-hematologic toxicity (excluding inadequately managed nausea and vomiting, alopecia or grade 3 fatigue lasting < 7 days),
- Grade 4 myelosuppression ≥ 7 days, febrile neutropenia or ≥ grade 3 thrombocytopenic bleeding,
- Other toxicity of concern to the investigators including toxicities requiring delays ≥ 14 days.

9.4. SAFETY PLAN

A number of measures will be taken to ensure the safety of patients participating in this study. Patients enrolled in this trial will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of tumor assessments performed every 8 weeks, and routine hematology, serum chemistry, and urinalysis profiles will be obtained for all patients.

The study period will begin on Day 1 and will continue until documented disease progression.

All enrolled patients who are treated with at least 1 dose of CX-4945 will be monitored for adverse events. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5.0).

If a treatment interruption occurs, and it is determined that CX-4945 will be re-started, the dose modification plan in Section 11.6 will be followed.

Treatment with CX-4945 may be interrupted for up to 2 weeks for evaluation of an intolerable toxicity finding or up to 4 weeks for a planned surgical procedure. The Medical Monitor must be consulted in cases where study drug will be interrupted. In general, when treatment is held because of drug related adverse effects for > 2 weeks without recovery to the degree required for restarting treatment, the patient should go off protocol therapy.

Intolerable toxicities are defined as new (not present at baseline) Grade 3 or 4 adverse events considered related to CX-4945 that are likely to be life-threatening or irreversible, and when in the opinion of the investigator, the risk outweighs the benefit of continued treatment with CX-4945. The following adverse events are not considered intolerable:

- Grade 3 or 4 events that in the opinion of the investigator are more likely related to ongoing or recent procedures or concomitant medications other than CX-4945
- Hematologic or metabolic/chemistry laboratory abnormalities that are found on routine testing and are not considered clinically significant
- Musculoskeletal abnormalities, skin ulceration, fracture, debridement or wound care, and dental or periodontal disease related to underlying medical conditions (e.g., basal cell carcinoma, nevoid basal cell carcinoma [Gorlin] syndrome)
- Nausea, vomiting, or diarrhea that are adequately controlled after optimization of medical management.
- Grade 3 infection that is transient and treatable or manageable
- Grade 3 sterility
- Asymptomatic thromboembolism found incidentally on imaging and managed with anti-coagulation therapy

Patients with an asymptomatic or tolerable severe adverse event may continue to receive study drug, provided that the adverse event is manageable and the patient and the investigator agree that continued study participation is acceptable.

The teratogenic potential of CX-4945 has not been investigated. Women who are pregnant or nursing are excluded from this study.

Women of childbearing potential are defined in Appendix D, and those enrolled in this study are required to have a negative serum pregnancy test at screening, followed by urine pregnancy tests on Day 1 and every 4 weeks while in the study. If a urine pregnancy test is positive, it must be confirmed with a serum pregnancy test. If pregnancy is confirmed with serum pregnancy test, the subject should be discontinued from the study and complete the early termination visit. Women of childbearing potential are required to use two effective methods of contraception (including one barrier method) during the study and for 6 months after discontinuation of CX-4945. During the study, the investigator must confirm the use of two acceptable contraceptive methods and the patient's understanding of the teratogenic potential of CX-4945, as well as document a negative pregnancy test

prior to dispensing CX-4945 to a woman of childbearing potential. Not all methods of contraception are acceptable; see Appendix D.

Male patients (including those who have undergone vasectomy) with female partners of childbearing potential should use a latex condom during any sexual contact and should advise their partners to use an additional method of contraception during the study and for at least 6 months after discontinuation of CX-4945.

10. SELECTION OF STUDY POPULATION

10.1. PATIENT SELECTION

Eligible patients with locally advanced and metastatic BCC who are in conformance with the following inclusion and exclusion criteria may enroll in this study.

10.1.1. Inclusion Criteria

Patients must meet the following criteria to be eligible for study entry:

1. Signed, written IRB-approved informed consent.
2. Men and women age ≥ 18 years
3. ECOG Performance status 0 or 1 (see Appendix I)
4. For patients with mBCC, histologic confirmation of distant BCC metastasis (e.g., lung, liver, lymph nodes, or bone), with metastatic disease that is RECIST measurable using CT or MRI

   Phase I Expansion
   If a patient with locally advanced BCC also has a tumor that is not contiguous with cutaneous BCC, e.g., regional lymph nodes (if confirmed on biopsy as BCC and RECIST measurable), the patients should be considered as having mBCC and should be enrolled in the mBCC cohort

5. For patients with locally advanced BCC, histologically confirmed disease with at least one lesion that was 10 mm or more in at least 1 dimension by color photograph that is considered to be inoperable or medical contraindication to surgery (see below), in the opinion of a Mohs dermatologic surgeon, head and neck surgeon, or plastic surgeon
6. Acceptable medical contraindications to surgery include:
   a. BCC that has recurred in the same location after two or more surgical procedures and curative resection is deemed unlikely.
   b. Anticipated substantial morbidity and/or deformity from surgery (e.g., removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation).
   c. Other conditions considered to be medically contraindicating must be discussed with the Medical Monitor before enrolling the patient.

7. For all patients, smoothened inhibitor should have been previously administered for their locally advanced or metastatic BCC, unless smoothened inhibitor is inappropriate (e.g., patient has received a smoothened inhibitor but became intolerant to the therapy). For patients whose BCC has been treated with smoothened inhibitor, disease must have progressed after treatment.
8. For patients with locally advanced BCC, radiotherapy should have been previously administered for their locally advanced BCC, unless radiotherapy is contraindicated or inappropriate (e.g., hypersensitivity to radiation due to genetic syndrome such as Gorlin syndrome, limitations because of location of tumor, or cumulative prior radiotherapy dose). For patients whose locally advanced BCC has been irradiated, disease must have progressed after radiation.
9. Previous Therapy
    - Surgery: Previous surgery is permitted provided that a minimum of 28 days (4 weeks) have elapsed between any major surgery and date of registration, and that wound healing has occurred.
    - Cytotoxic Chemotherapy: There is no limit to the number of prior regimens received.
    - Other Systemic Therapy: Previous treatment with Hh pathway antagonists is not allowed (except for Smoothened inhibitors). There is no limit to the other prior therapies received (see Appendix K).

      Patients must have recovered (to baseline or ≤ grade 1) from all reversible toxicity related to prior chemotherapy or systemic therapy and have adequate washout as follows:

      Longest of one of the following:
        - Two weeks,
        - 5 half-lives for investigational agents,
            - For anti-cancer therapies with half-lives > 8 days, a washout period of at least 28 days will be acceptable,
        - Standard cycle length of standard therapies.

10. Patients with nevoid BCC syndrome (Gorlin syndrome) may enroll in this study but must meet the criteria for locally advanced or metastatic disease listed above.
11. For patients with locally advanced BCC, willingness to consent to biopsy of tumor(s) at baseline and during the study, as mandated by the protocol.
12. Adequate hematopoietic capacity, as defined by the following:
    - Hemoglobin ≥ 9.0 g/dL and not transfusion dependent
    - Platelets ≥ 100,000/mm^3
    - Absolute neutrophil count ≥ 1500 cells/mm^3
13. Adequate hepatic function, as defined by the following:
    - AST and ALT ≤ 2.5 times upper limit of normal (ULN) or ≤ 5 times ULN if liver metastases are present

- Total bilirubin ≤ 1.5 x ULN or within 3x the ULN for patients with Gilbert disease
- Albumin ≥ 3.0 g/dL

14. Adequate renal function, as defined by the following:
    - Renal: calculated creatinine clearance >45 mL/min for patients between 18 and 70 years old with abnormal, increased, creatinine levels (Cockcroft-Gault formula; Appendix J). For patients who are greater than 70 years old, investigator judgment may be used to assess the renal risk of study participation.
15. Women/men of childbearing potential must have agreed to use two effective contraceptive methods while on study and for 6 months after the last dose of CX-4945 (see Appendix D for definition of women of childbearing potential and acceptable and unacceptable methods of contraception)

10.1.2. Exclusion Criteria

Patients who meet the following criteria will be excluded from study entry:

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. Concurrent non–protocol-specified anti-tumor therapy (e.g., chemotherapy, other targeted therapy, radiation therapy, or photodynamic therapy)

   - For patients with multiple cutaneous BCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target BCCs with surgery may be permitted but must be discussed with the Medical Monitor prior to any surgical procedure.

   - For patients with locally advanced BCC whose target lesion(s) is/are inoperable at baseline but is/are later deemed potentially operable because of tumor response to CX-4945, surgery with curative intent may be permitted but must be discussed with the Medical Monitor prior to any surgical procedure.

3. History of other malignancies within 3 years of Day 1, except for tumors with a negligible risk for metastasis or death, such as adequately treated squamous-cell carcinoma of the skin, ductal carcinoma in situ of the breast, or carcinoma in situ of the cervix.
4. Active or uncontrolled infections or with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol.
5. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a

disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or renders the patient at high risk from treatment complications.
6. Difficulty with swallowing oral medications.
7. Chronic diarrhea (excess of 2-3 stools/day above normal frequency).

10.2. ENROLLMENT AND REGISTRATION PROCEDURES

10.2.1. Enrollment Procedures

A signed, Institutional Review Board (IRB) approved, informed consent must be obtained from patients before any study-specific procedures or registration can occur.

10.2.2. Registration Procedures

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-study evaluations.

Upon signing the informed consent, the patient will be given a screening number. Once the patient has been confirmed eligible to be enrolled in the study, a patient identification number will be assigned via the Medidata RAVE® (refer to the eCRF completion guidelines for specific instructions) that will be used on all documentation for the subject throughout the study. Patient identification numbers will be assigned in ascending order, and numbers will not be omitted or reused. Investigator will verify that patients are eligible per the protocol specific Inclusion and Exclusion criteria. No patient is allowed to begin study treatment prior to registration and assignment of a patient identification number. The maximum allowable time between registration and the first administration of study treatment is 7 calendar days.

10.3. PATIENT DISCONTINUATION

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, visits); if the patient becomes pregnant; or if the investigator determines it is in the best interest of the patient.

Please see the Study Flowchart provided in Appendix A for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

10.4. PATIENT REPLACEMENT

If a patient is not evaluable for toxicity for Cycle 1, that patient will be replaced to ensure the minimum number of patients are evaluable. Patients must receive ≥ 75%

planned dose to be considered evaluable for toxicity unless study drug was held or discontinued for toxicity and/or DLT has occurred.

All patients who are removed from the study for any reason other than for adverse events or for disease progression (e.g., voluntary discontinuation at the patient's request, or a severe violation of the study protocol) will be replaced. Data from these removed patients will be included in the overall safety analysis but will not be included in the assessment of relative dose intensity.

11. STUDY TREATMENT

11.1. STUDY DRUG DESCRIPTION AND ALLOCATION

Senhwa Biosciences Inc. will supply study drug. At the time of delivery to the site, the Investigator, designee, or Pharmacist will sign a Drug Receipt Form or Investigational Product Packing Slip to confirm the supplies for the study have been received. This form will specify lot numbers, quantities shipped/delivered, date of receipt and condition of the product upon receipt.

Study drug must be stored in a secure, limited-access location. Accountability for study drug is the responsibility of the Investigator, designee or pharmacist.

Study drug must only be dispensed by a Pharmacist or medically qualified staff and is to be dispensed only to patients enrolled in this trial. Once study medication is dispensed to any patient, it can only be administered to that patient and study drug remaining in the dispensed bottle should not be used for another patient. All dispensed bottles of study drug will be returned by a patient at the next visit for drug accountability and compliance review.

11.2. IDENTITY OF INVESTIGATIONAL PRODUCT

[redacted]

11.3. ADMINISTRATION INSTRUCTION

Patients will receive 1000 mg of CX-4945 twice daily by mouth, beginning on Day 1, and continuously until one of the following occurs:

- Disease Progression:
  If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.
- Intolerable toxicity most probably attributable to CX-4945.
- Withdrawal from the study.

Patients will be instructed to take oral antiemetic prophylaxis at least 1 hour prior to taking the study drug. Other oral medications should be taken at least one hour before or 2 hours after ingesting the dose of CX-4945 capsules.

Patients will take five 200-mg CX-4945 capsules twice daily, two hours after the morning meal and two hours after the evening meal (dinner) with water. Patients are advised to take 1 capsule at a time with a pause in between each. This method may prevent a clumping effected in the stomach, so patient can take as much as 10 minutes to swallow each capsule.

The study drug will be taken on an empty stomach with at least six ounces (180 mL) of water. After CX-4945 administration, all patients will be NPO (except for water) for 2 hours, after which, the patient may eat.

At each study visit, patients will be given enough capsules for dosing until the next study visit. The investigator is required to confirm that any woman of childbearing potential has a negative pregnancy test, understands the teratogenic potential of CX-4945, and is using two forms of acceptable contraception, including one barrier method, prior to dispensing CX-4945.

When CX-4945 capsules are dispensed, each patient will be provided with specific dosing instructions, including the number of capsules to take at each morning and evening dose. The number of containers and capsules being dispensed, the patient number, and the date dispensed will be recorded on the Case Report Form.

The patients will be instructed to store the study drug in the original containers at room temperature in a safe location. Each patient will be shown the desiccant container found in each bottle of study medication and instructed not to remove or eat this desiccant. Patients will be instructed to avoid storing the study drug in areas

of excessive heat (vehicle glove box) or excessive moisture (bathroom medicine cabinets). Patients will be instructed on the use of the dosing record form and will be asked to keep a dosing record for all dose administrations.

Patients will be instructed to bring the dosing record form and all unused study medication and empty study medication containers at each study visit, as applicable. At each visit, the dosing record will be reviewed and the amount of used and unused study medication that is returned will be recorded. Every effort will be made to obtain all dispensed containers. If such effort fails, a dated note of the reason for the failure will be recorded.

If a patient misses a dose, he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up and should be documented in the dosing record form.

If a patient is suspected to be pregnant, CX-4945 must be immediately discontinued. If it is subsequently confirmed that the patient is not pregnant, dosing may be resumed. If pregnancy is confirmed with serum pregnancy test, the subject should be discontinued from the study and complete the early termination visit.

11.4. STORAGE AND HANDLING OF TEST ARTICLE

The stability of test materials used in this study will be known and monitored to ensure suitability for use throughout the study. CX-4945 capsules should be stored in their original containers and should be protected from moisture, freezing, bright light, and heat. Drug supplies must be stored in a secure, lockable area.

The pharmacy or medically qualified staff will prepare and dispense CX-4945 capsules to enrolled patients. The number of containers and capsules being dispensed, the patient number, patient initials, and the date dispensed will be recorded. The patient will be instructed to store the study drug in the original containers at room temperature between 15°C-30°C (59°F-86°F), in a safe location.

11.5. CONCOMITANT AND EXCLUDED THERAPIES

Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the screening evaluation and the end of study visit. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Excluded Therapy

Although no specific concomitant medications are prohibited during this study, concomitant medications should be used with care, and the risk–benefit profile of each agent should be taken into consideration. Concomitant medications that may

potentially interact with CX-4945 are listed in Appendix F. This is not necessarily a complete list; other medications may also interact with CX-4945.

11.6. DOSE MODIFICATION FOR CX-4945

The most common drug related adverse events reported for CX-4945 are predominantly gastrointestinal disorders, including nausea, vomiting and diarrhea.

Toxicities related to CX-4945			
Event Grade (CTCAE 5.0)	Dose Interruption	Dose Reduction	Dose for subsequent cycle
Grade 1	Treat on time	No change	No change
Grade 2	Hold until ≤ Grade 1	Resume at same dose	No change
Grade 3	Hold until < Grade 2	Reduce by 1 dose level (200 mg)	If toxicity remains <Grade 2, dose re-escalation can be considered at the discretion of the Investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Hold until < Grade 2	Reduce by 1 dose level (200 mg). Permanent discontinuation can be considered at the Investigator's discretion	

11.7. PREMEDICATION

[redacted]

[redacted]

[redacted]
[redacted]

[redacted]

[redacted]

11.8. VITAMIN D SUPPLEMENT

[redacted]

12. STUDY ASSESSMENTS

12.1. DEFINITION OF STUDY ASSESSMENTS

The study period will begin on Day 1, and patients will be followed until disease progression, death, or withdrawal of consent from the study.

Screening tests and evaluations will be used to determine the eligibility of each patient for study inclusion. All patients must provide written informed consent before any study-specific procedures and assessments are performed and any exclusionary medications are discontinued for the purposes of establishing eligibility. Screening evaluations will be performed within the 14 days preceding Day 1, unless otherwise specified (for list of study assessments, see the study flowchart in Appendix A). Results of tests or examinations performed as standard of care prior to obtaining informed consent prior to study entry may be used rather than repeating required tests.

a. Physical Examination

The initial complete physical examination should include the evaluation of the head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Height and weight will also be recorded. Subsequent limited physical examinations for assessment of toxicity may be restricted to evaluation of specific systems or areas of interest, including those with previously abnormal findings or associated with symptomatic or laboratory evidence of toxicity. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

b. Vital Signs

Vital signs will include measurements of pulse, systolic and diastolic blood pressure while the patient is in a seated position, respiratory rate, and temperature. Vital signs will be recorded at screening and at regular intervals throughout the study, including at the end of the study or early termination, as appropriate.

c. Electrocardiographic Assessment

Twelve-lead electrocardiograms (ECGs) are required at screening.

d. Vitamin D level Assessment

Measurement of serum 25-hydroxyvitamin D (25[OH]D or calcidiol) is required at screening. Follow-up 25(OH)D measurements will be performed every three months.

e. Tumor and Response Assessments

Baseline Assessments

For patients with mBCC, computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis must be performed for all patients. For patients with known involvement of the head and/or neck, CT or MRI of the

head and neck is also required. Additional areas of known tumor involvement (e.g., limbs) should also be evaluated on CT or MRI. The same imaging modality used at baseline must be used throughout the study. Baseline imaging studies must be performed within the 14 days preceding Day 1. Patients with mBCC are required to have disease that is measurable by RECIST using CT or MRI.

For patients with locally advanced BCC, CT or MRI of the area(s) involved by the locally advanced tumor(s) should be performed at baseline for all patients to determine whether a RECIST-measurable component is present in externally visible lesions. Measurements of externally visible tumor dimension, assessment of tumor ulceration, description of the lesion at baseline, digital photography of target lesion(s), and a baseline tumor biopsy must be performed in accordance with biopsy guidelines (see Appendices C and G). Baseline imaging studies must be performed within the 14 days preceding Day 1. If locally advanced BCC lesions with a RECIST measurable component are identified, the same imaging modality used at baseline must be used throughout the study.

Tumor Assessments during Treatment, End of Study, or Early Termination

During treatment, tumor assessments will be performed every 8 weeks and at the study completion or early termination visit, as appropriate.

For patients with mBCC, response assessments by the investigator will be categorized as complete response, partial response, stable disease, or progressive disease using RECIST. Objective responses using RECIST should be confirmed on repeat assessments 4 or more weeks after initial documentation of response. The same imaging modality (CT or MRI) used to define measurable disease sites at baseline must be used throughout the study (e.g., the same contrast protocol for CT scans). All patients are required to have imaging of the chest, abdomen, and pelvis; any additional areas imaged during screening (e.g., head or neck, limbs) should also be imaged at each tumor assessment. If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.

For patients with locally advanced BCC, response assessments by the investigator will be categorized as response, stable disease, or progressive disease using the composite tumor assessment criteria (see Appendix C). Measurements of externally assessable tumor, assessment of tumor ulceration, description of the lesion and any changes since the previous assessment, and digital photography of target lesion(s) will be performed. If the patient has a target lesion(s) containing a RECIST-measurable component by CT or MRI, radiographic assessment is also required and should be incorporated into the response assessment according to Appendix C. If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment

with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.

f. Tumor Biopsy

Representative tumor biopsies are required from patients with locally advanced BCC at screening, at week 8, and again either at the time of investigator-assessed clinical or clinical/RECIST response (if before 24 weeks), or at 24 weeks if the patients are still in the study without evidence of progression. At any time during a patient's participation in the study, an optional tumor biopsy may be requested to clarify the response status of the patient. In addition, biopsy of any accessible target lesion(s) is highly recommended at the time of progression and will be used for exploratory molecular and histologic analyses. The sites, number, and technique of representative biopsies will be determined by the investigator on the basis of the size and location of the accessible lesions. It is recommended that any areas suspicious for residual disease be biopsied, as well as areas which appear to be free of disease. These biopsies will be reviewed by site's pathologist. For additional details regarding the guidelines for tissue biopsy, see Appendix G.

g. Laboratory Assessments

Local Laboratory Assessments. Samples for hematology, serum chemistry, urinalysis, and pregnancy will be analyzed at the study site's local laboratory.

- Hematology (hemoglobin, hematocrit, platelet count, red blood cell [RBC] count, white blood cell [WBC] count, and percent or absolute differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells])
- Serum chemistry (including glucose, blood urea nitrogen [BUN], creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, and ALT)
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood)
- Pregnancy test:
  All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, followed by urine pregnancy tests on Day 1, and every 4 weeks. A positive urine pregnancy test must be confirmed with a serum pregnancy test.

Central Laboratory Assessments. Samples tissue of locally advanced BCC patients in the expansion phase obtained at baseline and 8-week visits will be sent to a central laboratory for analysis.

- Sample analysis (fresh frozen tissue or formalin fixed paraffin embedded):
  Tumor histology will be reviewed and Hh pathway target gene (*GLI1*) and reference gene expression profiling will also be performed on the tumor tissue sample obtained from patients with locally advanced BCC at baseline

and at 8 weeks following CX-4945 treatment in order to evaluate the effect of CX-4945 treatment on the Hh signaling pathway.

h. Early Termination or End of Study Assessments

Patients who discontinue from the study will be asked to return to the clinic within 30 days of the last dose of CX-4945 for a follow-up visit. In patients with locally advanced BCC, biopsy of tumor at the time of progression for submittal for pathology review is strongly encouraged.

i. Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to < grade 2) and late toxicities (including second malignancies). For patients who go off protocol treatment with CR, PR, or SD ongoing, follow-up will be required every 3 months until relapse (see Appendix A for investigations to be performed). Death report will be required on all patients unless advised by the Sponsor and due within 2 weeks of knowledge of death (see Section 16.3.1).

12.2. SCREENING AND PRETREATMENT ASSESSMENTS

Screening tests and evaluations will be used to determine the eligibility of each patient for study inclusion. All patients must provide written informed consent (one for study participation and a separate informed consent detailing teratogenic risk) before any study-specific procedures and assessments are performed and any exclusionary medications are discontinued for the purposes of establishing eligibility. Screening evaluations will be performed within the 14 days preceding Day 1, unless otherwise specified (for list of study assessments, see the study flowchart in Appendix A). Results of tests or examinations performed as standard of care prior to obtaining informed consent and within 14 days prior to study entry may be used rather than repeating required tests. Please see the Study Flowchart provided in Appendix A for the schedule of screening and pretreatment assessments.

12.3. ASSESSMENTS DURING TREATMENT

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration (Day 1) of each cycle should be performed prior to study drug administration, unless otherwise noted.

Please see the Study Flowchart provided in Appendix A for the schedule of treatment period assessments.

12.4. STUDY COMPLETION/EARLY TERMINATION VISIT

Patients who discontinue from the study will be asked to return to the clinic within 30 days of the last dose of CX-4945 for a follow-up visit.

Please see the Study Flowchart provided in Appendix A for assessment to be performed at the study completion/early termination visit.

13. STUDY DISCONTINUATION – STUDY STOPPING RULES

The sponsor has the right to terminate this study at any time. Reasons for terminating the study may include the following:

1. The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
2. A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.
3. Patient enrollment is unsatisfactory.
4. Data recording is inaccurate or incomplete.
5. The Investigator fails to comply with pertinent regulations of appropriate regulatory authorities or there are persistent serious violations of the protocol.

14. ASSAY METHODS

14.1. EVALUATION OF HH PATHWAY STATUS USING QRT-PCR IN FRESH FROZEN TISSUE OR FORMALIN FIXED PARAFFIN EMBEDDED

[redacted]

15. STATISTICAL CONSIDERATIONS

15.1. SAFETY ANALYSES

Unless otherwise noted, all safety analyses will be performed using the all treated patient population. Safety will be assessed through summaries of laboratory test results, all adverse events, including serious adverse events, study drug−related adverse events, and adverse events leading to discontinuation of CX-4945. All treatment-emergent adverse events will be mapped to thesaurus terms and graded according to the NCI CTCAE, version 5.0.

Relative dose intensity (expressed as a percentage) defined for each cycle as the ratio between 'actual dose/actual duration' over 'intended dose/intended duration' will be assessed for all patients enrolled in the expansion cohorts. Patients who are removed from the study for any reason other than for adverse events or for disease progression will not be included in the relative dose intensity assessment.

15.2. EFFICACY ANALYSES

Unless otherwise noted, all efficacy analyses will be performed using the all treated patient population, defined as all enrolled patients who receive any amount of study drug. Patients for whom the pathologist's interpretation of baseline biopsy is not consistent with BCC will not be included in the efficacy analyses. More details regarding analyses involving missing or uninterpretable biopsies can be found in Section 15.5.

Patients with measurable disease will be evaluated for clinical benefit as determined by objective response. Objective response will be determined as a function of a radiographic, photographic and pathological review (See Appendices B, C, G and H). Objective response is defined as a complete or partial response determined on two consecutive assessments ≥ 4 weeks apart. The objective response observed in this trial will be described separately for the mBCC and locally advanced BCC.

The endpoint of the Hh pathway signaling study is the relative expression of *Gli1* in fresh-frozen tissues as measured by qRT-PCR. The relative expression of *Gli1* will be summarized by [Δ]Ct. Patients with missing or unevaluable results will be excluded from these analyses. The fresh-frozen tissues will be sent to Oncocyte Corporation for analysis.

15.3. ANALYSIS OF THE CONDUCT OF THE STUDY

The number of patients who are enrolled will be tabulated by center. Major protocol deviations, study discontinuation reasons, and exposure will be summarized for all enrolled patients.

15.4. LENGTH OF TRIAL

This study is expected to remain open until approximately 25 months following the first treatment of the first patient with CX-4945. The final analysis will commence at least 9 months following the first treatment of the last enrolled patient in the expansion cohort. All outstanding study data will be collected from Senhwa's designated CROs (hereafter referred to as the CRO) and sites, and data queries will be resolved. After data queries are resolved, the database will be locked and the final analysis will be performed and described in the Clinical Study Report.

15.5. HANDLING OF MISSING CLINICAL DATA

Patients without interpretable baseline tissue, as determined by the pathologist, or by pathology report from the study site documenting a pathologist's determination

of BCC, will be excluded from the efficacy analyses. No imputations will be made for missing data. The data will be analyzed as observed cases only.

15.6. SAMPLE SIZE CONSIDERATIONS

In the treatment duration increment part of the study, a 3+3 study design will be utilized, therefore approximately 3-6 patients will be enrolled to define the RP2D.

In the expansion part of the study, a total sample size of 20 patients is proposed; 10 patients with local advanced BCC and 10 patients with metastatic BCC. Assume that CX-4945 is of no interest if its true response is 5% or lower, the proposed sample size for each sub-population will provide an 80% confidence interval of (5.5%, 45.0%) given that there are 2 responses out of the 10 patients. This would provide adequate evidence to suggest that additional studies with this agent may be warranted.

15.7. DATA QUALITY ASSURANCE

The CRO will perform oversight of the data management of this trial. The CRO will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data will be sent directly to the CRO, using its standard procedures to handle and process the electronic transfer of these data. eCRFs and data queries documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

16. ASSESSMENT OF SAFETY

16.1. SAFETY VARIABLES AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

Senhwa Biosciences is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with regulatory requirements.

Senhwa Biosciences or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or facsimile within 7 calendar days after being notified of the event. Senhwa Biosciences or its designee will report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for

reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

16.1.1. Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with advanced BCC that were not present prior to the AE reporting period (see Section 16.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g. invasive procedures such as biopsies, medication washout, or no treatment run-in).
- Preexisting medical conditions (other than the condition being studied), judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

16.1.2. Serious Adverse Event

An SAE is any AE that is any of the following:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Is considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria

usually associated with events that pose a threat to a patient's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

16.1.3. Other Protocol Reportable Events – Pregnancy Reporting

If a patient becomes pregnant during the course of the study, the investigational agent should be discontinued immediately.

Pregnancy itself - occurring in female participants, and female partners of male participants - is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

The investigator is required to report to the CRO any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 6 months after the last dose of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning. All follow-up reports must be submitted to the CRO in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to the CRO.

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labor/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting. Refer to Section 16.4.2 for SAE reporting instructions.

16.2. METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 16.1) are recorded on the eCRF and reported to the CRO in accordance with protocol instructions.

16.2.1. Adverse Event Reporting Period

After informed consent, but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

After initiation of study drug, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 16.6). Additional guidance is provided for pregnancy events occurring within 6 months after the last dose of CX-4945 in Section 16.1.3.

16.2.2. Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the appropriate AE/SAE eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 16.1.2 for seriousness criteria), severity, and causality.

The following criteria provides guidance for grading AE severity. The AE grading (severity) scale found in the CTCAE, v5.0, will be used for AE reporting.

1. **Mild:** Nuisance, barely noticeable.
2. **Moderate:** Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.
3. **Severe/Disabling:** Symptoms significantly interfere with daily activities or sleep.
4. **Life threatening:** Event places the patient at risk of death.
5. **Fatal:** Event caused the death of the patient.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?

YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

16.3. PROCEDURES FOR RECORDING ADVERSE EVENTS

16.3.1. Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF and should avoid colloquialisms and abbreviations. Only one medical concept should be recorded in the event field on the AE/SAE eCRF page.

A. Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

B. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

C. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation timepoints. Such events should only be recorded once on the

eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on an AE/SAE eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation timepoints and subsequently recurs. All recurrent AEs should be recorded on an AE/SAE eCRF.

D. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the AE/SAE eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

E. Deaths

Deaths that occur during the protocol-specified AE reporting period (see Section 16.2.1) that are attributed by the investigator solely to progression of advanced BCC will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be reported to the Clinical Safety Management at the CRO within 24 hours of learning of the events. Refer to Section 16.4.2 for reporting instructions.

When recording a death on an SAE eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the SAE eCRF.

F. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF. A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on an AE/SAE eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

G. Worsening of Advanced Basal Cell Carcinoma

Worsening and/or progression of advanced BCC should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

H. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

I. Pregnancy

Pregnancy is reportable event. The CRO must be notified within 24 hours of learning of the pregnancy to facilitate outcome follow-up. Please refer to Section 16.1.3 for additional specific instructions.

16.4. EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND OTHER PROTOCOL REPORTABLE EVENTS

16.4.1. Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be reported to the Clinical Safety Management at the CRO within 24 hours of learning of the events. Refer to Section 16.4.2 for reporting instructions.

16.4.2. Reporting Requirements for All SAEs and Other Protocol Reportable Events

Investigators will submit reports of all SAEs, regardless of attribution, and other protocol reportable events to the Clinical Safety Management at the CRO within 24 hours of learning of the events. For initial SAE and other protocol reportable events, investigators may fax, phone or email the events to the Clinical Safety Management. A phoned SAE report must be followed by a written report as soon as possible. The SAE information will be entered to the EDC system as soon as possible. The study supplied reporting form along with any medical comments from medical monitor will be sent to Sponsor.

Relevant follow-up information should be submitted to the CRO as soon as it becomes available and/or upon request.

Email: Safety-Inbox@novellaclinical.com, or

Country Name	Telephone Number	Fax Number
Worldwide Toll	1-919-313-7111	1-919-313-1412
USA (Toll Free)	1-866-758-2798	1-866-761-1274

16.5. TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE/SAE eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the CRO may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

16.6. POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the CRO of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The CRO should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study (refer to Section 16.1.3). The investigator should report these events following the reporting procedures specified in the Section 16.4. If the CRO or the EDC is no longer available, the investigator should report the event directly to Sponsor Drug Safety via safety@senhwabio.com

17. INVESTIGATOR REQUIREMENTS

17.1. STUDY INITIATION

The following documentation must be received by the Sponsor prior to initiation of the trial:

1. Original US FDA Form 1572 (for all studies conducted under US Investigational New Drug [IND] regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
2. Current curricula vitae of the Principal Investigator and all sub-investigators.
3. Institutional Review Board (IRB) membership list and/or Department of Health and Human Services number.
4. Written documentation of IRB approval of protocol (identified by protocol number or title and date of approval) and informed consent document (identified by protocol number or title and date of approval).
5. A copy of the IRB-approved informed consent document.
6. Current laboratory certification of the laboratory performing the analysis (issuing agency and expiration date), as well as current normal laboratory ranges for all laboratory tests.
7. A signed Clinical Research (Protocol) Agreement.
8. Certified translations of IRB approval letters, pertinent correspondence, and approved informed consent document (when applicable).
9. Financial disclosure form for Principal Investigator and all sub-investigators.

17.2. STUDY COMPLETION

The following data and materials are required by the Sponsor before the study can be considered complete or terminated:

1. Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period.
2. eCRFs properly completed by appropriate study personnel and signed and dated by the investigator.
3. Completed drug accountability records.
4. Copies of protocol amendments and IRB approval/notification, if appropriate.
5. A summary of the study prepared by the Principal Investigator (an IRB summary close letter is acceptable).

17.3. INFORMED CONSENT FORMS

A sample Informed Consent Form will be provided to each site. Please note that the patient must sign the Study Informed Consent in order to participate in this study. The Sponsor or its designee must review and approve any proposed deviations from the sample Informed Consent Form or any alternate consent form proposed by the site (collectively, the "Consent Form") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Form during their participation in the study. The final IRB/EC-approved Consent Form must be provided to the Sponsor for regulatory purposes.

The Consent Form must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Forms should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Forms for continued participation in the study. The final revised IRB/EC-approved Informed Consent Forms must be provided to the Sponsor for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

17.4. COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only

about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor or its designee. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

17.5. STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized representative of the Sponsor to inspect study data, patient's medical records, and CRFs in accordance with current standard operating procedures of the Sponsor or its CRO.

The Principal Investigator will permit authorized representatives of the Sponsor (including its CRO), the US FDA, and the respective national and local authorities to inspect facilities and records relevant to this study.

17.6. CASE REPORT FORMS

Data collected during the study will be entered in the patient's eCRF by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the eCRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the eCRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. To facilitate photocopying, entries on original records must be written legibly in black ink only. Erroneous entries will be crossed out with a single line, so as to remain legible. The correct value will be entered above the error and then initialed and dated by the person authorized to make the correction.

17.7. SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered on the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

17.8. STUDY DRUG ACCOUNTABILITY AND DISPOSITION OF UNUSED STUDY DRUG

The Investigator must maintain accurate records demonstrating dates and amount of study drug received, lot numbers, to whom dispensed (patient-by-patient accounting) and accounts of any study drug accidentally or deliberately destroyed.

CX-4945 inventory forms and drug accountability will be examined and reconciled periodically by the study monitor throughout the course of the study and at the end of the study. All partially used or empty containers returned by patients who will no longer participate in the trial should be disposed of at the study site according to institutional standard operating procedures after the monitor has completed drug accountability record review for these articles. The sponsor will request documentation of the accountability and disposal procedures. Unopened, expired, or unused study drug should be returned with the appropriate accountability and shipment forms as directed by the sponsor or the CRO at the end of the trial, overall inventory and accountability of study drug will be conducted. Any missing containers must be explained.

All CX-4945 drug product required for completion of this study will be provided by the Sponsor. The recipient will provide written acknowledgement of receipt after checking for shipment content and condition. All damaged or expired supplies will be replaced.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

17.9. CONFIDENTIALITY OF DATA

Patients' medical information obtained during this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her care and welfare.

Data generated by this study must be available for inspection by representatives of the FDA, national and local health authorities, the Sponsor and its designated CRO, and the IRB.

Doctors, hospitals and other health care professionals, their employers, insurance companies, or others who handle individuals' health care information associated with the conduct of this study are responsible for maintaining the privacy of that information in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data collected from the Investigator by the Sponsor's designated CRO will be maintained in confidentiality and will only be reviewed during internal quality checks or external audits by regulatory authorities.

17.10. RETENTION OF RECORDS

US regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, patient informed consent forms, laboratory test results, and medical records, must be retained by the Principal Investigator for 2 years beyond the FDA's approval date of CX-4945 's marketing application. If no marketing application is filed, these records and documents must be kept for 2 years beyond the date when the FDA and the applicable national and local health authorities are notified by the Sponsor of the discontinuation of further development of CX-4945. The Sponsor or its CRO will inform the Principal Investigator should either of these events occur.

17.11. PUBLICATION AGREEMENT

The Investigator agrees that no interim publications regarding the study or this study's patients will occur without the written agreement of Senhwa Biosciences.

17.12. PROTOCOL ADHERENCE

Each Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved first by the Sponsor, and then by the IRB before being enacted. Each Investigator must agree to enroll only those patients who meet all protocol eligibility criteria.

18. ADMINISTRATIVE STRUCTURE

Senhwa Biosciences Inc., will sponsor this study. A contract research organization (CRO) will perform study management, including project management, statistical programming, clinical monitoring, medical monitoring, data monitoring, and data management. One hundred percent source document verification will be conducted for all enrolled patients. Approximately 26 patients will be enrolled at approximately 6 sites in the United States.

19. REFERENCES

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APPENDIX A

STUDY FLOWCHART

Assessment or Procedure	Screening	Day 1	Treatment						4 weeks after completion of protocol therapy	3 month follow-up (only required for pts without confirmed PD and ongoing toxicities [n])
	Days –14 to –1		Every 4 Weeks (± 3 Days)	Every 8 Weeks (± 3 Days)	Week 8 (± 3 Days)	Every Week 12 (± 3 Days)	Clinical Response if before Wk 24	Week 24 (± 3 Days)		
Informed Consent [a]	X									
Inclusion/Exclusion	X									
Medical, surgical, and cancer history, and demographics	X									
Complete physical examination [b]	X									
Limited physical examination			X						X	
Weight and Vital Signs [c]	X	X	X						X	
ECOG Performance Status (*Appendix I*)	X	X	X						X	
12-Lead Electrocardiogram	X									
Tumor Assessments [d]	X			X					X	X[r,s]
Digital photographs [e]	X			X					X	
Tumor biopsy [f]	X				X[f]		X[f]	X[f]	X[f]	
Hematology [g]	X		X						X[q]	X[q]
Serum Chemistry [h]	X		X						X[q]	X[q]
Urinalysis [i]	X									
Serum vitamin D level [j]	X					X				
Serum or urine pregnancy test [k]	X	X	X						X	
CX-4945 accountability [l]			X						X	
Dispense CX-4945 [l]		X	X							
Concomitant medications [m]	X	X	X						X	
Evaluation of Adverse Events	X[n]	X	X						X	X[n]
Cancer-related medical or surgical procedures [o]		X	X						X	
Dispense antiemetics and loperamide [p] (IMODIUM®)		X	X							

BCC = basal cell carcinoma

Note: Results of tests or examinations performed as standard of care prior to obtaining informed consent and within 14 days prior to study entry may be used rather than repeating required tests.

a. All patients must provide written informed consent prior to any study-specific procedure being performed and any exclusionary medications are discontinued for the purposes of establishing eligibility. Patients will sign two informed consent forms: one for study participation, and a separate consent detailing teratogenic risk.
b. A complete physical exam includes evaluation of the head, eyes, ears, nose and throat; cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.
c. Vital signs include pulse, systolic and diastolic blood pressure while the patient is in a seated position, respiratory rate, and temperature.
d. Tumor assessments must be performed at screening and every 8 weeks thereafter. Assessments should include an evaluation of all sites of disease. Patients in the metastatic BCC cohort will undergo tumor assessments per the Response Evaluation Criteria in Solid Tumors (see Appendix B). Patients in the locally advanced BCC cohort will undergo tumor assessments per the composite tumor response criteria (see Appendix C).
e. Instructions for obtaining digital photographs are given in Appendix H.
f. For patients with locally advanced BCC, a baseline tumor biopsy must be performed in accordance with guidelines (see Appendix G). Perform biopsy again on Week 8. Repeat biopsy either at best clinical response if achieved prior to Week 24 or at Week 24. A tumor biopsy is recommended at the time of progression.
g. Hematology consists of hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, and percent or absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells).
h. Serum chemistry includes glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, and ALT.
i. Urinalysis includes pH, specific gravity, glucose, protein, ketones, and blood.
j. Measurement of serum 25-hydroxyvitamin D (25[OH]D or calcidiol) is required at screening. Follow-up 25(OH)D measurements will be performed every three months. Patients found to have serum 25-hydroxyvitamin D (25[OH]D) concentration lower than 20 ng/mL during the screening period should receive vitamin D supplement.
k. For women of childbearing potential, including those who have had a tubal ligation. A serum pregnancy test is required at screening and urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
l. Dispense, administer, and maintain drug accountability of CX-4945. For women of childbearing potential, the investigator must confirm the patient's negative pregnancy test, the patient's understanding of the teratogenic potential of CX-4945, and the use of two acceptable methods of contraception prior to dispensing CX-4945.

m. The recording of concomitant medications will begin at the time of informed consent and continues through the end of the study period. Record all concomitant medications administered to the patient within the 14 days preceding Day 1.

n. The reporting period for adverse events (AEs) will begin at the time of informed consent signed and continues until 30 days after the last dose of CX-4945. During screening (i.e., after informed consent, but prior to initiation of study drug), only SAEs related to protocol-mandated procedures should be reported. At the end of the study period, any patient with an ongoing AE or SAE leading to CX-4945 discontinuation will be followed until the event resolves, the investigator assesses the event as stable, or the patient is lost to follow-up.

o. The recording of cancer-related medical and surgical procedures begins on Day 1 and continues through the end of the study period.

p. [redacted]

q. At 4 weeks then every 3 months thereafter only to follow abnormal results felt related until resolved to ≤ Grade 2.

r. Patients with a CR or PR should have scans repeated after 4 weeks to confirm response.

s. Every three months until relapse or progression for patients with CR, PR, SD response.

APPENDIX B

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.0 (RECIST)

1. Introduction

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST) are below. [1] Modifications to the RECIST for the purposes of this study are also described. For this protocol, RECIST will be used to evaluate tumor lesions on standard radiologic imaging modalities (computed tomography [CT] or magnetic resonance imaging [MRI]) in non-skin organs, such as metastatic disease in lymph node, soft tissue, lung, or liver, or subcutaneous disease in patients with locally advanced disease. Evaluation of externally measurable lesions (such as visible locally advanced lesions) for patients with locally advanced disease will be performed using the criteria listed in Appendix C.

2. Measurability of Tumor Lesions at Baseline

2.1. Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as 20 mm with conventional imaging techniques or as 10 mm with spiral CT scan [see Section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan] and truly nonmeasurable lesions).

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment. Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Tumor lesions that are situated in a previously irradiated area may be considered measurable if an increase in the size of that tumor lesion has been documented since the time of irradiation.

2.2. Specifications by Methods of Measurements

The same imaging-based method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up. CT and MRI are acceptable (see below). Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

[1] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to

treatment in solid tumors. J Natl Cancer Inst 2000; 92:205–16.

2.2.1. Clinical examination. For lesions that are only evaluable on clinical examination in patients with locally advanced disease, refer to criteria for evaluation in Appendix C.

2.2.2. Chest X-ray. Lesions on chest X-rays are not acceptable as measurable lesions.

2.2.3. CT and MRI. CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities usually require specific protocols. More details concerning the use of these methods of assessment for objective tumor response evaluation are provided in Appendix I.[2]

2.2.4. Ultrasound. Ultrasound should not be used to measure tumor lesions.

2.2.5. Endoscopy and laparoscopy. These techniques should not be used to measure tumor lesions.

2.2.6. Tumor markers. Tumor markers should not be used to measure tumor lesions.

3. Tumor Response Evaluation

3.1. Baseline Evaluation

3.1.1. Assessment of overall tumor burden and measurable disease. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as defined in Section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.2. Baseline documentation of "target" and "nontarget" lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

3.2. Response Criteria

3.2.1. Evaluation of target lesions. This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions:

Complete Response—the disappearance of all target lesions; Partial Response at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; Progressive Disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; Stable Disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started. If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.

3.2.2. Evaluation of nontarget lesions. This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response—the disappearance of all nontarget lesions; incomplete response/stable disease—the persistence of one or more nontarget lesion(s); and progressive disease—the appearance of one or more new radiographically identified lesions and/or unequivocal progression of existing nontarget lesions. A new radiographically identified lesion is defined as a lesion that has not previously been seen in prior imaging studies, and that has increased in size to either a diameter larger than the size of the slice thickness being used for that imaging modality or at least 5 mm, whichever is larger.

3.2.3. Evaluation of best overall response. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 3.5.1). Table 1 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

[2] See Appendix I of the Therasse et al. 2000 article.

Table 1. Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions

RECIST Best Overall Response: Patients with Measurable Disease			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. See text for more details.

Note: If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status.

3.2.4. Frequency of tumor re-evaluation. Frequency of tumor re-evaluation while on treatment is defined in this study as every 8 weeks.

3.3. Confirmatory Measurement/Duration of Response

3.3.1. Confirmation. The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary endpoint. In this setting, to be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

APPENDIX C

COMPOSITE TUMOR RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED BASAL CELL CARCINOMA

For all patients with locally advanced basal cell carcinoma (BCC), externally visible target lesions will be chosen by the investigator *and* must include any lesions that are both externally visible and measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST). The externally visible component of all target lesions should be at least 10 mm in the longest dimension, to facilitate accurate and reproducible measurement. Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each tumor assessment (see Appendix H). For patients with a target lesion that contains both an externally visible and a RECIST-measurable component, appropriate imaging studies (computed tomography or magnetic resonance imaging) will be used to assess the RECIST component of tumor response (see Appendix B). Investigators must also provide a clinical description of the target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

All patients will undergo baseline and on-study biopsies of target lesions per Appendix G; in patients achieving a clinical response, histologic analysis of on-study biopsies will be used for final determination of complete versus partial response (see below).

<u>Clinical Response Criteria</u> (for all patients with locally advanced BCC)

A. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured in the longest dimension at each tumor assessment and will be documented using standardized digital photography. If the border of the tumor is no longer visible but a scar is present, the dimensions of the scar should be measured.

Response criteria for tumor dimension are as follows:

- Complete Response (CR): *all* target lesion(s) no longer visible, maintained for at least 4 weeks
- Partial Response (PR): decrease of 30% or greater in the sum of the longest dimension of target lesion(s), maintained for at least 4 weeks
- Stable Disease (SD): not meeting criteria for CR, PR, or progressive disease (PD)
- Progressive Disease (PD): increase of ≥ 20% in the sum of the longest dimension of target lesion(s)

B. Tumor Ulceration (only for patients whose target lesion[s] are ulcerated at baseline)

Response criteria are as follows:

- CR: re-epithelialization of the entire baseline area of ulceration of target lesion(s), maintained for at least 4 weeks
- PR: there are no criteria for PR
- SD: not meeting criteria for CR or PD
- PD: new ulceration of target lesion(s), not related to (i.e., in a location separate from) tissue biopsy or other known trauma, persisting without evidence of healing for at least 2 weeks

Overall Clinical Responses for All Possible Combinations of Tumor Responses for Locally Advanced BCC			
Externally Visible Tumor Dimension	**Tumor Ulceration (If Applicable)**	**New Lesions [a]**	**Clinical Response**
CR or PR	Non-PD	No	Response [b]
SD	CR	No	Response [b]
SD	SD	No	SD
PD	Any	Any	PD [c]
Any	PD	Any	PD [c]
Any	Any	Yes	PD [c]

CR = complete response; PD = progressive disease; SD = stable disease.

[a] See above for definitions.
[b] In patients achieving clinical response, histologic analysis of biopsies will be used for final determination of CR vs. PR; see below and Appendix G.
[c] If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.

Clinical plus RECIST (for patients with locally advanced BCC whose target lesion[s] have both externally visible and RECIST-measurable components)

See Appendix B for RECIST; also see Section C above with respect to the criteria for new skin lesions.

Clinical Response	**RECIST Response**	**Clinical + RECIST Response**
Response	Non-PD	Response [a]
SD	CR or PR	Response [a]
SD	SD	SD
PD	Any	PD [b]
Any	PD	PD [b]

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] In patients achieving clinical response, histologic analysis of biopsies will be used for final determination of CR vs. PR; see below and Appendix G.

[b] If the investigator's assessment of progressive disease is equivocal, and in the investigator's opinion the patient is still deriving benefit from treatment, treatment with CX-4945 should be continued, and the patient should be re-evaluated at the next tumor assessment timepoint.

In patients with a clinical response, histologic analysis of biopsies will be used for final determination of CR (absence of residual BCC) versus PR (residual BCC present); see Appendix G.

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously inoperable lesion to be potentially operable, the Medical Monitor should be consulted prior to any surgical procedure

APPENDIX D

DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND ACCEPTABLE AND UNACCEPTABLE FORMS OF CONTRACEPTION

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 45 years old.
- Women of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 6 months following discontinuation of CX-4945.

The following are acceptable forms of barrier contraception:

- Latex condom (always used with spermicide)
- Diaphragm (always used with spermicide)
- Cervical cap (always used with spermicide)

The following are acceptable forms of secondary contraception, when used with a barrier method:

- Tubal ligation
- Partner's vasectomy
- Hormonal contraception including birth control pills, patches, rings, or injections, with the exception of the progesterone-only "minipill"
- Intrauterine device (non–progesterone T)
- Vaginal sponge (containing spermicide)

In addition, 100% commitment to abstinence is considered an acceptable form of contraception.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- Progesterone-only "minipill"
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness

- Withdrawal
- Cervical shield

APPENDIX E

VITAMIN D DOSING RECOMMENDATION[1]

[redacted]

APPENDIX F

MEDICATIONS WITH THE POTENTIAL TO INTERACT WITH CX-4945

APPENDIX G

GUIDELINES FOR TISSUE BIOPSY IN PATIENTS WITH LOCALLY ADVANCED BASAL CELL CARCINOMA

Representative tumor biopsies are required for patients in the locally advanced basal cell carcinoma (BCC) cohort at the following timepoints:

- At screening, Week 8 and
- Either at the investigator's assessment of best clinical response or best clinical/RECIST response, if occurring prior to 24 weeks,

  or

  At 24 weeks, if patient is still in study and is without evidence of progression

Required Tumor Biopsy	Screening (Day -14 to -1)	Week 8 (± 3 Days)	Clinical Response if before Wk 24	Week 24 (± 3 Days)	At disease progression
Tumor biopsy for Hh pathway measurement (for laBCC patients in expansion cohort only)	X	X			
Tumor biopsy for tumor response assessment	X		X	X	X[1]

[1]Recommended for all locally advanced BCC patients.

At any time during a patient's participation in the study, an optional tumor biopsy may be requested to clarify the response status of a patient. In addition, biopsy of any accessible target lesion(s) is highly recommended at the time of progression.

The sites, number, and technique of representative biopsies will be determined by the investigator on the basis of the size and location of the accessible lesions. It is recommended that any areas suspicious for residual disease be biopsied, as well as areas which appear to be free of disease. These biopsies will be reviewed by site's pathologist.

Two separate biopsies should be obtained rather than splitting the biopsies for response assessment and Hh pathway activity measurement.

For Hh pathway activity measurement, at least one and up to two punch biopsies of at least 4 mm in size, or 14-gauge or larger core needle biopsies should be obtained. It is recommended that approximately 0.1 cm^3 of the tissue specimen, which should yield sufficient mRNA for this study. Tumor samples should immediately be snap frozen in

either liquid nitrogen or dry ice following surgical resection and stored at −80°C or below in a proper pre-cooled cryovial. It is highly recommended that biopsies should be snap frozen immediately and to be maintained frozen. Samples should be transported to Oncocyte Corporation per the "Sample Storage and Shipping Instructions" attached to this Guideline.

For tumor response assessment, at least one and up to five punch biopsies of at least 3 mm in size, or 14-gauge or larger core needle biopsies, as determined by the investigator, should be obtained. For large, accessible lesions in the skin and/or soft tissues, punch biopsies of 3 to 4 mm are strongly recommended to allow for optimal assessment of residual disease.

Biopsies for tumor response assessment should be fixed and paraffin embedded according to site standards.

The site pathologist's assessment will be used in the determination of response. The hematoxylin- and eosin-stained slides will be reviewed by site's pathologist to determine whether residual BCC is present. Epithelial rests or tumors consisting of epithelium with abnormal follicular differentiation, while not necessarily definitive evidence of residual BCC, will be interpreted as residual BCC.

If a biopsy obtained after administration of CX-4945 cannot be interpreted because of technical issues (e.g., crush artifact), then additional biopsies will be requested, if available.

Patients experiencing a clinical response whose biopsies show no evidence of residual BCC on biopsy will be considered to have a complete response; those experiencing a clinical response, but whose biopsies show evidence of residual BCC, will be considered to have a partial response.

Sample Storage and Shipping Instructions

(Refer to the most current version of the Pharmacodynamics Manual)

Tissue Biopsy Specimen Submission Form

(Refer to the most current version of the Pharmacodynamics Manual)

Specimen Shipment Notification Form

(Refer to the most current version of the Pharmacodynamics Manual)

APPENDIX H

DIGITAL PHOTOGRAPHIC PROCEDURES FOR SERIAL PHOTOGRAPHIC DOCUMENTATION OF BASAL CELL CARCINOMA

(Refer to the most current version of the Photo Manual)

APPENDIX I

ECOG PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

APPENDIX J

EQUATION FOR CALCULATING AN ESTIMATED GLOMERULAR FILTRATION RATE

The Cockcroft and Gault formula:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{Age}) \times \text{Weight} \times 0.85 \text{ (if female)}}{72 \times \text{Serum Creatinine}}$$

Abbreviations/ Units:

CrCl (creatinine clearance) = mL/minute

Age = years

Weight = kg

Serum creatinine = mg/dL

[If serum creatinine is in μmol/L, multiply the above Cockcroft and Gault equation with 1.4 for females or 1.23 for males]

APPENDIX K

HEDGEHOG PATHWAY ANTAGONISTS IN USE OR WITH POTENTIAL INTERACTION OF THE HEDGEHOG PATHWAY

The table below lists experimental compounds in columns under the designation of specific target of the Hedgehog pathway.

This is not necessarily a complete list; other medications may also interact with Hh pathway.

Target	**Inhibitor**
Gli	ATO
Gli	GANT58, 61
Gli	HPI 1-4
Gli	Glabrescione B
Gli	JQ1
PKA	Imiquimod
RARβ/RARγ	Tazarotene
aPKC	PSI

Abbreviations: Hh, Hedgehog; BCC, basal cell carcinoma; PKA, protein kinase A; aPKC, atypical protein kinase C ι/λ; RARβ/RARγ, retinoic acid receptor β/γ; ATO, arsenic trioxide; PSI, specific peptide inhibitor; Gli, Gli transcription factors.

Senhwa Biosciences, Inc.

Protocol CX-4945-07 Version 6.0

Approved by

John Soong, MD, Chief Medical Officer	Date